ADDENDUM TO *IN VITRO* OCULAR TOXICITY DRAFT BACKGROUND REVIEW DOCUMENTS

July 25, 2005

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LIST OF ACRONYMS AND ABBREVIATIONS

AG	Aktiengesellschaft (incorporated)
Assn.	Association
BASF	Badische Anilin- & Soda Fabrik AG
BCOP	Bovine Corneal Opacity and Permeability
BRD	Background review document
CAM	Chorioallantoic membrane
CASRN	Chemical Abstracts Service Registry Number
CC	Conjunctival chemosis
Co.	Company
CO	Corneal opacity
Conc.	Concentration
Corp.	Corporation
CR	Conjunctival redness
CTFA	Cosmetic, Toiletries and Fragrance Association
CV	Coefficient of variation
D	Day
EC/HO	European Commission/British Home Office
ECETOC	European Center for Ecotoxicology and Toxicology Of Chemicals
ECVAM	European Center for the Validation of Alternative Methods
EPA	United States Environmental protection Agency
EU	European Union
FHSA	Federal Hazardous Substance Act
FR	*Federal Register*
GHS	Globally Harmonized System
GmbH	Gesellschaft mit beschränkter Haftung (Inc.)
GSK	GlaxoSmithKline
HET-CAM	Hen's Egg Test-Chorioallantoic Membrane
I	Iritis

ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
ICE	Isolated Chicken Eye
IRE	Isolated Rabbit Eye
IS	Irritation score
ISOPA	European Diisocyanate and Polyol Producers Association
ITC	Irritation threshold concentration
Lab.	Laboratory
LNS	Laboratoire National de la Sante
Ltd.	Limited
LLC	Limited Liability Company
MeSH	Medical Subject Headings
MMAS	Modified Maximum Average Score
MW	Molecular weight
n.a.	Not available
NICEATM	National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods
NTP	United States National Toxicology Program
OTWG	Ocular Toxicity Working Group
PPM	Parts per million
SCNM	Study criteria not met
SD	Standard deviation
TSA	Test Substance Applicator
TSCA	Toxic Substances Control Act
ZEBET	German Center for Documentation and Evaluation of Alternative Methods to Animal Experiments

ACKNOWLEDGEMENTS

NICEATM gratefully acknowledges the generous contributions of the companies and individuals who provided data or additional information for this addendum. Their time and efforts to sort through study archives and compile data for this document are greatly appreciated.

GlaxoSmithKline

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Johnson & Johnson Pharmaceutical R&D

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ADDENDUM PREFACE

On November 1, 2004, the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) made available draft background review documents (BRDs) that provided information and data about the current validation status of four *in vitro* test methods for detecting ocular corrosives and severe irritants (Available: http://iccvam.niehs.nih.giv/methods/ocudocs/ocu_brd.htm). The four test methods were the Bovine Corneal Opacity and Permeability (BCOP) assay, the Hen's Egg Test - Chorioallantoic Membrane (HET-CAM) assay, the Isolated Chicken Eye (ICE) assay, and the Isolated Rabbit Eye (IRE) assay. These draft BRDs were based on published studies using the identified test methods, and other data and information submitted in response to a 2004 *Federal Register* (*FR*) request (Available: http://iccvam.niehs.nih.gov/methods/eyeirrit.htm)

The Interagency Coordinating committee on the Validation of Alternative Methods (ICCVAM) convened an Expert Panel meeting on January 11-12, 2005, to independently assess the validation status of these four *in vitro* test methods for identifying ocular corrosives or severe irritants (Available: http://iccvam.niehs.nih.gov/methods/eyeirrit.htm). Public comments at the meeting revealed that additional relevant data was available that had not yet been provided in response to earlier requests for data. The Expert Panel recommended that the additional data be requested and that a reanalysis of the accuracy and reliability of each test method be conducted where appropriate.

In response to this recommendation, an *FR* notice was published on February 28, 2005 (Available: http://iccvam.niehs.nih.gov/methods/eyeirrit.htm). The notice requested all available *in vitro* data on these four *in vitro* ocular irritancy test methods and corresponding *in vivo* rabbit eye test method data, as well as any human exposure data (either via ethical human studies or accidental exposure). A request for relevant data was re-sent directly to the primary developers or users of each test method. In response to these requests, additional *in vitro* test method data and corresponding *in vivo* rabbit eye test results were submitted for the BCOP, HET-CAM, and ICE test methods, which were used for the reanalyses in this BRD addendum.

Further clarification of hazard classification rules for severe irritants was also obtained subsequent to the release of the four draft BRDs. This change resulted in a small number of substances previously classified as nonsevere irritants now being classified as severe irritants (from 10 to 15, depending on the test method and the classification system used). However, this change necessitated a reanalysis of the accuracy and reliability of all four of the test methods, which are provided in this BRD addendum.

The original draft BRDs also provided an evaluation of the accuracy of each test method by chemical class. The chemical classes assigned to each test substance were revised based on a chemical classification system consistent with the U.S. National Library of Medicine's Medical Subject Headings (MeSH; Available: http://www.nlm.nih.gov/mesh), an internationally recognized standardized classification scheme. This scheme was used to

ensure consistency in classifying substances by chemical class among all the *in vitro* ocular test methods under consideration, and resulted in some chemicals being re-classified into different chemical classes. As a result, the accuracy of each test method by chemical class was reanalyzed; the results of each reanalysis are also provided in this BRD addendum.

The original BRD proposed a list of 89 reference substances that could be used for the optimization and/or validation of test methods proposed to identify severe and/or irreversible ocular effects. This reference substance list also was proposed as a source to use in selecting substances for performance standards and proficiency testing. The Expert Panel concluded that the list of proposed substances was fairly comprehensive in that the three major groups of products to which the eye is exposed (i.e., industrial chemicals, pharmaceuticals, cosmetics) were represented, and that individual substances were appropriately chosen. However, the Expert Panel also made several recommendations about the list of proposed reference substances. Additionally, the number of potential candidate substances was increased as a result of additional data provided in response to the February 2005 *FR* notice (Available: http://iccvam.niehs.nih.gov/methods/eyeirrit.htm). Accordingly, a revised list of proposed reference substances has been developed and is provided in this BRD addendum.

This BRD addendum is available in electronic format on the ICCCVAM/NICEATM website (Available: http://iccvam.niehs.nih.gov/methods/ocudocs/reanalysis.htm); a paper copy can be obtained from NICEATM on request (niceatm@niehs.nih.gov). Comments from the public and scientific community are welcome and will be made available on the ICCVAM/NICEATM website (Available: http://iccvam.niehs.nih.gov/methods/eyeirrit.htm). The information in the BRD addendum also will be provided to the Expert Panel for their review and comment.

The ICCVAM and its Ocular Toxicity Working Group (OTWG) will consider the Expert Panel report, the revised accuracy and reliability analyses, and any public comments in preparing its final test method recommendations. These recommendations will be made available to the public and provided to the U.S. Federal agencies for consideration, in accordance with the ICCVAM Authorization Act of 2000 (Public Law 106-545) (Available: http://iccvam.niehs.nih.gov/about/PL106545.pdf).

We want to again acknowledge the excellent cooperation and contributions from the many organizations and scientists who provided critical data and information necessary for the original BRD and this addendum. The efforts of the many individuals who contributed to the preparation of this addendum also are gratefully acknowledged. These include Drs. David Allen and Neepa Choksi, Mr. Bradley Blackard, and Mr. James Truax, of Integrated Laboratory Systems (ILS), Inc., the NICEATM Support Contractor, as well as the members of the ICCVAM OTWG and ICCVAM representatives who reviewed various drafts. We also acknowledge Dr. Raymond Tice for his efforts in developing and reviewing this addendum as the Principal Investigator of the ILS, Inc. NICEATM Support Contract until June 26, 2005, when he became the Deputy Director of NICEATM. Finally, we want to recognize the excellent leadership of the OTWG Co-chairs, Dr. Karen Hamernik (U.S. Environmental Protection Agency) and Dr. Jill Merrill (U.S. Food and Drug Administration).

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July 25, 2005

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EXECUTIVE SUMMARY

This addendum to the draft Background Review Documents (BRDs) on four *in vitro* test methods – the Isolated Rabbit Eye (IRE) assay, the Isolated Chicken Eye (ICE) assay, the Bovine Corneal Opacity and Permeability (BCOP) assay, and the Hen's Egg Test - Chorioallantoic Membrane (HET-CAM) assay – for detecting ocular corrosives and severe irritants (Available: http://iccvam.niehs.nih.giv/methods/ocudocs/ocu_brd.htm [NICEATM 2004]) contains the results of the accuracy and reliability reassessment conducted on each of the four test methods (Available: http://iccvam.niehs.nih.gov/methods/ocudocs/reanalysis.htm [NICEATM 2005b]). This reassessment was in response to:

- the submission of additional *in vitro* test data and/or corresponding *in vivo* rabbit eye test data provided to the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) in response to a second *Federal Register* (*FR)* notice (Available: http://iccvam.niehs.nih.gov/methods/eyeirrit.htm [NIEHS 2005] requesting all available *in vitro* data on these four *in vitro* ocular irritancy test methods and corresponding *in vivo* rabbit eye test method data, as well as any human exposure data (either via ethical human studies or accidental exposure)
- clarification of the European Union (EU) (EU 2001) and United Nations (UN) Globally Harmonized System (GHS) (UN 2003) ocular hazard classification rules for severe irritants (Available: http:/www.unece.org/trans/danger/publi/ghs/ghs_rev00/00files_e.html); this resulted in the reclassification of 10 to 15 substances from nonsevere to severe irritants, depending on the *in vitro* ocular irritancy test method and the ocular hazard classification system used
- the reassignment of substances to chemical classes using Medical Subject Headings (MeSH) (Available: http://www.nlm.nih.gov/mesh [NLM 2005]), an internationally recognized standardized classification system that would ensure consistency in classifying substances by chemical class
- a recommendation that the accuracy analysis consider whether a substance was classified as corrosive or severely irritating based on the severity of the response and/or its persistence to day 21 post-treatment

A list of proposed reference substances for validation of *in vitro* tests to detect ocular corrosives and severe irritants was included in the draft BRDs released on November 1, 2004 [NICEATM 2004]. This addendum provides a revised list of proposed reference chemicals, which was prepared after consideration of the following:

- recommendations of the Expert Panel that resulted from their deliberations on January 11-12, 2005 (Available: http://iccvam.niehs.nih.gov/methods/eyeirrit.htm [NICEATM 2005a])
- clarification regarding the GHS rules for classification of severe irritants [UN 2003] that resulted in the reclassification of two proposed reference substances from nonsevere to severe irritants
- reassignment of the candidate reference substances to chemical classes using MeSH [NLM 2005]

- submission of additional Draize rabbit eye test results for approximately 300 substances

Table ES-1 provides a comparison of the accuracy statistics for each *in vitro* test method re-evaluated in this addendum, when results are compared to the GHS ocular hazard classification system.

IRE Test Method

The IRE test method was developed by Burton et al. (1981) and proposed as a preliminary *in vitro* screen for the assessment of severe eye irritants. This organotypic test method is also referred to as the Rabbit Enucleated Eye Test (REET) (e.g., Guerriero et al. [2004]). The principal advantage of the IRE test is that it eliminates the use of live animals for ocular irritancy testing and thus the pain and suffering potentially associated with the *in vivo* Draize rabbit eye test. Another advantage of the IRE test method is that it typically uses eyes isolated from euthanized rabbits used for other research purposes or from animals sacrificed commercially as a food source. In the IRE, liquid or solid substances are placed directly on the corneal surface of isolated rabbit eyes, which are held and maintained in a temperature-controlled chamber. After a 10-second exposure, followed by rinsing, the treated eye is evaluated for corneal opacity, corneal swelling, fluorescein penetration, and effects on the corneal epithelium at various times over a four-hour observation period. Substances that exceed a defined cut-off value for any single one of these endpoints are then identified as corrosives or severe irritants.

No additional data were submitted for the IRE test method. The existing database of substances tested using the four ocular endpoints recommended in the draft IRE BRD (corneal opacity, corneal swelling, fluorescein penetration, and epithelial integrity) remained limited to the Guerriero et al. (2004) study. As recommended by the Expert Panel, a reanalysis was performed in which substances in the CEC (1991), Balls et al. (1995), and Gettings et al. (1996) studies that had been identified as ocular corrosives/severe irritants using appropriate decision criteria (i.e., a corneal opacity score greater than or equal to 3, or a corneal swelling equal to or greater than a 25%) were considered together with the test results obtained by Guerriero et al. (2004). This database is referred to as the "Expanded Data Set."

Substances that were identified as ocular corrosives/severe irritants based on *in vitro* results by any single endpoint were, therefore, included in the reanalysis as part of the expanded data set. Substances in the CEC (1991), Balls et al. (1995), and Gettings et al. (1996) studies that were identified as nonsevere irritants or nonirritants, based on *in vitro* results, were not included in the expanded data set. These substances were not included because an evaluation that included any of the omitted endpoints might have resulted in a severe irritant classification. For example, a substance that did not produce ≥ 25% corneal swelling might have produced a corneal opacity score, fluorescein penetration score, or damage to the epithelium that would have classified it as a severe irritant had these endpoints been evaluated.

Table ES-1. Comparative Overall Test Method Accuracy Characteristics for IRE[1], ICE[2], HET-CAM[3], and BCOP[4] in Identifying GHS[5] Ocular Corrosives/ Severe Irritants (UN[6] [2003]) – Reanalyses

Statistic	IRE			ICE		HET-CAM			BCOP	
	Old[7] (n = 36)[8]	New[7] (n = 38)	Expanded-New[9] (n = 76)	Old (n = 92)	New (n = 144)	Old (n = 52)	New[10] (n = 101)	New[11] (n = 143)	Old (n = 120)	New (n = 147)
Accuracy	78% (28/36)	79% (30/38)	68% (52/76)	82% (75/92)	83% (120/144)	85% (44/52)	68% (69/101)	53% (76/143)	79% (95/120)	81% (119/147)
Sensitivity	100% (12/12)	100% (11/11)	100% (33/33)	60% (15/25)	50% (15/30)	100% (12/12)	70% (28/40)	85% (35/41)	76% (32/42)	84% (36/43)
Specificity	67% (16/24)	70% (19/27)	44% (19/43)	90% (60/67)	92% (105/114)	80% (32/40)	67% (41/61)	40% (41/102)	81% (63/78)	80% (83/104)
Positive Predictivity	60% (12/20)	58% (11/19)	58% (33/57)	68% (15/22)	63% (15/24)	60% (12/20)	58% (28/48)	36% (35/96)	69% (34/49)	63% (36/57)
Negative Predictivity	100% (16/16)	100 (19/19)	100% (19/19)	86% (60/70)	88% (105/120)	100% (32/32)	77% (41/53)	87% (41/47)	86% (61/71)	92% (83/90)
False Positive Rate	33% (8/24)	30% (8/27)	56% (24/43)	10% (7/67)	8% (9/114)	20% (8/40)	33% (20/41)	60% (61/102)	19% (15/78)	20% (21/104)
False Negative Rate	0% (0/12)	0% (0/11)	0% (0/33)	40% (10/25)	50% (15/30)	0% (0/12)	30% (12/40)	15% (6/35)	24% (10/42)	16% (7/43)

[1]IRE = Isolated Rabbit Eye assay.
[2]ICE = Isolated Chicken Eye assay.
[3]HET-CAM = Hen's Egg Test – Chorioallantoic Membrane assay.
[4]BCOP = Bovine Corneal Opacity and Permeability assay.
[5]GHS = Globally Harmonized System.
[6]UN = United Nations.
[7]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on the analysis included in the IRE draft BRD with corrections.
[8]n = number of substances tested; the numbers in parentheses in each row indicates the data on which the percentage calculation is based.
[9]Includes the 38 substances tested by Guerriero et al. (2004) and 38 unique substances classified as severe irritants in Balls et al. (1995) and Gettings et al. (1996), based either on an *in vitro* corneal opacity score of at least 3.0 or an *in vitro* corneal swelling of at least 25%; these were among the criteria used by Guerriero et al. (2004) to identify corrosive/severe irritants.
[10]These data are for the IS(B) method (described by Kalweit et al. 1987) when testing substances as a 10% solution *in vitro*.
[11]These data are for the IS(B) method (described by Kalweit et al. 1987) when testing substances at a 100% concentration *in vitro*.

A reanalysis of the accuracy of the IRE test method for identifying ocular corrosives and severe irritants based on the reclassification of some nonsevere irritants as severe irritants was conducted. The results are independent of the three classification systems used; thus the discussion here is limited to the GHS classification system. When the reanalysis is restricted to Guerriero et al. (2004), the accuracy[1] changed from 78% (28/36) in the draft IRE BRD to 79% (30/38) in the reanalysis, the false negative rate stayed the same (draft IRE BRD = 0% [0/12]; reanalysis: 0% [0/11]) and the false positive rate decreased from 33% (8/24) in the draft IRE BRD to 30% (8/27) in the reanalysis.

For the expanded data set and using the GHS ocular hazard classification system, the accuracy was 68% (52/76), the false negative rate was 0% (0/33), and the false positive rate was 56% (24/43). The expanded data set used for this evaluation include the 38 substances evaluated by Guerriero et al. (2004) and an additional 38 substances tested by Balls et al. (1995) and Gettings et al. (1996) and classified by IRE as severe irritants, 22 of which were also severe irritants *in vivo* and 16 of which were nonsevere irritants or nonirritants *in vivo*. The expanded data set is potentially confounded by the exclusion of substances with true negative outcomes (matching *in vivo* and *in vitro* nonsevere or nonirritant classifications), which would affect both specificity and the false positive rate.

In order to further evaluate discordant responses of the IRE test method relative to the *in vivo* hazard classification, several accuracy sub-analyses were performed. These included specific classes of chemicals with sufficiently robust numbers of substances ($n \geq 5$), as well as certain properties of interest considered relevant to ocular toxicity testing (e.g., pesticides, surfactants, pH, physical form). Because the international community will soon adopt the GHS classification system for hazard labeling (UN [2003]), and considering that there were only modest differences in overall IRE test method accuracy among the three regulatory classification systems (i.e., EPA, EU, GHS), these sub-analyses are focused only on the GHS classification system, using the expanded data set.

The chemical classes that had the highest rate of IRE test method overprediction according the GHS classification system (i.e., were false positives) were ketones (67%, [4/6]), esters (67%, [4/6]), and alcohols (60%, [6/10]). Among the 10 surfactants tested, the false positive rate was 50% (2/4) and the false negative rate was 0% (0/6). The seven cationic surfactants included in this group had a false positive rate of 100% (1/1) and a false negative rate of 0% (0/6).

[1] Accuracy is defined as the proportion of correct outcomes (positive and negative) of a test method; Sensitivity is defined as the proportion of all positive substances that are classified as positive; Specificity is defined as the proportion of all negative substances that are classified as negative; Positive predictivity is defined as the proportion of correct positive responses among substances testing positive; Negative predictivity is defined as the proportion of correct negative responses among substances testing negative; False positive rate is defined as the proportion of all negative substances that are falsely identified as positive; False negative rate is the defined as the proportion of all positive substances that are falsely identified as negative (ICCVAM 1997).

With regard to physical form of the substances overpredicted by the IRE test method, liquids had a higher overprediction rate (83%, [19/23]) than solids (25%, [5/20]). There was insufficient data to analyze the effect of pH on overprediction.

No substances were underpredicted (i.e., were false negatives) by the IRE test method. Thus, an analysis of underprediction based on chemical class, physical form, pH, or NICEATM GHS Category I subclassification was not possible.

In the original draft IRE BRD (NICEATM [2004]), no data was provided for the assessment of intralaboratory repeatability and reproducibility. Since no additional data was submitted for the IRE test method following the Expert Panel meeting, an analysis of intralaboratory reliability still could not be conducted.

The original IRE test method reliability analysis included an evaluation of interlaboratory reproducibility using both qualitative and quantitative approaches. While the quantitative analysis was unaffected by the reclassification of the ocular irritancy of some test substances, the qualitative analysis (correct classification as an ocular corrosive/severe irritant or as a non-corrosive/non-severe irritant) of the individual laboratory test results obtained for the EC/HO validation study (Balls et al., [1995]) and for the CEC (1991) collaborative study was affected.

Overall, in the Balls et al. (1995) study, the number of substances with 100% agreement among the four participating laboratories was 59-61% (35-36/59) in the original analysis and 59-63% (35-37/59) in the reanalysis. The number of substances with 75% agreement among laboratories was 24-25% (14-15/59) in the original analysis and 22-25% (13-15/59) in the reanalysis. The number of substances with 50% agreement among laboratories did not change due to the reanalysis (15% [9/59 substances]).

Overall, in the CEC (1991) study, the number of substances with 100% agreement among the three participating laboratories decreased from 86% (18/21) to 81% (17/21) in the reanalysis. The number of substances with 67% agreement among laboratories remained the same at 14% (3/21), while the number of substances with 33% agreement was increased from 0% to 5% (1/21).

ICE Test Method

The ICE test method protocol (also referred to as the Chicken Enucleated Eye Test [CEET]) was first described by Prinsen and Koëter (1993) and was developed based on the IRE test developed by Burton et al. (1981). In this *in vitro* bioassay, the test substance is applied to the cornea of eyes isolated from chickens that have been slaughtered for human consumption. Three parameters are evaluated to measure the extent of damage to the eye following exposure to a chemical substance: corneal swelling, corneal opacity, and fluorescein retention. While the latter two parameters involve a subjective assessment, analysis of corneal swelling provides an objective measurement, thus potentially providing improved precision and reduced interlaboratory variability compared to the traditional *in vivo* rabbit eye test, which relies only on subjective measurements.

For this reanalysis, additional ICE test method data and corresponding *in vivo* rabbit eye test data were submitted by the TNO Nutrition and Food Institute for the 44 substances tested in Prinsen (1996) and for an additional 50 substances (Prinsen [2005]). Also, the TNO Nutrition and Food Institute provided replicate ICE test data and the corresponding *in vivo* EU hazard classification for four substances (Prinsen [2000]). The additional data increased the number of substances in the comparative ICE:*in vivo* rabbit eye test database from 92 to 149 substances for the GHS classification system (UN [2003]), from 90 to 148 for the U.S. Environmental Protection Agency (EPA) classification system (EPA [1996]), and from 121 to 155 for the EU classification system (EU [2001]).

Depending on the classification system used, the overall accuracy of the ICE test method changed from 82-83% (old analysis) to 83-84% (reanalysis), the false positive rate was reduced from 8-10% (old analysis) to 6-8% (reanalysis), while the false negative rate was increased from 30-40% (old analysis) to 40-50% (reanalysis).

Consistent with the original analysis, the reanalysis indicated that alcohols are overpredicted (50% [5/10] false positive rate) in the ICE test method. Carboxylic acids were shown to have a false negative rate of 43% (3/7).

The total database for surfactants was increased from 13 to 21 substances. However, given the stability of the false negative rate (old analysis: 57% [4/7]; new analysis 56% [5/9]), these substances still appear to be underpredicted by the ICE test method. With the additional data, it was now possible to evaluate the accuracy of the ICE test method for pesticides. While the false positive rate for these substances was 0% (0/6), the false negative rate for pesticides was 60% (3/5).

Eight of the fifteen underpredicted substances were liquids while seven were solids. However, considering that the total number of solids (36) in the database is much smaller than the number of liquids (108), solids appear more likely to be underpredicted (58%) than liquids (44%) by the ICE test method. In comparison to the original analysis, the false negative rate of solid substances increased from 55% (6/11) to 58% (7/12), while that for liquids increased from 29% (4/14) to 44% (8/18).

Using the expanded database, an analysis was conducted of the ability of the ICE test method to identify ocular corrosives and severe irritants, depending on the nature of the *in vivo* ocular lesions (i.e., severity and/or persistence) responsible for classification of a substance as an ocular corrosive/severe irritant. Underpredicted substances were more likely to be substances classified *in vivo* based on persistent lesions only (false negative rate = 70% [7/10]), than on severe lesions (false negative rate = 45% [9/20]).

A new analysis not included originally was an evaluation of accuracy related to acidic or basic pH. Among the eight underpredicted substances for which pH information was available, four were acidic (pH < 7.0) and four were basic (pH > 7.0). Again, basic substances (8) occupy a smaller proportion of the total database than acidic substances (12),

and were more often underpredicted (50% vs. 33%). However, pH information was obtained for only 20 of the 30 total Category 1 substances.

Previously, an evaluation of the intralaboratory repeatability and reproducibility of the ICE test method could not be conducted. However, subsequent to the original reliability analysis, data were received that allowed for a quantitative analysis of intralaboratory repeatability and reproducibility of ICE test method endpoints.

The range of percent coefficient of variation (%CV) values for the corneal thickness measurement, when results were compared within experiments, was from 0.9% to 6.1%. The other endpoints evaluated produced ranges of %CV values that were larger, with variability most prominent with the nonirritating substance (SP-1). However, this could be an exaggeration of variability given the relatively small values that were produced from the nonirritating substance relative to the irritating and corrosive substances (i.e., corneal swelling values of 2, 0, and 3 yield a higher %CV than values of 11, 14, and 18). A similar discussion can also be applied to the variability among the qualitative endpoints (i.e., corneal opacity and fluorescein retention) given the small dynamic range of their scores (0-4 or 0-3, respectively).

The range of %CV values for the corneal thickness measurement, when results were compared across laboratories, was from 1.8% to 6.3%. The %CV values for the remaining endpoints had a larger range (e.g., corneal swelling %CV = 13.9% to 138.7%). However, if the nonirritating substance is removed, the range of %CV values is reduced (e.g., corneal swelling %CV = 13.9% to 22.4%).

The previous analysis also included an evaluation of interlaboratory reproducibility using both qualitative and quantitative approaches. While the quantitative analysis was unaffected by the new information that was received, the qualitative analysis (correct classification as an ocular corrosive/severe irritant or as a non-corrosive/non-severe irritant) of the individual laboratory test results obtained for the EC/HO validation study (Balls et al., [1995]) needed to be repeated. However, the results obtained in the revised analysis were not different from the original analysis.

BCOP Test Method

The BCOP assay is an *in vitro* eye irritation test method using isolated bovine eyes from cattle that have been slaughtered for meat or other purposes. In the BCOP assay, opacity is determined by the amount of light transmission through the cornea, and permeability is determined by the amount of sodium fluorescein dye that passes through all corneal cell layers. More recent additions/endpoints to the BCOP assay are assessment of corneal swelling or hydration, and histological assessment of morphological alterations in the cornea (Bruner et al. [1998]; Ubels et al. [1998]; Cooper et al. [2001]; Jones et al. [2001]). When histological assessment is added to the BCOP assay, the type and depth of corneal injury can be evaluated, as well as whether the tissue damage is permanent (e.g., damage to the endothelium) (Gran et al. [2003]).

Subsequent to the draft BCOP BRD, *in vivo* rabbit eye test data that corresponded to the substances tested in BCOP in the Gautheron et al. (1994) study were received from Johnson & Johnson Pharmaceutical R&D. Individual cornea data from the BCOP tests evaluating these 52 substances were also provided subsequent to the meeting. Johnson & Johnson Pharmaceutical R&D also provided individual cornea data for 20 substances evaluated in the BCOP test method, comparing results achieved using corneas from adult animals (>24 months) versus those from young animals (6 - 8 months). The additional data increased the size of the comparative BCOP:*in vivo* rabbit eye test database from 120 to 147 substances for the GHS classification system (UN [2003]), 117 to 143 for the EPA classification system (EPA [1996]). In contrast, due to changes in study acceptability criteria (i.e., the classification call needed to be based on *in vivo* rabbit eye test data), the size of the comparative BCOP:*in vivo* rabbit eye test database was decreased from 157 to 143 substances for the EU classification system (EU [2001]).

The overall accuracy stayed the same in the reanalysis evaluation (original analysis: 77-80%, depending on the classification system used; reanalysis: 80% for all classification systems). The false positive rate was reduced from 23% (original analysis) to 21% (reanalysis) for the EU classification system (EU [2001]), but was increased from 17-19% (original analysis) to 19-20% (reanalysis) for the EPA (EPA [1996]) and GHS (UN [2003]) classification systems, respectively; while the false negative rate was reduced for all three classification systems (from 23-27% [original analysis] to 16-25% [reanalysis]).

Similar to the original analysis, the reanalysis indicated that alcohols are often overpredicted (50% [9/18] false positive rate) in the BCOP test method. Carboxylic acids (3/9) and heterocyclic compounds (2/6) had a false negative rate of 33%.

Eighteen of the 20 overpredicted substances were liquids while two were solids. Considering the proportion of the total available database, liquids (93) appear more likely than solids (34) to be overpredicted by the BCOP test method. In comparison to the original analysis, the overprediction of solid substances was reduced (from 44% [4/9] to 10% [2/20] false positive rate), while the false positive rate for liquids was increased from 21% (14/66) to 26% (18/69).

With regard to physical form of the substances underpredicted by the BCOP test method, six were solids and one was a liquid. In comparison to the original analysis, the false negative rate for solid substances was increased from 31% (4/13) to 43% (6/14), while the false negative rate for liquids was reduced in the revised analysis from 18% (5/28) to 4% (1/24).

Using the expanded database, an analysis was conducted of the ability of the BCOP test method to identify ocular corrosives and severe irritants, depending on the nature of the *in vivo* ocular lesions (i.e., severity and/or persistence) responsible for classification of a substance as an ocular corrosive/severe irritant. The underpredicted substances were more likely to be substances classified *in vivo* based on persistent lesions (false negative rate = 23% [3/13]), rather than on severe lesions (false negative rate = 17% [4/24]).

A new analysis not included originally was an evaluation of accuracy related to acidic or basic pH. Among the five underpredicted substances for which pH information was available, two (18% [2/11]) were acidic (pH < 7.0) and three (23% [3/13]) were basic (pH > 7.0). pH information was obtained for only 24 of the 43 total Category 1 substances.

The analyses of intralaboratory reliability were not affected by the information received subsequent to the release of the draft BCOP BRD. However, the previous analysis also included an evaluation of interlaboratory reproducibility using both qualitative and quantitative approaches. While the quantitative analysis was unaffected by the new information that was received, the qualitative analysis (correct classification as an ocular corrosive/severe irritant or as a non-corrosive/nonsevere irritant) of the data provided for multiple laboratories in three studies (Gautheron et al. [1994]; Balls et al. [1995]; Southee [1998]) needed to be repeated.

The results obtained in the revised analysis of interlaboratory reproducibility were not different from the original analysis. The five participating laboratories for the Balls et al. (1995) study were in 100% agreement in regard to the ocular irritancy classification for 40 (67%) of the 60 substances tested *in vitro* in the study. In general, the extent of agreement between testing laboratories was greatest for substances identified from *in vivo* rabbit eye data as corrosives or severe irritants when compared to any other combination of *in vivo* and *in vitro* results (76% to 86%, depending on the classification system used, of the accurately identified severe substances were shown to have 100% classification agreement among testing laboratories). For the study by Gautheron et al. (1994), there was 100% agreement in regard to the ocular irritancy classification for 35 to 36 (67% to 69%) of the 52 substances, which were tested in either 11 or 12 laboratories. Finally, for the study by Southee (1998), there was 100% agreement in regard to the ocular irritancy classification for 15 (94%) of the 16 substances.

HET-CAM Test Method

The HET-CAM test method uses the chorioallantoic membrane (CAM), which is a vascular fetal membrane composed of the fused chorion and allantois. The method is proposed to provide information on the effects that may occur in the conjunctiva following exposure to a test substance. It was assumed that acute effects induced by a test substance on the small blood vessels and proteins of this soft tissue membrane are similar to effects induced by the same test substance in the eye of a treated rabbit. The CAM has been proposed as a model for a living membrane (such as the conjunctiva) since it comprises a functional vasculature. Additionally, evaluation of coagulation (i.e., protein denaturation) may reflect corneal damage that may be produced by the test substance. The CAM is evaluated for the development of irritant endpoints (hyperemia, hemorrhage, and coagulation). Depending on the method used to collect data on the endpoints (time to development, severity of observed effect), qualitative assessments of the irritation potential of test substances are made.

Additional HET-CAM test method data and corresponding *in vivo* rabbit eye test data were received from ZEBET for substances that were originally described in Spielmann et al. (1996) (Spielmann and Liebsch [2005a]). HET-CAM test data previously discussed in

Section 9.0 of the draft HET-CAM BRD also were included in this reanalysis (Gilleron et al. [1996, 1997]). Results from control studies run concurrently with HET-CAM studies also were provided (Vanparys and VanGoethem [2005b]; Spielmann and Liebsch [2005b]). In addition, replicate intralaboratory and interlaboratory HET-CAM test data were obtained (Vanparys and VanGoethem [2005a]).

When the reanalyses were conducted with the IS(A) and IS(B) methods[2], based on the additional data received, wherein substances tested at either 10% or 100% concentration were compared only against *in vivo* studies which had been conducted with undiluted test substances, the following patterns were noted. For the IS(A) analysis method, test method accuracy increased when substances were evaluated at 100% concentration *in vitro* compared to the 10% concentration (e.g., 85% [17/20] for IS(A)-100 vs. 50% [12/24] for IS(A)-10; GHS classification system). In comparison, the opposite pattern was observed for the IS(B) analysis method; test method accuracy increased when substances were evaluated at 10% concentration (IS(B)-10) *in vitro* compared to the 100% concentration (IS(B)-100) (e.g., 68% [69/101] for IS(B)-10 vs. 53% [76/143] for IS(B)-100; GHS classification system).

Unlike the draft HET-CAM BRD analysis, where only formulations were evaluated by the IS(B) method, additional chemical classes were available for this reassessment. The revised analysis indicated that there are several chemical classes that are overpredicted by the HET-CAM IS(B) analysis methods when testing substances at either a 10% or at 100%. These chemical classes include alcohols (IS(B)-10: 90% [9/10]; IS(B)-100: 91% [10/11]), ethers (IS(B)-10: 50% [5/10]; IS(B)-100: 60% [9/15]), amines (IS(B)-10: 60% [3/5]; IS(B)-100: 83% [5/6]), organic salts (IS(B)-10: 57% [4/7]; IS(B)-100: 88% [7/8]), and heterocycles (IS(B)-10: 83% [5/6]; IS(B)-100: 75% [6/8]). Additionally, the IS(B)-100 analysis method overpredicted esters (83% [10/12]). The chemical class that was consistently underpredicted by the analysis methods was formulations (IS(B)-10: 44% [7/16]; IS(B)-100: 35% [7/13]).

An evaluation based on the physical form of the test substance depended on the analysis method being evaluated. Liquids could only be evaluated for the IS(B)-10 analysis method while solids and liquids could be evaluated for the IS(B)-100 analysis method. In the case of the IS(B)-100 evaluation, solids had a higher false positive rate when compared to liquids (76% [16/21] vs. 60% [36/60]). In contrast, the false negative rates for solids and liquids were approximately equal (IS(B)-10: 30%, 10/33 for liquids; IS(B)-100: 28% [7/25] and 26% [5/19] for solids). The false positive and false negative rate for liquids (when tested by the IS(B)-10 method) also were approximately equal (false positive: 34% [21/62]; false negative: 30% [10/33]).

An analysis of the ability of the HET-CAM test method to identify ocular corrosives and severe irritants, depending on the nature of the *in vivo* ocular lesions (i.e., severity and/or persistence) responsible for classification of a substance as an ocular corrosive/severe irritant,

[2] IS(A) analysis method refers to the method of Luepke (1985). This method evaluates the development of endpoints at pre-determined time points (e.g., 0.5, 2 and 5 minutes) and assigns a score based on the time of appearance of endpoint. The scores are totaled to determine an irritation score. IS(B) analysis method refers to the method Kalweit et al. (1987). This method determines the time required for endpoints to develop and uses these values to develop an irritation score.

indicated that, for IS(B)-10, the underpredicted substances were more likely to be substances classified as corrosive or severely irritating *in vivo* based on persistent lesions, with a false negative rate of 37% (10/27) compared to 15% (2/13) for substances classified as corrosive or severely irritating *in vivo* based on severity. This was not true for IS(B)-100, where the false negative rates for both persistent and severely irritating substances were the same (11% [2/18] and 11% [2/19], respectively).

Previously, an evaluation of the intralaboratory repeatability and reproducibility of the HET-CAM test method could not be conducted. However, subsequent to the release of the draft HET-CAM BRD, replicate within and among test data were received that allowed for a quantitative analysis of intralaboratory repeatability and reproducibility of HET-CAM test method endpoints.

The analysis of intralaboratory repeatability (i.e., the extent of variability among replicate eggs in the same study) was evaluated using data from two different publications (Gilleron et al. [1996, 1997]) that were provided by the authors in response to a request from NICEATM. In both studies, the highest %CV values were associated with the hemorrhage endpoint (104-117%), while the lowest %CV values were associated with the measurement of coagulation (38%-115%). However, the actual values were quite disparate between the two studies (e.g., Gilleron et al. [1996] coagulation %CV = 115.07, Gilleron et al. [1997] coagulation %CV = 37.78). The difference in the numbers between the two studies may be due to several factors including the nature of the test substances evaluated and differences in the test method protocols used. The mean and median overall *in vitro* score %CV for all substances tested was 32.52% for Gilleron et al. (1996) and 7.61 for Gilleron et al. (1997). The calculated intralaboratory repeatability for the endpoints and the overall test method may be exaggerated because of the relatively small values that are obtained from each of the endpoints (from 0 to 5 for hemorrhage, 0 to 7 for lysis, and 0 to 9 for coagulation).

Similar results were obtained from the analysis of intralaboratory reproducibility. The overall %CV values were 53.0% and 17.5% for the two studies evaluated. For the study by Gilleron et al. (1997), where substances could be classified according to the GHS and EPA classification systems, %CV values for severe irritants were similar to the values obtained for the overall database.

The previous analysis also included an evaluation of interlaboratory reproducibility using both qualitative and quantitative approaches. Additional data received subsequent to the draft HET-CAM BRD allowed for a more in-depth quantitative and qualitative analysis of interlaboratory reproducibility. A qualitative evaluation of data from Spielmann et al. (1996) indicates that that the level of agreement in classification of a test substance between testing laboratories, when evaluated per the GHS classification system, is 79% (85/107) and 82% (81/99) for the IS(B)-10 and IS(B)-100 analysis methods, respectively. A quantitative evaluation of the interlaboratory reproducibility of the test method based on a %CV analysis resulted in a mean %CV values of 60.17 for the IS(B)-10 analysis method and 35.21 for the IS(B)-100 analysis method.

The previous interlaboratory reproducibility analyses also were modified based on the reclassification of substances as an ocular corrosive/severe irritant or as a noncorrosive/ nonsevere irritant. However, the overall results obtained in the revised analysis were not different from the original analysis.

Finally, historical positive and negative control data were provided by two different sources. The negative control substance evaluated was 0.9% sodium chloride. The positive control substances were dimethylformamide, imidazole, 1% sodium dodecyl sulfate, and 0.1 N sodium hydroxide. The studies showed that all control substances consistently produced appropriate responses (e.g., negative control consistently produced a response that would be classified as nonirritant and positive controls consistently produced a response that would be classified as severe irritant).

Reference Substances

Included in each draft BRD [NICEATM 2004] were a list of proposed reference substances for the optimization and/or validation of *in vitro* tests to detect ocular corrosives and severe irritants (available electronically at http://iccvam.niehs.nih.gov/methods/ocudocs/ocu_brd.htm). The proposed reference substances are intended to:

- represent the range of ocular responses (i.e., corrosive/severe irritant; nonsevere irritant/noncorrosive) that the test method is expected to be capable of predicting
- represent the range of chemical/product classes and physicochemical properties (e.g., solid, liquid) that the test method is expected to be capable of testing
- represent the range of known or anticipated mechanisms or modes of action for severe/irreversible ocular irritation or corrosion
- have been generated by high-quality *in vivo* rabbit eye test method studies following Organization for Economic Cooperation and Development (OECD) Test Guideline (TG) 405 (OECD [1987]) and preferably conducted in compliance with Good Laboratory Practices (GLP) guidelines (OECD [1998]; EPA [2004a, 2004b]; FDA [2004])
- have a well-defined chemical composition
- be tested at a defined concentration and at a defined purity[3]
- be readily available

[3]Information on purity and the concentration tested were not available for all substances included in the NICEATM *in vivo* rabbit eye test results database. A decision was made to exclude nonsevere irritants (i.e., GHS Category 2A or 2B irritants) or non-irritants but not corrosive/severe irritants (i.e., GHS Category 1) that lacked concentration data from consideration as proposed reference substances. GHS category 1 substances were included because testing at a potentially higher concentration would not likely alter their classification as a GHS Category 1 substance although it might alter the criteria by which they were classified as an ocular corrosive/severe irritant. Where information on purity was lacking, an assumption was made that testing would have been conducted with a relatively pure substance. For substances included because they cause severe ocular effects in humans but lacked appropriate *in vivo* rabbit eye test data, information on concentration and purity were not available.

The Expert Panel concluded that the list of proposed substances is fairly comprehensive in that the three major groups of products to which the eye is exposed (i.e., industrial chemicals, pharmaceuticals, cosmetics) are represented and that, in general, individual substances were appropriately chosen. The Expert Panel also suggested several changes to the list of proposed reference substances. In response to their recommendations, a revised list of proposed reference substances has been developed. This list includes 11 more inorganic substances (especially those used in consumer products) and ten substances that are known human ocular corrosives or severe irritants (even in the absence of high quality Draize rabbit eye test data), contains fewer surfactants, and excludes formulations. In contrast, all 12 formulations in the original proposed list have been excluded, and the number of surfactants has been reduced from 12 to seven. In addition,

- the source of the Draize rabbit eye test data has been provided for each proposed reference substance
- where applicable and to the extent possible, within a chemical class, substances of lower, medium and higher molecular weight have been included (the molecular weight of each proposed substance is now provided)
- information is provided on whether each proposed reference substance has been tested in the proposed version of BCOP, HET-CAM, ICE, and IRE test methods

In addition to considering the recommendations of the Expert Panel, clarification regarding the rules for classification of severe irritants was obtained subsequent to the release of the four BRDs that resulted in changes to the hazard classification of a few of the substances included in the original list of proposed reference substances. Also, the chemical classes assigned to each reference substance were revised to be consistent with MeSH, an internationally recognized standardized classification scheme (Available: http://www.nlm.nih.gov/mesh [NLM 2005]). Finally, additional Draize rabbit eye test results for about 300 substances were obtained from several sources that expanded the number of potential candidate substances for consideration.

The revised list contains 122 substances including 79 GHS Category 1 substances (10 of which were classified as severe irritants based on human data only), 28 GHS Category 2 substances (14 Category 2A, 13 GHS Category 2B, 1 GHS Category 2A/2B) and 15 noninrritants. For the detection of ocular corrosives and severe irritants, the list of reference substances needs to include substances that:

- induce very severe responses within a relatively short time period, as well as those where the toxic response is delayed
- adversely affect the cornea, iris, and/or conjunctiva
- induce persistent versus non-persistent lesions (when assessed at 21 days post treatment)
- represent diverse chemical classes and physicochemical properties

The total number of proposed reference substances reflects the additional substances recommended by the Expert Panel and the need to ensure, to the extent possible, that the substances covered the range of responses of interest, chemical/product classes and

physicochemical properties of interest, and known or anticipated mechanisms or modes of action for severe/irreversible ocular irritation or corrosion. Nevertheless, power calculations are being conducted by NICEATM to evaluate the appropriateness of this number of substances for evaluating the accuracy of an *in vitro* ocular irritancy test method.

This list of proposed reference substances is intended to represent the minimum number of substances considered critical to an evaluation of the validity of alternative *in vitro* ocular irritancy test methods, while subsets of substances from this list may be considered for:

- optimization of a test method protocol
- performance standard reference substances for use in the validation of test methods that are functionally and mechanistically similar to a validated ocular irritancy test method
- proficiency testing to ensure the competency of a laboratory in performing a validated ocular irritancy test method

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SECTION I

ISOLATED RABBIT EYE (IRE) TEST METHOD

ACCURACY AND RELIABILITY REANALYSIS

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1.0 INTRODUCTION

On November 1, 2004, the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) released draft Background Review Documents (BRDs) on the current status of four *in vitro* test methods for detecting ocular corrosives and severe irritants (see http://iccvam.niehs.nih.gov/methods/ocudocs/ocu_brd.htm). The test methods reviewed were the Bovine Corneal Opacity and Permeability (BCOP), the Hen's Egg Test - Chorioallantoic Membrane (HET-CAM), the Isolated Rabbit Eye (IRE), and the Isolated Chicken Eye (ICE) assays. On January 11-12, 2005, the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) convened an Expert Panel to independently evaluate the validation status of these four *in vitro* test methods for identifying ocular corrosives or severe irritants. The Expert Panel Report, *Evaluation of the Current Validation Status of In Vitro Test Methods for Identifying Ocular Corrosives and Severe Irritants*, can be obtained directly from NICEATM or electronically from http://iccvam.niehs.nih.gov/methods/eyeirrit.htm). Public comments at the meeting revealed that additional data could be made available that had not yet been provided in response to earlier requests for data. The Expert Panel subsequently recommended that the additional data be requested and that a reanalysis of the accuracy and reliability of each test method be conducted, to the extent possible.

In response to this recommendation, a second *Federal Register* (*FR*) notice was published on February 28, 2005 (*FR* Vol. 70, No. 38, pp. 9661-9662; http://iccvam.niehs.nih.gov/methods/eyeirrit.htm) requesting all available *in vitro* data on these four *in vitro* ocular irritancy test methods and corresponding *in vivo* rabbit eye test method data, as well as any human exposure data (either via ethical human studies or accidental exposure). The first *FR* notice requesting these data had been published on March 24, 2004 (*FR* Vol. 69, No. 57, pp. 13859-13861; http://iccvam.niehs.nih.gov/methods/eyeirrit.htm). Also, a request for relevant data was re-sent directly to the primary developers or users of each test method and sent to other scientists who participated in or attended the Expert Panel Meeting on January 11-12, 2005 and who had indicated a desire to provide additional data. No human exposure data was obtained for the substances evaluated in the IRE test method, and therefore no calculations could be made for the accuracy of the IRE test method for predicting human severe ocular irritancy.

Other factors also necessitated a reanalysis of the accuracy of the IRE test method for detecting ocular corrosives and severe irritants. First, clarification regarding the rules for classification of severe irritants was obtained subsequent to the release of the four BRDs that resulted in changes to the hazard classification of some of the substances used in the original analysis. For the original analysis, reversibility of ocular effects for the European Union (EU) and United Nations (UN) Globally Harmonized System (GHS) hazard classification systems was considered to be achieved if, by post-exposure day 21, the endpoint scores fell below the threshold that resulted in a test substance being classified as a severe irritant (EU [2001]; UN [2003]). The new information obtained indicated that reversibility of ocular effects is achieved only when all scores reach zero by post-exposure day 21. This change

resulted in nine substances previously classified as EU nonsevere irritants now being classified as EU severe irritants. One substance previously classified as GHS nonsevere irritant was reclassified as GHS severe irritant.

Second, the chemical classes assigned to each test substance were revised to reflect a standardized classification scheme (based on the Medical Subject Headings [MeSH]; http://www.nlm.nih.gov/mesh) that would ensure consistency in classifying substances among all *in vitro* ocular test methods under consideration. This resulted in some chemicals being re-classified. The accuracy of the IRE test method, by chemical class and using the GHS classification system (UN [2003]), has been reanalyzed to reflect these changes.

Finally, an additional accuracy analysis was conducted. In this analysis, the accuracy of each *in vitro* ocular irritancy test method for detecting ocular corrosives or severe irritants, depending on whether the classification was based on the severity of the response and/or its persistence to day 21 post-exposure, was determined.

For the IRE test method, the changes to the existing database that resulted from using the appropriate persistence classification criteria and any new data and/or information received subsequent to the release of the draft BRD are summarized in **Table I-1**. For the IRE test method, the changes to the existing database that resulted from using the appropriate persistence classification criteria and any new information received in response to the Expert Panel meeting and to additional requests for information are summarized in **Table I-1**.

No additional comparative *in vitro-in vivo* test results data were submitted for the IRE test method. The existing database of substances tested using the four ocular endpoints recommended in the draft IRE BRD (corneal opacity, corneal swelling, fluorescein penetration, and epithelial integrity) remained limited to the Guerriero et al. (2004) data set. However, as recommended by the Expert Panel, a reanalysis was performed in which substances in the CEC (1991), Balls et al. (1995), and Gettings et al. (1996) studies that had been identified as corrosives/severe irritants using appropriate decision criteria (a corneal opacity score greater than or equal to 3, or a corneal swelling equal to or greater than a 25%) were considered together with the test results obtained by Guerriero et al. (2004). This database is referred to as the "Expanded Data Set."

Substances that were identified as corrosives/severe irritants based on *in vitro* results by any single endpoint were, therefore, included in the reanalysis as part of the "Expanded Data Set." Substances in CEC (1991), Balls et al. (1995), and Gettings et al. (1996) that were identified as nonsevere irritants, based on *in vitro* results, were not included in the "Expanded Data Set," because any of the omitted endpoints might have resulted in a severe irritant classification. For example, in Gettings et al. (1996), only corneal swelling was measured. Substances that produced corneal swelling ≥ 25% were classified as severe irritants and were included in the "expanded data set." However, a substance that did not produce ≥ 25% corneal swelling, might have produced a corneal opacity score, fluorescein penetration score, or damage of the epithelium that would have classified it as a severe irritant had those endpoints been evaluated.

92 **Table I-1. Summary of IRE Database Changes**
93

Data Source	Data Set	Number of Available Substances	Number of Acceptable Substances by Ocular Irritancy Classification System			Comments
			EPA[1]	EU[2]	GHS[3]	
			Cat[4] I/Total[5]	R41/Total	Cat 1/Total	
CEC (1991)[6]	New[7]	21	-	5/15	-	Six substances were excluded from the original database (n=21) because their EU classification was based on pH extreme or skin corrosivity information rather than *in vivo* rabbit eye test data.
	Old[7]	21	-	11/21	-	
Balls et al. (1995)	New	59	19/53	19/49	22/54	The decrease in the total number of usable substances is due to excluding substances from consideration due to insufficient rabbit eye test data for classification (See **Appendix I-A**).
	Old	59	20/54	21/59	22/56	
Gettings et al. (1996)	New	25	17/25	16/24	16/24	The increase in the number of corrosive/severe irritants is due to the reclassification of several substances based on the presence of ocular damage at day 21 post-treatment.
	Old	25	12/25	12/25	12/25	
Guerriero et al. (2004)	New	44	11/38	11/38	11/38	Six substances were excluded from the original database because their classification was based on pH extremes or skin corrosivity information rather than *in vivo* rabbit eye test data.
	Old	44	16/41	15/41	16/41	
Expanded Data Set[8]	New	91[1]	31/76	37/80	33/76	From 11-15 substances were excluded from the original database, because specific regulatory classification criteria were not met (e.g., persistence could not be determined due to study termination).

94 [1]EPA = U.S. Environmental Protection Agency (EPA [1996]).
95 [2]EU = European Union (EU [2001]).
96 [3]GHS = Globally Harmonized System (UN [2003]).
97 [4]Cat = Category.
98 [5]Number of severe irritants by regulatory classification/number of classifiable substances.
99 [6]When the same substance was evaluated in multiple laboratories, the IRE ocular irritancy potential for each independent test result was determined.
100 Subsequently, an overall IRE ocular irritancy classification was assigned for each substance based on the majority of ocular irritancy classification calls and this
101 call was used in the analysis of IRE test method accuracy (approach described in **Section I-2.1**).
102 [7]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on the previous analysis included in the draft IRE BRD.

[8]Includes the 38 substances tested by Guerriero et al. (2004) that could be classified and additional substances classified as severe irritants from CEC (1991) (EU classification system only), Balls et al. (1995), and Gettings et al. (1996), based either on an *in vitro* corneal opacity score of at least 3.0 or an *in vitro* corneal swelling of at least 25%; these were among the criteria used by Guerriero et al. (2004) to identify corrosive/severe irritants.

2.0 ACCURACY OF THE IRE TEST METHOD - REANALYSIS

The ability of the IRE test method to correctly identify ocular corrosives and severe irritants, as defined by the U.S. Environmental Protection Agency (EPA), EU, and GHS classification systems (EPA [1996]; EU [2001]; UN [2003])[1], was evaluated. The three regulatory ocular hazard classification systems considered during this analysis use different classification systems and decision criteria to identify ocular corrosives and severe irritants based on *in vivo* rabbit eye test results. All three classification systems are based on individual animal data in terms of the magnitude of the response and on the extent to which induced ocular lesions fail to reverse by day 21. However, there are differences among the three classification systems in regard to their criteria used by NICEATM for distinguishing between a severe and a nonsevere response (see **Appendix A**). Thus, to evaluate the accuracy of the IRE test method for identifying ocular corrosives and severe irritants, individual rabbit data collected at the different observation times was needed for each substance.

The ability of the IRE test method to correctly identify ocular corrosives and severe irritants, as defined by the EPA, EU, and GHS classification systems (EPA [1996]; EU [2001]; UN [2003]), was evaluated using two approaches. In the first approach, the accuracy of IRE was assessed separately for each *in vitro-in vivo* comparative study (i.e., publication) reviewed in Sections 4.0 and 5.0 of the draft IRE BRD. In the second approach, an overall analysis of IRE test method accuracy was conducted by combining results from each study, and then an overall ocular irritancy classification was assigned for each substance. When the same substance was evaluated in multiple laboratories, the overall IRE ocular irritancy classification was based on the majority of calls among all of the studies. When there was an even number of different irritancy classifications for substances (e.g., two tests classified a substance as a nonsevere irritant and two tests classified a substance as a severe irritant), the more severe irritancy classification was used for the overall classification for the substance (severe irritant, in this case).

Based on the revisions made to the IRE and *in vivo* test method databases, a revised accuracy analysis has been conducted. The calculations were performed as described previously in Section 6.0 of the draft IRE BRD. To allow for a comparison of the results obtained in the revised analysis relative to those obtained previously, the data tables below include accuracy statistics from both analyses. However, the discussion of the results in the sections that follow relate to the revised analysis only.

2.1 GHS Ocular Hazard Classification System

Three studies (Balls et al. [1995]; Gettings et al. [1996]; Guerriero et al. [2004]) contained IRE test data on 128 substances, 116 of which had sufficient *in vivo* data to be assigned an

[1] For the purposes of this analysis, an ocular corrosive or severe irritant was defined as a substance that would be classified as Category 1 according to the GHS classification system (UN [2003]), as Category I according to the EPA classification system (EPA [1996]), or as R41 according to the EU classification system (EU [2001]).

ocular irritancy classification as defined by the GHS classification system (UN [2003])[2] (see **Appendix I-A**). Based on results from *in vivo* rabbit eye experiments, 49[3] of the 116 substances were classified as severe irritants (i.e., Category 1), the other 67 substances were classified as nonsevere irritants (either Category 2A, 2B) or nonirritants (**Table I-2**). The 12 substances that could not be classified according to the GHS classification system due to the lack of adequate animal data are so noted in **Appendix I-A**.

2.1.1 Balls et al. (1995)

Based on the reclassification process, 54 of the 59 substances tested in this study could be assigned a GHS classification (**Table I-2**). The remaining five substances had inadequate *in vivo* data for assigning a classification according to the GHS system (UN [2003]). For the 54 substances assigned a GHS classification, the IRE test method has an accuracy[4] of 54% (29/54), a sensitivity of 68% (15/22), a specificity of 44% (14/32), a false positive rate of 56% (18/32), and a false negative rate of 32% (7/22).

2.1.2 Gettings et al. (1996)

Based on the reclassification process, 24 of the 25 substances tested in this study could be assigned a GHS classification **(Table I-2)**. The remaining substance had inadequate *in vivo* data for assigning a classification according to the GHS system (UN [2003]). For the 24 substances that could be evaluated, the IRE test method has an accuracy of 67% (16/24), a sensitivity of 63% (10/16), a specificity of 75% (6/8), a false positive rate of 25% (2/8), and a false negative rate of 38% (6/16).

2.1.3 Guerriero et al. (2004)

Based on the reclassification process, 38 of 44 substances tested in this study could be assigned a GHS classification (**Table I-2**). The remaining six substances had inadequate *in vivo* data for assigning a classification according to the GHS system (UN [2003]). For the 38 substances that could be evaluated, the IRE test method has an accuracy of 79% (30/38), a sensitivity of 100% (11/11), a specificity of 70% (19/27), a false positive rate of 30% (8/27), and a false negative rate of 0% (0/11).

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[2] For the purpose of this accuracy analysis, *in vivo* rabbit study results were used to identify GHS Category 1 irritants (i.e., severe irritants); substances classified as GHS Category 2A and 2B irritants were identified as nonsevere irritants.

[3] One chemical (benzalkonium chloride, 1%) was tested *in vivo* twice in the same laboratory. The results were discordant with respect to GHS classification. According to one test, the classification was Category 1, while results from the other test yielded a Category 2B classification. The accuracy analysis was performed with the substance classified as Category 1.

[4] Accuracy is defined as the proportion of correct outcomes (positive and negative) of a test method; Sensitivity is defined as the proportion of all positive substances that are classified as positive; Specificity is defined as the proportion of all negative substances that are classified as negative; Positive predictivity is defined as the proportion of correct positive responses among substances testing positive; Negative predictivity is defined as the proportion of correct negative responses among substances testing negative; False positive rate is defined as the proportion of all negative substances that are falsely identified as positive; False negative rate is the defined as the proportion of all positive substances that are falsely identified as negative.

Table I-2. Evaluation of the Performance of the IRE Test Method In Predicting Ocular Corrosives and Severe Irritants Compared to the *In Vivo* Rabbit Eye Test Method, as Defined by the GHS[1] Classification System, by Study and Overall

Data Source	Data Set	N[2]	Accuracy		Sensitivity		Specificity		Positive Predictivity		Negative Predictivity		False Positive Rate		False Negative Rate	
			%	No.[3]	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Balls et al. (1995)[4,5]	New[6]	54/59	54	29/54	68	15/22	44	14/32	45	15/23	67	14/21	56	18/32	32	7/22
	Old[6]	56/59	50	28/56	64	14/22	41	14/34	41	14/34	64	14/22	59	20/34	36	8/22
Gettings et al. (1996)	New	24/25	67	16/24	63	10/16	75	6/8	83	10/12	50	6/12	25	2/8	38	6/16
	Old	25/25	64	16/25	56	9/16	78	7/9	82	9/11	50	7/14	22	2/9	44	7/16
Guerriero et al. (2004)	New	38/44	79	30/38	100	11/11	70	19/27	58	11/19	100	19/19	30	8/27	0	0/11
	Old	36/44	78	28/36	100	12/12	67	16/24	60	12/20	100	16/16	33	8/24	0	0/12
Expanded Data Set[7]	New	76/91	68	52/76	100	33/33	44	19/43	58	33/57	100	19/19	56	24/43	0	0/33

[1]GHS = United Nations Globally Harmonized System (UN [2003]).
[2]N = number of substances included in this analysis/the total number of substances in the study.
[3]Data used to calculate the percentage.
[4]One chemical (benzalkonium chloride, 1%) was tested *in vivo* twice within the same laboratory. The results were discordant with respect to GHS classification; the analysis was performed assuming Category 1 classification.
[5]Performance calculated using the overall *in vitro* classification based on the majority and/or most severe classification among the four laboratories.
[6]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on analysis included in the draft IRE BRD with corrections.
[7]Includes the 38 substances tested by Guerriero et al. (2004) that could be classified and 38 additional substances classified as severe irritants from Balls et al. (1995) and Gettings et al. (1996), based either on an *in vitro* corneal opacity score of at least 3.0 or an *in vitro* corneal swelling of at least 25%; these were among the criteria used by Guerriero et al. (2004) to identify corrosive/severe irritants. When the same substance was evaluated in multiple laboratories, the IRE ocular irritancy potential for each independent test result was determined. Subsequently, an overall IRE ocular irritancy classification was assigned for each substance based on the majority of ocular irritancy classification calls and this call was used in the analysis of IRE test method accuracy (approach described in **Section I-2.0**); this process reduced the total number of substances in the expanded data set to 76 for the GHS classification system (UN [2003]).

2.1.4 Expanded Data Set

Subsequent to the original IRE test method accuracy analysis, the total data base of 149 substances was mined to established an expanded data set that included: (1) all substances evaluated by Guerriero et al. (2004) that could be assigned an GHS classification (UN [2003]), and (ii) any additional substances classified as severe irritants by Balls et al. (1995) and Gettings et al. (1996), based either on an *in vitro* corneal opacity score of at least 3.0 or an *in vitro* corneal swelling of at least 25%, that had corresponding *in vivo* rabbit eye test data that would allow the substances to be classified according to the GHS system (UN [2003]). These two criteria were among those used by Guerriero et al. (2004) to identify corrosive/severe irritants. When the same substance was evaluated in multiple laboratories, the IRE ocular irritancy potential for each independent test result was determined. Subsequently, an overall IRE ocular irritancy classification was assigned for each substance based on the majority of ocular irritancy classification calls and this call was used in the analysis of IRE test method accuracy (approach described in **Section I-2.0**).

Using this approach, the total number of substances in the expanded data set was 76 for the GHS classification system (UN [2003]). For these 76 substances (**Table I-2**), the IRE test method has an accuracy of 68% (52/76), a sensitivity of 100% (33/33), a specificity of 44% (19/43), a false positive rate of 56% (24/43), and a false negative rate of 0% (0/33).

2.2 EPA Ocular Hazard Classification System

Three studies (Balls et al. [1995]; Gettings et al. [1996]; Guerriero et al. [2004]) contained IRE test method data on 128 substances, 116 of which had sufficient *in vivo* data to be assigned an ocular irritancy classification according to the EPA classification system (EPA [1996])[5] (see **Appendix I-A**). Based on results from the *in vivo* rabbit eye test, 47 of these 116 substances were classified as severe irritants (i.e., Category I), while the other 69 substances were classified as nonsevere irritants or nonirritants (Categories II, III, or IV). The 12 substances that could not be classified according to the EPA classification system are so noted in **Appendix I-A**.

2.2.1 Balls et al. (1995)

Based on the reclassification process, 53 of the 59 substances tested in this study could be assigned an EPA classification (**Table I-3**). The remaining five substances had inadequate *in vivo* data for assigning a classification according to the EPA system (1996). For the 53 substances that could be evaluated, the IRE test method has an accuracy of 51% (27/53), a sensitivity of 65% (13/20), a specificity of 42% (14/33), a false positive rate of 58% (19/33), and a false negative rate of 35% (7/20).

[5] For the purpose of this accuracy analysis, *in vivo* rabbit study results were used to identify EPA Category I irritants (i.e., severe irritants); substances classified as EPA Category II, III, or IV irritants were defined as nonsevere irritants.

Table I-3. Evaluation of the Performance of the IRE Test Method In Predicting Ocular Corrosives and Severe Irritants Compared to the *In Vivo* Rabbit Eye Test Method, as Defined by the EPA[1] Classification System, by Study and Overall

Data Source	Data Set	N[2]	Accuracy		Sensitivity		Specificity		Positive Predictivity		Negative Predictivity		False Positive Rate		False Negative Rate	
			%	No.[3]	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Balls et al. (1995)[4,5]	New[6]	53/59	51	27/53	65	13/20	42	14/33	41	13/32	67	14/21	58	19/33	35	7/20
	Old[6]	52/59	48	25/52	61	11/18	41	14/34	35	11/31	67	14/21	59	20/34	39	7/18
Gettings et al. (1996)	New	25/25	64	16/25	59	10/17	75	6/8	83	10/12	46	6/13	25	2/8	41	7/17
	Old	25/25	60	15/25	53	9/17	75	6/8	82	9/11	43	6/14	25	2/8	47	8/17
Guerriero et al. (2004)	New	38/44	79	30/38	100	11/11	70	19/27	58	11/19	100	19/19	30	8/27	0	0/11
	Old	36/44	78	28/36	100	12/12	67	16/24	58	12/20	100	16/16	33	8/24	0	0/12
Expanded Data Set[7]	New	76/91[5]	66	50/76	100	31/31	42	19/45	54	31/57	100	19/19	58	26/45	0	0/31

[1]EPA = U.S. Environmental Protection Agency (EPA [1996]).
[2]N = number of substances included in this analysis/the total number of substances in the study.
[3]Data used to calculate the percentage.
[4]One chemical (benzalkonium chloride, 1%) was tested *in vivo* twice within the same laboratory. The results were discordant with respect to EPA classification; the analysis was performed assuming Category I classification.
[5]Performance calculated using the overall *in vitro* classification based on the majority and/or most severe classification among the four laboratories.
[6]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on analysis included in the draft IRE BRD with corrections.
[7]Includes the 38 substances tested by Guerriero et al. (2004) that could be classified and 38 additional substances classified as severe irritants from Balls et al. (1995) and Gettings et al. (1996), based either on an *in vitro* corneal opacity score of at least 3.0 or an *in vitro* corneal swelling of at least 25%; these were among the criteria used by Guerriero et al. (2004) to identify corrosive/severe irritants. When the same substance was evaluated in multiple laboratories, the IRE ocular irritancy potential for each independent test result was determined. Subsequently, an overall IRE ocular irritancy classification was assigned for each substance based on the majority of ocular irritancy classification calls and this call was used in the analysis of IRE test method accuracy (approach described in **Section I-2.0**); this process reduced the total number of substances in the expanded data set to 76 for the EPA classification system (EPA [1996]).

2.2.2 Gettings et al. (1996)

Based on the reclassification process, 25 of the 25 substances tested in this study could be assigned an EPA classification (**Table I-3**). For these 25 substances, the IRE test method has an accuracy of 64% (16/25), sensitivity of 59% (10/17), a specificity of 75% (6/8), a false positive rate of 25% (2/8), and a false negative rate of 41% (7/17).

2.2.3 Guerriero et al. (2004)

Based on the reclassification process, 38 of the 44 substances tested in this study could be assigned an EPA classification **(Table I-3)**. The remaining six substances had inadequate *in vivo* data for assigning a classification according to the EPA system (EPA [1996]). For the 38 substances that could be evaluated, the IRE test method has an accuracy of 79% (30/38), a sensitivity of 100% (11/11), a specificity of 70% (19/27), a false positive rate of 30% (8/27), and a false negative rate of 0% (0/11).

2.2.4 Expanded Data Set

Subsequent to the original IRE test method accuracy analysis, the total data base of 149 substances was mined to established an expanded data set that included: (1) all substances evaluated by Guerriero et al. (2004) that could be assigned an EPA classification (EPA [1996]), and (ii) any additional substances classified as severe irritants by Balls et al. (1995) and Gettings et al. (1996), based either on an *in vitro* corneal opacity score of at least 3.0 or an *in vitro* corneal swelling of at least 25%, that had corresponding *in vivo* rabbit eye test data that would allow the substances to be classified according to the EPA system (EPA [1996]). As noted previously, these two criteria were among those used by Guerriero et al. (2004) to identify corrosive/severe irritants. Rules for classifying a substance that was evaluated in multiple laboratories are the same as described in **Section I-2.1.4**. Based on this approach, the total number of substances in the expanded data set was 76 for the EPA classification system (EPA [1996]). For these 76 substances (**Table I-3**), the IRE test method has an accuracy of 66% (50/76), a sensitivity of 100% (31/31), a specificity of 42% (19/45), a false positive rate of 58% (26/45), and a false negative rate of 0% (0/31).

2.3 EU Ocular Hazard Classification System

Four studies (CEC [1991]; Balls et al. [1995]; Gettings et al. [1996]; Guerriero et al. [2004]) contained IRE test method data on 149 substances, 126 of which had sufficient *in vivo* data to be assigned an ocular irritancy classification according the EU classification system (EU [2001])[6] (see **Appendix I-A**). Based on results from the *in vivo* rabbit eye test, 51[7] of the 126 substances were classified as severe irritants (i.e., R41) and the other 75 substances were classified as nonsevere irritants (either R36) or nonirritants. The two substances that could not be classified according to the EU classification system are so noted in **Appendix I-A**.

[6] For the purpose of this accuracy analysis, *in vivo* rabbit study results were used to identify R41 irritants (i.e., severe irritants); substances classified as R36 were defined as nonsevere irritants.

[7] One chemical (benzalkonium chloride, 1%) was tested *in vivo* twice in the same laboratory. The results were discordant with respect to EU classification. According to one test, the classification was R41, while results from the other test yielded an R36 classification. The accuracy analysis was performed with the substance classified as R41.

2.3.1 CEC (1991)

Based on the reclassification process, 15 of the 21 substances tested in this study were included in an analysis of accuracy (**Table I-4**). The remaining six substances had inadequate *in vivo* data for assigning a classification according to the EU system (EU [2001]). Based on the available *in vivo* rabbit eye data or the EU ocular irritancy classification for each substance provided in the published study (individual rabbit eye test data was not available for all of the substances), the IRE test method has an accuracy of 87% (13/15), a sensitivity of 100% (5/5), a specificity of 80% (8/10), a false positive rate of 20% (2/10), and a false negative rate of 0% (0/5).

2.3.2 Balls et al. (1995)

Based on the reclassification process, 49 of the 59 substances tested in this study could be assigned a EU classification (**Table I-4**). The remaining ten substances had inadequate *in vivo* data for assigning a classification according to the EU system (EU [2001]). For the 49 substances assigned an EU classification, the IRE test method has an accuracy of 55% (27/49), sensitivity of 74% (14/19), a specificity of 43% (13/30), a false positive rate of 57% (17/30), and a false negative rate of 26% (5/19).

2.3.3 Gettings et al. (1996)

Based on the reclassification process, 24 of the 25 substances tested in this study could be assigned a EU classification (**Table I-4**). The remaining substance had inadequate *in vivo* data for assigning a classification according to the EU system (EU [2001]). For the 24 substances that could be evaluated, the IRE test method has an accuracy of 67% (16/24), a sensitivity of 63% (10/16), a specificity of 75% (6/8), a false positive rate of 25% (2/8), and a false negative rate of 38% (6/16).

2.3.4 Guerriero et al. (2004)

The original IRE test method accuracy analysis included 44 substances. Upon reclassification, sufficient data were available to permit EU classification on 38 of the 44 original substances and were used for the accuracy analysis (**Table I-4**). The remaining six substances had inadequate *in vivo* data for assigning a classification according to the EU system (EU [2001]). For the 38 substances, the IRE test method has an accuracy of 79% (30/38), sensitivity of 100% (11/11), specificity of 70% (19/27), a false positive rate of 30% (8/27), and false negative rate of 0% (0/11).

2.3.5 Expanded Data Set

Subsequent to the original IRE test method accuracy analysis, the total data base of 149 substances was mined to established an expanded data set that included: (1) all substances evaluated by Guerriero et al. (2004) that could be assigned an EU classification (EU [2001]), and (ii) any additional substances classified as severe irritants by CEC (1991), Balls et al. (1995), and Gettings et al. (1996), based either on an *in vitro* corneal opacity score of at least 3.0 or an *in vitro* corneal swelling of at least 25%, that had corresponding *in vivo* rabbit eye test data that would allow the substances to be classified according to the EU system (EU [2001]). As noted previously, these two criteria were among those used by Guerriero et al. (2004) to identify corrosive/severe irritants. Rules for classifying a substance that was evaluated in multiple laboratories are the same as described in **Section I-2.1.4**.

Table I-4. Evaluation of the Performance of the IRE Test Method In Predicting Ocular Corrosives and Severe Irritants Compared to the *In Vivo* Rabbit Eye Test Method, as Defined by the EU[1] Classification System, by Study and Overall

Data Source	Data Set	N[2]	Accuracy		Sensitivity		Specificity		Positive Predictivity		Negative Predictivity		False Positive Rate		False Negative Rate	
			%	No.[3]	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
CEC (1991)	New[4]	15/21	87	13/15	100	5/5	80	8/10	71	5/7	100	8/8	20	2/10	0	0/5
	Old[4]	21/21	86	18/21	100	8/8	77	10/13	73	8/11	100	10/10	23	3/13	0	0/8
Balls et al. (1995)[5,6]	New	49/59	55	27/49	74	14/19	43	13/30	45	14/31	72	13/18	57	17/30	26	5/19
	Old	59/59	53	31/59	67	14/21	45	17/38	40	14/35	71	17/24	55	21/38	33	7/21
Gettings (1996)	New	24/25	67	16/24	63	10/16	75	6/8	83	10/12	50	6/13	25	2/8	38	6/16
	Old	25/25	52	13/25	43	3/7	56	10/18	27	3/11	71	10/14	44	8/18	57	4/7
Guerriero et al. (2004)	New	38/44	79	30/38	100	11/11	70	19/27	58	11/19	100	19/19	30	8/27	0	0/11
	Old	44/44	77	34/44	100	15/15	66	19/29	60	15/25	100	19/19	34	10/29	0	0/15
Expanded Data Set[7]	New	80/91	70	56/80	100	37/37	44	19/43	61	37/61	100	19/19	56	24/43	0	0/37

[1]EU = European Union (EU [2001]).
[2]N = Number of substances included in this analysis/the total number of substances in the study.
[3]Data used to calculate the percentage.
[4]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on the previous analysis included in the draft IRE BRD.
[5]One chemical (benzalkonium chloride, 1%) was tested *in vivo* twice within the same laboratory. The results were discordant with respect to EU classification; the analysis was performed assuming an R41 classification.
[6]Performance calculated using the overall *in vitro* classification based on the majority and/or most severe classification among the four laboratories.
[7]Includes the 38 substances tested by Guerriero et al. (2004) that could be classified and 42 additional substances classified as severe irritants from Balls et al. (1995) and Gettings et al. (1996), based either on an *in vitro* corneal opacity score of at least 3.0 or an *in vitro* corneal swelling of at least 25%; these were among the criteria used by Guerriero et al. (2004) to identify corrosive/severe irritants. When the same substance was evaluated in multiple laboratories, the IRE ocular irritancy potential for each independent test result was determined. Subsequently, an overall IRE ocular irritancy classification was assigned for each substance based on the majority of ocular irritancy classification calls and this call was used in the analysis of IRE test method accuracy (approach described in **Section I-2.0**); this process reduced the total number of substances in the expanded data set to 80 for the EU classification system (EU 2001).

Using this approach, the total number of substances in the expanded data set was 80 for the EU classification system (EU [2001]). For these 80 substances (**Table I-4**), the IRE test method has an accuracy of 70% (56/80), a sensitivity of 100% (37/37), a specificity of 44% (19/43), a false positive rate of 56% (24/43), and a false negative rate of 0% (0/37).

2.4 Accuracy of the IRE Test Method for the GHS Ocular Hazard Classification System, by Chemical Class and Property of Interest - Reanalysis

In order to further evaluate discordant responses of the IRE test method relative to the *in vivo* hazard classification, several accuracy sub-analyses were performed. These included specific classes of chemicals with sufficiently robust numbers of substances ($n \geq 5$), as well as certain properties of interest considered relevant to ocular toxicity testing (e.g., pesticides, surfactants, pH, physical form). Because the international community will soon adopt the GHS classification system for hazard labeling (UN [2003]), and considering that there were only modest differences in overall IRE test method accuracy among the three regulatory classification systems (i.e., EPA, EU, GHS), these sub-analyses are focused only on the GHS classification system, using the Expanded Data Set (**Table I-5**).

Limiting this evaluation to chemical classes with at least 5 substances, the chemical classes that had the highest rate of IRE test method overprediction according the GHS classification system (i.e., were false positives) were ketones (67%, [4/6]), esters (67%, [4/6]), and alcohols (60%, [6/10]).

Ten surfactants were evaluated (seven cationic and 3 nonionic). Overall, surfactants had a false positive rate of 50% (2/4) and a false negative rate of 0% (0/6). Cationic surfactants had a false positive rate of 100% (1/1) and a false negative rate of 0% (0/6).

With regard to physical form of the substances overpredicted by the IRE test method, liquids had a higher overprediction rate (83%, [19/23]) than solids (25%, [5/20]). There was insufficient data to analyze the effect of pH on overprediction. The false positive rates may be exaggerated by the lack of inclusion of additional true negative substances to those tested by Guerriero et al. (2004).

No substances were underpredicted (i.e., were false negatives) by the IRE test method (for the Expanded Data Set) according to the GHS classification system (see **Table I-5**). Thus, an analysis of underprediction based on chemical class, physical form, pH, or NICEATM GHS Category I subclassification was not possible.

2.5 Accuracy of the IRE Test Method for Identifying Ocular Corrosives and Severe Irritants – Summary of Reanalysis

As detailed in **Section I-1.0**, no additional IRE test method data was received after the Expert Panel meeting on January 11 and 12, 2005. However, as recommended by the Expert Panel, a reanalysis was conducted on an expanded data set that included (1) all substances evaluated by Guerriero et al. (2004) that could be assigned an GHS/EPA/EU classification based on *in*

Table I-5. False Negative and False Positive Rates of the IRE Test Method, by Chemical Class and Properties of Interest, for the GHS[1] Classification System (Analysis Based on the Expanded Data Set)

Category	N[2]	False Positive Rate[3]		False Negative Rate[4]	
		%	No.[5]	%	No.
Overall	76	56	24/43	0	0/33
Chemical Class[6]					
Alcohol	11	60	6/10	0	0/1
Amide	5	0	0/3	0	0/2
Amine	9	60	3/5	0	0/4
Carboxylic acid	5	67	2/3	0	0/2
Ester	6	67	4/6	-	0/0
Ether	8	40	2/5	0	0/3
Formulation	12	100	2/2	0	0/10
Heterocycle	16	50	4/8	0	0/8
Ketone	6	67	4/6	-	0/0
Onium compound	9	33	1/3	0	0/6
Sulfur compound	7	20	1/5	0	0/2
Properties of Interest					
Liquid/Solution	43	83	19/23	0	0/20
Solid	33	25	5/20	0	0/13
Surfactant – Total	10	50	2/4	0	0/6
-nonionic	3	50	1/2	0	0/1
-anionic	-	-	-	-	-
-cationic	7	100	1/1	0	0/6
pH – Total[7]	0	-	-	-	-
- acidic (pH < 7.0)	0	-	-	-	-
- basic (pH > 7.0)	0	-	-	-	-
NICEATM GHS Category 1 Subgroup[8]	21	-	-	0	0/0
- Total	4	-	-	0	0/4
- 4 (CO=4 at any time)	3	-	-	0	0/3
- 3 (severity/persistence)	2	-	-	0	0/2
- 2 (severity)	*9*	-	-	0	0/9
- *2-4 combined*[9]	12	-	-	0	0/12
- 1 (persistence)					

[1]GHS = United Nations Globally Harmonized System (UN [2003]).
[2]N = number of substances.
[3]False Positive Rate = the proportion of all negative substances that are falsely identified as positive *in vitro*.
[4]False Negative Rate = the proportion of all positive substances that are falsely identified as negative *in vitro*.
[5]Data used to calculate the percentage.
[6]Chemical classes included in this table are represented by at least five substances tested in the IRE test method and assignments are based on the MeSH categories (www.nlm.nih.gov/mesh). See **Appendix B**.
[7]Total number of GHS Category 1 substances for which pH information was available.
[8]Subgroups assigned based on the whether classification as a GHS Category 1 substance was based on severity and/or persistence. 1: based on lesions that are persistent; 2: based on lesions that are severe (not including Corneal Opacity [CO]=4); 3: based on lesions that are both severe (not including CO=4) and persistent; 4: CO = 4 at any time.
[9]Subcategories 2 to 4 combined to allow for a direct comparison of GHS Category 1 substances classified *in vivo* based on some lesion severity component and those classified based on persistent lesions alone.

vivo rabbit eye test data, and (ii) any additional substances classified by IRE as severe irritants by CEC (1991), Balls et al. (1995), and Gettings et al. (1996) and that could also be assigned a GHS/EPA/EU classification based on *in vivo* rabbit eye test data. For the additional substances, a severe irritant classification was based either on an *in vitro* corneal opacity score of at least 3.0 or an *in vitro* corneal swelling of at least 25%. These two criteria were among the four used by Guerriero et al. (2004) to identify corrosive/severe irritants (the other endpoints used by Guerriero et al. (2004) included fluorescein penetration and epithelial integrity). Substances that were not classified as severe irritants in these IRE studies by CEC (1991), Balls et al. (1995) and Gettings et al. (1996) could not be used in the reanalysis, because an evaluation of any one of the parameters not evaluated in the respective studies could have resulted in the substance being classified as a corrosive or severe irritant. For example, in Gettings et al. (1996), only corneal swelling was measured. Substances that produced corneal swelling of at least 25% were included in the "Expanded Data Set" and used in the reanalysis. However, a substance that did not produce ≥ 25% corneal swelling might have produced a corneal opacity score, fluorescein penetration score, or damage of the epithelium that would have classified it as a severe irritant had any of these endpoints been evaluated. Accordingly, because substances classified as nonsevere irritants in Gettings et al. (1996) could potentially be classified as severe irritants using these other criteria, such substances are not included in the Expanded Data Set analysis.

The reanalysis of the accuracy of the IRE test method for identifying ocular corrosives and severe irritants also took into account the reclassification of some nonsevere irritants as severe irritants (see **Section I-1.0** and **Appendix I-A**). As the changes in accuracy are independent of the ocular hazard classification system used, this discussion is limited to the GHS classification system.

When the reanalysis is restricted to Guerriero et al. (2004), the IRE test method version that evaluated the greatest number of endpoints, the reclassification changed from 78% (28/36) in the draft IRE BRD to 79% (30/38) in the reanalysis. The false negative rate stayed the same. (draft IRE BRD = 0% [0/12]; reanalysis: 0% [0/11]). The false positive rate decreased from 32% (8/24) in the draft IRE BRD to 30% (8/27) in the reanalysis.

With the addition of some substances classified as corrosive/severe irritants in Balls et al. (1995) and Gettings et al. (1996), the overall accuracy was 68% (52/76), the false negative rate was 0% (0/33), while the false positive rate was 56% (24/43) (i.e., the additional data included 38 substances classified by IRE as severe irritants, 22 of which were also severe irritants *in vivo* and 16 of which were nonsevere irritants or nonirritants *in vivo*). The expanded data set is potentially confounded by the exclusion of substances with true negative outcomes (matching *in vivo* and *in vitro* nonsevere or nonirritant classifications), which would affect both specificity and the false positive rate.

Table I-6 provides a summary of the revised analysis of the overall performance of the Expanded Data Set, when compared to the GHS classification system (UN [2003]). As noted from this analysis, the false positive substances included 11 nonirritants, three Category 2B substances, and 10 Category 2A substances. No severe irritants (0/33) were underpredicted.

Table I-6. Overall Accuracy of the IRE Test Method in Predicting the Irritancy of a Substance as Defined by the GHS[1] Classification System (Analysis Based on the Expanded Data Set)[2]

		In Vitro Classification		
		Severe Irritant	**Nonsevere Irritant**	**TOTAL**
***In Vivo* Classification[3]**	**1**	33	0	33
	2A	10	1	11
	2B	3	3	6
	Nonirritant	11	15	26
	TOTAL	57	19	76

[1]GHS = United Nations Globally Harmonized System (UN [2003].

[2]Includes the 38 substances tested by Guerriero et al. (2004) that could be classified and 38 additional substances classified as severe irritants from Balls et al. (1995) and Gettings et al. (1996), based either on an *in vitro* corneal opacity score of at least 3.0 or an *in vitro* corneal swelling of at least 25%; these were among the criteria used by Guerriero et al. (2004) to identify corrosive/severe irritants. When the same substance was evaluated in multiple laboratories, the IRE ocular irritancy potential for each independent test result was determined. Subsequently, an overall IRE ocular irritancy classification was assigned for each substance based on the majority of ocular irritancy classification calls and this call was used in the analysis of IRE test method accuracy (approach described in **Section I-2.0**); this process reduced the total number of substances in the expanded data set to 76 for the GHS classification system (UN [2003]).

[3]Thirty-four substances included in **Appendix I-A** had insufficient data with which to assign a GHS classification and therefore were not included in this table.

3.0 RELIABILITY OF THE IRE TEST METHOD - REANALYSIS

As discussed in the draft IRE BRD, an assessment of test method reliability (intralaboratory repeatability and intra- and inter-laboratory reproducibility) is an essential element of any evaluation of the performance of an alternative test method (ICCVAM [2003]). Repeatability refers to the closeness of agreement between test results obtained within a single laboratory when the procedure is performed on the same substance under identical conditions within a given time period (ICCVAM [1997, 2003]). Intralaboratory reproducibility refers to the determination of the extent to which qualified personnel within the same laboratory can replicate results using a specific test protocol at different times. Interlaboratory reproducibility refers to the determination of the extent to which different laboratories can replicate results using the same protocol and test chemicals, and indicates the extent to which a test method can be transferred successfully among laboratories. A reliability assessment includes reviewing the rationale for selecting the substances used to evaluate test method reliability, a discussion of the extent to which the substances tested represent the range of possible test outcomes and the properties of the various substances for which the test method is proposed for use, and a quantitative and/or qualitative analysis of repeatability and intra- and inter-laboratory reproducibility. In addition, measures of central tendency and variation are summarized for historical control data (negative, vehicle, positive), where applicable.

3.1 Substances Used to Re-evaluate the Reliability of the IRE Test Method

An evaluation of the intralaboratory repeatability and reproducibility of the IRE test method could not be conducted in the original reliability analysis due to the lack of appropriate data (see draft IRE BRD, Nov 1, 2004). No additional IRE test method data was submitted in response to the *FR* notice (see **Section I-1.0**). However, due to the *in vivo* reclassification of some substances from nonsevere irritants/nonirritants to severe irritants and to the development of the Expanded Data Set (see **Section I-1.0**), a reanalysis of the reproducibility of the IRE test method was conducted. The sources of data available for conducting an assessment of IRE test method interlaboratory reproducibility were the EC/HO validation study from Balls et al. (1995) and the CEC (1991) prevalidation study. In the Balls et al. (1995) validation study, four laboratories evaluated the accuracy and reliability of the IRE test method using 60 substances (i.e., there were 52 different substances with four substances tested at two different concentrations and two substances tested at three different concentrations, for a total of 60 possible ocular irritation outcomes). One substance (thiourea) was tested *in vitro* in the IRE assay but, due to its excessive toxicity *in vivo*, was excluded from the comparison of *in vitro* and *in vivo* test results. In the CEC (1991) collaborative study, three laboratories evaluated the accuracy and reliability of the IRE test method using 21 substances.[8]

3.2 Reanalysis of IRE Test Method Intralaboratory Repeatability

Generally, analyses of intralaboratory repeatability have included approaches such as:

- a coefficient of variation (CV) analysis, which is a statistical measure of the deviation of a variable from its mean (e.g., Holzhütter et al. [1996])
- analysis of variance (ANOVA) methods (e.g., Holzhütter et al. [1996]; ASTM [1999]).

Due to the lack of available IRE test data for replicate enucleated rabbit eyes within individual experiments performed by the same laboratory and for repeat experiments conducted on the same substance under exactly the same conditions, an evaluation of the intralaboratory repeatability of the IRE test method could not previously be conducted (see draft IRE BRD). As noted above, no additional data were received that would enable an analysis of intralaboratory repeatability.

3.3 Reanalysis of IRE Test Method Intralaboratory Reproducibility

Generally, analyses of intralaboratory reproducibility have included approaches such as:

- CV analysis, which is a statistical measure of the deviation of a variable from its mean (e.g., Holzhütter et al. [1996])
- ANOVA methods (e.g., Holzhütter et al. [1996]; ASTM [1999]).

[8] Some severely irritating substances tested by the CEC (1991) were excluded from this evaluation due to the lack of individual *in vivo* rabbit eye data. Classification of these substances had been based on ocular effects in humans, dermal studies, or pH.

Due to the lack of available IRE test data for experiments conducted multiple times in the same laboratory, an evaluation of IRE test method intralaboratory reproducibility could not conducted in the original IRE BRD (see draft IRE BRD). No additional IRE data has been received that would enable an evaluation of intralaboratory reproducibility.

3.4 Reanalysis of IRE Test Method Interlaboratory Reproducibility

Generally, analyses of interlaboratory variability have included approaches such as:

- the extent of concordance among laboratories in assigning the same regulatory classification for a particular substance (e.g., Holzhütter et al. [1996])
- a CV analysis, which is a statistical measure of the deviation of a variable from its mean (e.g., Holzhütter et al. [1996])
- ANOVA methods (e.g., Holzhütter et al. [1996]; ASTM [1999])
- bivariant scatter diagrams/correlation analyses for pairs of laboratories to assess the extent possibility of divergence (e.g., Holzhütter et al. 1996)

3.4.1 Qualitative Assessment of Interlaboratory Reproducibility

Data from CEC (1991) and Balls et al. (1995) were used to qualitatively evaluate the interlaboratory reproducibility of the IRE test method. For an assessment of interlaboratory reproducibility, substances classified as corrosive/severe irritants or nonsevere irritants/nonirritants were further classified within the EPA, EU, and GHS classification systems (EPA [1996]; EU [2001]; UN [2003]) by their *in vivo* rabbit eye test results. Because the focus of this assessment is on the interlaboratory reproducibility of the IRE test method in identifying corrosives/severe irritants versus nonsevere irritants/ nonirritants, considerable variability could exist among laboratories in their classification of substances as nonsevere irritants or nonirritants (e.g., three laboratories could classify a substance as a nonirritant and one laboratory could classify the same substance as a moderate irritant; for the purpose of the analysis, this would be considered 100% agreement between laboratories).

3.4.1.1 *GHS Ocular Hazard Classification System*

For this classification system, one study could be used to assess the interlaboratory reproducibility of the IRE test method: Balls et al. (1995). The four participating laboratories in the EC/HO study (Balls et al. [1995]) were in 100% agreement in regard to the ocular irritancy classification (corrosive/severe irritant or nonsevere irritant/nonirritant) of 35 (59%) of the 59 substances tested (see **Table I-7**).

As shown in **Table I-7:**

- All four participating laboratories agreed on the classification of 14 (100%) of the 14 substances that were GHS corrosives/severe irritants[9].
- Five (55%) of the nine substances classified according to the GHS based on *in vivo* rabbit eye data as corrosives/severe irritants were incorrectly classified by all four participating laboratories as nonsevere irritants (i.e., Category 2A and

[9] The overall *in vitro* classification for each substance was determined based on the most frequent individual laboratory classification, or in the case of an even number of discordant responses, the most severe classification.

2B irritants) or nonirritants, whereas four of the nine substances (44%) had 75% agreement among the laboratories. The five substances incorrectly classified by all four laboratories were Captan 90 concentrate, dibenzoyl-L-tartaric acid, 2,5-dimethylhexanediol, 15% sodium lauryl sulfate, and sodium perborate tetrahydrate.

- Eight (40%) of the 20 substances classified according to the GHS based on *in vivo* rabbit eye data as nonsevere irritants were incorrectly classified by the four laboratories as corrosives or severe irritants. Of the 12 substances (60%) with discordant results among the four laboratories, three (15%) (ethyl acetate, iso-propanol, and methyl acetate) were incorrectly classified by three of the four laboratories and nine (45%) (acetone, 0.1% cetylpyridinium bromide, ethyl-2-methylacetoacetate, Fomesafen, Maneb, methylisobutylketone, n-octanol, polyethylene glycol 400, and toluene) were incorrectly classified by two of the four laboratories.
- All four laboratories agreed on the classification of six (43%) of the 14 substances classified as GHS nonsevere irritants/nonirritants. Of the eight substances (57%) with discordant classification results, all eight substances (ammonium nitrate, butyl acetate, dibenzyl phosphate, 2,6-dichorobenzoyl chloride, methyl acetate, tetra-aminopyrimidine sulfate, 3% trichloroacetic acid, and Tween 20) were correctly classified by three of the four laboratories.
- Due to the lack of appropriate *in vivo* data (e.g., studies were terminated too early to assess reversibility of effects), two (3%) of the 59 test substances could not be classified according to the GHS classification scheme. All four laboratories were in agreement with the classification of one of these substances as nonsevere irritant/nonirritant and one substance as a corrosive/severe irritant.

3.4.1.2 *EPA Ocular Hazard Classification System*

The four participating laboratories in the EC/HO study (Balls et al. [1995]) were in 100% agreement for the ocular irritancy classification (corrosive/severe irritant or nonsevere irritant/nonirritant) of 36 (61%) of the 59 substances tested. As shown in **Table I-8**:

- All four participating laboratories agreed on the classification of 18 (100%) of the 18 substances that were EPA corrosives/severe irritants[10].
- Four (57%) of the seven substances classified according to the EPA (1996) based on *in vivo* rabbit eye data as corrosives/severe irritants were incorrectly classified by all four participating laboratories as nonsevere irritants/nonirritants. Three substances (43%) were shown to have discordant *in vitro* classification results among the four participating laboratories (Captan 90 concentrate, 2,5-dimethylhexanediol, and sodium lauryl sulfate [15%]). These substances were incorrectly classified by three of the four laboratories.

[10] As described in **Section I-2.0**, the overall *in vitro* classification for each substance was determined based on the most frequent individual laboratory classification, or in the case of an even number of discordant responses, the most severe classification.

Table I-7. Interlaboratory Variability of Balls et al. (1995) for Substances Classified as Ocular Corrosives/Severe Irritants or Nonsevere Irritants/Nonirritants Using the GHS[1] Classification System

Classification (*in vivo*/ *in vitro*)[2]	Data Set	Number of Substances	Number of Testing Labs	Substances with 100% Agreement Among Labs	Substances with 75% Agreement Among Labs	Substances with 50% Agreement Among Labs
+/+	New[3]	14	4	14 (100%)	0 (0%)	0 (0%)
	Old[3]	14	4	14 (100%)	0 (0%)	0 (0%)
+/-	New	9	4	5 (55%)	4 (44%)	0 (0%)
	Old	8	4	4 (50%)	4 (50%)	0 (0%)
-/+	New	20	4	8 (40%)	3 (15%)	9 (45%)
	Old	20	4	8 (40%)	3 (15%)	9 (45%)
-/-	New	14	4	6 (43%)	8 (57%)	0 (0%)
	Old	14	4	6 (43%)	8 (57%)	0 (0%)
?/-	New	1	4	1 (100%)	0 (0%)	0 (0%)
	Old	2	4	2 (100%)	0 (0%)	0 (0%)
?/+	New	1	4	1 (100%)	0 (0%)	0 (0%)
	Old	1	4	1 (100%)	0 (0%)	0 (0%)
TOTAL	New	59	4	35 (59%)	15 (25%)	9 (15%)
	Old	59	4	35 (59%)	15 (25%)	9 (15%)

[1]GHS = Globally Harmonized System (UN [2003]).
[2]A "+" indicates that the substance was assigned an overall classification of corrosive or a severe irritant (Category 1); a "-" indicates that the substance was assigned an overall classification of nonsevere irritant (Category 2A, 2B) or nonirritant; a "?" indicates that, due to the lack of appropriate *in vivo* data (e.g., studies were terminated too early to assess reversibility of effects), a GHS classification could not be made. See **Section 2.0** for a description of the rules followed to classify the ocular irritancy of test substances tested multiple times *in vitro*.
[3]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on the previous analysis included in the draft IRE BRD.

- Eight (40%) of the 20 substances classified according to the EPA based on *in vivo* rabbit eye data as a nonsevere irritant/nonirritant were incorrectly classified by all four participating laboratories as a corrosive/severe irritant. Of the 12 remaining substances (60%), three substances ((15%) ethyl acetate, iso-propanol, and methyl acetate) were incorrectly classified by three of the four laboratories and nine substances (45%) (acetone, cetylpyridinium bromide, ethyl-2-methylacetoacetate, Fomesafen, Maneb, methylisobutylketone, n-octanol, polyethylene glycol 400, and toluene) by two of the four laboratories.
- Six (43%) of the 14 substances classified according to the EPA (1996) based on *in vivo* rabbit eye data as nonsevere irritants or nonirritants were correctly classified by all four laboratories. All eight substances (57%) with discordant classification results (ammonium nitrate, butyl acetate, dibenzyl phosphate, 2,6-dichlorobenzoyl chloride, methyl acetate, tetra-aminopyrimidine sulfate,

3% trichloroacetic acid, and Tween 20) were correctly classified by three of the four laboratories.

- The three substances classified *in vitro* as nonsevere irritants and the two substances classified as corrosives or severe irritants, which originally could not be assigned an *in vivo* classification, were reclassified as severe irritants and correctly identified by all four laboratories. These substances were 2,2-dimethylbutanoic acid, imidazole, promethazine, and pyridine.

Table I-8. Interlaboratory Variability of Balls et al. (1995) for Substances Classified as Ocular Corrosives/Severe Irritants or Nonsevere Irritants/Nonirritants Using the EPA[1] Classification System

Classification (*in vivo*/ *in vitro*)[2]	Data Set	Number of Substances	Number of Testing Labs	Substances with 100% Agreement Among Labs	Substances with 75% Agreement Among Labs	Substances with 50% Agreement Among Labs
+/+	New[3]	18	4	18 (100%)	0 (0%)	0 (0%)
	Old[3]	13	4	13(100%)	0 (0%)	0 (0%)
+/-	New	7	4	4 (57%)	3 (43%)	0 (0%)
	Old	7	4	4 (57%)	3 (43%)	0 (0%)
-/+	New	20	4	8 (40%)	3 (15%)	9 (45%)
	Old	20	4	8 (40%)	3 (15%)	9 (45%)
-/-	New	14	4	6 (43%)	8 (57%)	0 (0%)
	Old	14	4	6 (43%)	8 (57%)	0 (0%)
?/-	New	0	4	0 (0%)	0 (0%)	0 (0%)
	Old	3	4	2 (66%)	1 (33%)	0 (0%)
?/+	New	0	4	0 (0%)	0 (0%)	0 (0%)
	Old	2	4	2 (100%)	0 (0%)	0 (0%)
TOTAL	New	59	4	36 (61%)	14 (24%)	9 (15%)
	Old	59	4	35 (59%)	15 (25%)	9 (15%)

[1]EPA = U.S. Environmental Protection Agency (EPA [1996]).

[2]A "+" indicates that the substance was assigned an overall classification of corrosive or a severe irritant (Category I); a "-" indicates that the substance was assigned an overall classification of nonsevere irritant (Category II, III) or nonirritant (category IV); a "?" indicates that, due to the lack of appropriate *in vivo* data (e.g., studies were terminated too early to assess reversibility of effects), an EPA classification could not be made. See **Section I-2.0** for a description of the rules followed to classify the ocular irritancy of test substances tested multiple times *in vitro*.

[3]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on the previous analysis included in the draft IRE BRD.

3.4.1.3 *EU Ocular Hazard Classification System*

Using the Balls et al. (1995) data set, the participating laboratories were in 100% agreement with regard to the ocular irritancy classification (corrosive/severe irritant or nonsevere irritant/nonirritant) of 37 (63%) of the 59 substances tested. As shown in **Table I-9**:

- All four participating laboratories agreed on the classification of 12 (100%) of the 12 substances that were EU corrosives/severe irritants

- Three (50%) of the six substances classified according to the EU based on *in vivo* rabbit eye data as corrosives/severe irritants were incorrectly classified by all four participating laboratories as nonsevere irritants/nonirritants. Of the three substances (50%) with discordant *in vitro* classification results among the four participating laboratories, all three substances (Captan-90 concentrate, dibenzoyl-L-tartaric acid, and 2,5-dimethylhexanediol) were incorrectly classified by three of the four laboratories.
- Seven (39%) of the 18 substances classified according to the EU based on *in vivo* rabbit eye data as a nonsevere irritants/nonirritant was incorrectly classified by all four participating laboratories as a corrosives/severe irritant. Of the 11 substances (61%) with discordant *in vitro* classification results among the four participating laboratories, two substances (44%), ethyl acetate and methyl acetate, were incorrectly classified by three laboratories and nine (50%) were incorrectly classified by two of the four laboratories (acetone, γ-butyrolactone, 0.1% cetylpyridinium bromide, ethyl-2-methylacetoacetate, Fomesafen, methylisobutylketone, n-octanol, polyethylene glycol 400, and toluene).
- All four laboratories agreed on the classification of six (50%) of the 12 substances classified as EU nonsevere irritants/nonirritants the four participating laboratories. Three of the four laboratories were in agreement for the six substances (50%) with discordant classification results (ammonium nitrate, 4-carboxybenzaldehyde, dibenzyl phosphate, tetra-aminopyrimidine sulfate, 3% trichloroacetic acid, and Tween 20).
- Four of six (67%) of substances classified *in vitro* as nonirritants, but could not be classified *in vivo* due to the lack of sufficient data, were classified as such by all four laboratories. Two of the six (33%) were classified as nonirritants *in vitro* by two of three laboratories.
- Five of five (100%) of substances were classified *in vitro* as corrosives or severe irritants by all four laboratories, but could not be classified *in vivo* due to the lack of appropriate data.

Table I-9. Interlaboratory Variability of Balls et al. (1995) for Substances Classified as Ocular Corrosives/Severe Irritants or Nonsevere Irritants/Nonirritants Using the EU[1] Classification System

Classification (*in vivo*/ *in vitro*)[2]	Data Set	Number of Substances	Number of Testing Labs	Substances with 100% Agreement Among Labs	Substances with 75% Agreement Among Labs	Substances with 50% Agreement Among Labs
+/+	New[3]	12	4	12 (100%)	0 (0%)	0 (0%)
	Old[3]	14	4	14 (100%)	0 (0%)	0 (0%)
+/-	New	6	4	3 (50%)	3 (50%	0 (0%)
	Old	7	4	4 (57%)	3 (43%)	0 (0%)
-/+	New	18	4	7 (39%)	2 (44%)	9 (50%)
	Old	21	4	9 (43%)	3 (14%)	9 (43%)
-/-	New	12	4	6 (50%)	6 (50%)	0 (0%)
	Old	17	4	9 (53%)	8 (47%)	0 (0%)
?/-	New	6	4	4 (67%)	2 (33%)	0 (0%)
	Old	0	4	0 (0%)	0 (0%)	0 (0%)
?/+	New	5	4	5 (100%)	0 (0%)	0 (0%)
	Old	0	4	0 (0%)	0 (0%)	0 (0%)
TOTAL	New	59	4	37 (63%)	13 (22%)	9 (15%)
	Old	59	4	36 (61%)	14 (24%)	9 (15%)

[1]EU = European Union (EU [2001]).
[2]A "+" indicates that the substance was assigned an overall classification of corrosive or severe irritant (Category R41); a "-" indicates that the substance was assigned an overall classification of nonsevere irritant (Category R36) or nonirritant; a "?" indicates that, due to the lack of appropriate *in vivo* data, an EU classification could not be made. See **Section I-2.0** for a description of the rules followed to classify the ocular irritancy of test substances tested multiple times *in vitro*.
[3]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on the previous analysis included in the draft IRE BRD.

Using the CEC (1991) data set, the three participating laboratories were in 100% agreement in regard to the ocular irritancy classification (corrosive/severe irritant or nonsevere irritant/nonirritant) of 17 (81%) of the 21 substances tested (**Table I-10**).

As shown in **Table I-10**:

- Three (60%) of five substances were classified according to *in vivo* rabbit eye data as corrosives or severe irritants and these were identified correctly by all three laboratories. One discordant substance (sodium dodecyl sulfate) was correctly classified by two of the three laboratories, and one (dibutyltin chloride) was correctly classified by one of two laboratories.
- No substances were identified as false positives (i.e., as severe irritants *in vivo* and as nonsevere irritants *in vitro*).
- Two of two (100%) nonsevere irritants *in vivo* were incorrectly classified as severe irritants *in vitro* by all three laboratories. There were no discordant substances.

- Six of eight (75%) substances were in complete agreement among laboratories for identification of nonsevere irritants. Two discordant substances (25%) (Brij-35 and 2-butoxyethylacetate) were identified as nonsevere irritants by two of the three testing laboratories.
- All three laboratories agreed in the identification of two substances as nonsevere irritants (100%) and another four as severe irritants, although no *in vivo* classification could be assigned to these substances.

Table I-10. Interlaboratory Variability of CEC Collaborative Study (1991) for Substances Classified as Ocular Corrosives/Severe Irritants or Nonsevere Irritants/Nonirritants Using the EU[1] Classification System

Classification (*in vivo*/ *in vitro*)[2]	Data Set	Number of Substances	Number of Testing Labs	Substances with 100% Agreement Among Labs	Substances with 67% Agreement Among Labs	Substances with 33% Agreement Among Labs
+/+	New[3]	5	3	3 (60%)	1 (20%)	1 (20%)[4]
	Old[3]	8	3	7 (88%)	1 (12%)	0 (0%)
+/-	New	0	3	0 (0%)	0 (0%)	0 (0%)
	Old	0	3	0 (0%)	0 (0%)	0 (0%)
-/+	New	2	3	2 (100%)	0 (0%)	0 (0%)
	Old	3	3	3 (100%)	0 (0%)	0 (0%)
-/-	New	8	3	6 (75%)	2 (25%)	0 (0%)
	Old	10	3	8 (80%)	2 (20%)	0 (0%)
?/-	New	2	2[5]	2 (100%)	0 (0%)	0 (0%)
	Old	0	-	0 (0%)	0 (0%)	0 (0%)
?/+	New	4	3	4 (100%)[6]	0 (0%)	0 (0%)
	Old	0	-	0 (0%)	0 (0%)	0 (0%)
TOTAL	New	21	3	17 (81%)	3 (14%)	1 (5%)
	Old	21	3	18 (86%)	3 (14%)	0 (0%)

[1]EU = European Union (EU [2001]).
[2]A "+" indicates that the substance was assigned an overall classification of corrosive or severe irritant (Category R41); a "-" indicates that the substance was assigned an overall classification of nonsevere irritant (Category R36) or nonirritant; a "?" indicates that, due to the lack of appropriate *in vivo* data, an EU classification could not be made. See **Section 2.0** for a description of the rules followed to classify the ocular irritancy of test substances tested multiple times *in vitro*.
[3]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on the previous analysis included in the draft IRE BRD.
[4]Agreement was among one of two laboratories (50% not 33%). The third laboratory did not test the material.
[5]Two of the three testing laboratories evaluated these two substances.
[6]One of the four substances was tested in two laboratories with severe classification assigned.

3.4.2 Quantitative Assessment of Interlaboratory Reproducibility

As detailed in the draft IRE BRD, to provide a quantitative assessment of interlaboratory variability, individual laboratory IRE test results were used to calculate a mean, standard deviation, and the %CV for corneal opacity, fluorescein retention, corneal swelling, and the

irritation index for each of the 59 substances tested in the Balls et al. (1995) study. Mean and median %CV values were calculated to provide an assessment of overall variability. This analysis was not affected by the information received subsequent to the release of the draft IRE BRD, and therefore is not presented here.

3.4.3 Additional Reanalyses of Interlaboratory Reproducibility

A comparison of the corneal opacity and corneal swelling measurements at one and four hours for substances that were tested in both the Balls et al. (1995) and Guerriero et al. (2004) data sets is presented in **Table I-11**. Correlation coefficients for corneal opacity scores at 1 and 4 hours were 0.77 and 0.78, respectively. Correlation coefficients for corneal swelling at 1 and 4 hours were 0.92 and 0.68, respectively. The corneal swelling measurements in Balls et al. (1995) were more variable than those in Guerriero et al. (2004). This might be attributed to differences in the methods of measurement of corneal thickness in the four contributing laboratories in the Balls et al. (1995) study employed amongst the various laboratories in this study to quantify corneal swelling (i.e., ultrasonic pachymeter vs. depth measuring gauge).

The draft IRE BRD also contains a description of the analysis performed by Balls et al. (1995) in which they determined the interlaboratory correlation between IRE test method endpoint data generated by each laboratory for all substances tested, as well as for subsets of test substances (water-soluble, water-insoluble, surfactants, solids, solutions, and liquids). This analysis was not affected by the information received subsequent to the release of the draft IRE BRD and therefore is not presented here.

3.5 IRE Test Method Historical Positive and Negative Control Data - Reanalysis

Concurrent positive control substances have not been employed in the IRE test method, and therefore, an evaluation of historical positive control data is not possible. One eye is traditionally included in each study as a negative/vehicle controls (isotonic saline).

3.6 Reliability of the IRE Test Method for Identifying Ocular Corrosives and Severe Irritants – Summary of Reanalysis

In the draft IRE BRD, no data was provided for the assessment of intralaboratory repeatability and reproducibility. Since no additional data was submitted for the IRE test method following the Expert Panel meeting, additional analyses of intralaboratory reliability could not be conducted.

The original IRE test method reliability analysis included an evaluation of interlaboratory reproducibility using both qualitative and quantitative approaches. While the quantitative analysis was unaffected by the reclassification of some nonsevere irritants/nonirritants as severe irritants, the qualitative analysis (correct classification as an ocular corrosive/severe irritant or as a non-corrosive/nonsevere irritant) of the individual laboratory test results obtained for the EC/HO validation study (Balls et al. [1995]) and for the CEC (1991) collaborative study were affected. Overall, in the Balls et al. (1995) study, the number of substances with 100% agreement between the four laboratories was 59-61% (35-36/59) in the

Table I-11. Interlaboratory Reproducibility of Corneal Endpoint Measures for Substances Tested in Common Between IRE Test Method Studies

***In Vitro* IRE Data**					
Test Material	**Endpoint**	**Balls et al. (1995)[1]**		**Guerriero et al. (2004)[2]**	
		Mean ± SD[3]			
		1 Hour	**4 Hours**	**1 Hour**	**4 Hours**
Sodium Hydroxide (10%)	Corneal Opacity Score[4]	3 ± 1.7	4 ± 0.0	3 ± 0.6	3 ± 0.6
	Swelling (%)[5]	102 ± 13.6	138 ± 25.3	111 ±28.8	NT[6]
Trichloroacetic Acid (30%)	Corneal Opacity Score	2 ± 0.5	2 ± 0.5	4 ± 0.0	4 ± 0.0
	Swelling (%)	24 ± 28.3	44 ± 33.1	12 ±1.3	54 ±9.5
Acetone	Corneal Opacity Score	0 ± 0.5	1 ± 1.1	2 ± 0.6	2 ± 0.6
	Swelling (%)	15 ± 12.0	32 ± 30.2	19 ± 9.7	50 ± 44.8
Allyl Alcohol[7]	Corneal Opacity Score	1 ± 0.9	2 ± 1.0	3 ± 0.6	3 ± 0.0
	Swelling (%)	16 ± 11.2	36 ± 20.2	41 ± 3.7	77 ± 2.9
n-Butanol	Corneal Opacity Score	1 ± 0.9	3 ± 0.6	2 ± 0.6	3 ± 0.6
	Swelling (%)	25 ± 11.0	75 ± 19.6	55 ± 5.9	92 ±19
Ammonium Nitrate	Corneal Opacity Score	0 ± 0.0	0 ± 0.0	0 ± 0.0	0 ± 0.0
	Swelling (%)	7 ± 3.1	10 ± 11.3	11 ± 1.4	15 ±3.4
Cetylpyridinium Bromide (10%)	Corneal Opacity Score	1 ± 0.9	2 ± 0.8	1 ± 0.6	1 ± 0.6
	Swelling (%)	18 ± 6.4	43 ± 29.4	49 (n=1)[8]	31 (n=1)
Methyl Ethyl Ketone	Corneal Opacity Score	1 ± 0.8	2 ± 0.4	3 ± 0.0	3 ± 0.0
	Swelling (%)	21 ± 6.3	61 ± 20.7	35 ± 8.3	105 ± 18.6

***In Vitro* IRE Data**					
Test Material	**Endpoint**	**Balls et al. (1995)[1]**		**Guerriero et al. (2004)[2]**	
		Mean ± SD[3]			
		1 Hour	**4 Hours**	**1 Hour**	**4 Hours**
Butyl Acetate	Corneal Opacity Score	0 ± 0.0	0 ± 0.4	0 ± 0.0	1 ± 0.6
	Swelling (%)	7 ± 4.9	15 ± 10.9	20 ± 1.3	30 ± 2.3
Toluene	Corneal Opacity Score	0 ± 0.51	0 ± 0.6	0 ± 0.0	0 ± 0.0
	Swelling (%)	14 ± 9.4	23 ± 13.9	7.4 ± 1.5	15 ± 2.6
Glycerol	Corneal Opacity Score	0 ± 0.0	0 ± 0.47	0 ± 0.0	0 ± 0.0
	Swelling (%)	8 ± 12.1	8 ± 14.7	13 ± 5.1	21 ± 4.6
Polyethylene Glycol 400	Corneal Opacity Score	0 ± 0.5	1 ± 0.6	0 ± 0.0	0 ± 0.0
	Swelling (%)	15 ± 12.1	18 ± 14.7	10 ± 1.9	16 ± 2.4

[1]Data were provided as mean scores of three isolated rabbit eyes from each of four laboratories. The mean corneal opacity score and corneal swelling measurement (and its standard deviation) of the four laboratories were then calculated.
[2]Data were provided as mean scores of three isolated rabbit eyes from which the standard deviation was calculated.
[3]SD = Standard deviation.
[4]Corneal opacity score represents a scale of 1-4.
[5]Corneal swelling was measured by either ultrasonic pachymeter or by depth gauge measurements in the Balls et al. (1995) study and by ultrasonic pachymeter in the Guerriero et al. (2004) study.
[6]NT = Not tested.
[7]Allyl alcohol was not used in the accuracy or reliability analyses because rabbit data from the Guerriero et al. (2004) study was not available.
[8]n = Number of eyes tested.

original analysis and 59-63% (35-37/59) in the reanalysis. The number of substances with 75% agreement between laboratories was 24-25% (14-15/59) in the original analysis and to 22-25% (13-15/59) in the reanalysis. The number of substances with 50% agreement between four laboratories did not change due to the reanalysis (15% [9/59 substances]).

Overall, in the CEC (1991) study, the number of substances with 100% agreement among the three laboratories decreased from 86% (18/21) to 81% (17/21) in the reanalysis. The number of substances with 67% agreement among the three laboratories remained the same at 14% (3/21), while the number of substances with 33% agreement was increased from 0% to 5% (1/21).

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APPENDIX I-A

SUBSTANCES USED IN THE IRE TEST METHOD REANALYSIS

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Substances Used in the IRE Test Method Reanalysis

Substance	CASRN[1]	Concentration Tested	Chemical Class	Product Class	pH	Form Tested	Purity	*In Vivo* Classification (GHS)[2,3]	Category 1 Subclass[4]	*In Vivo* Classification (EPA)[5,6]	*In Vivo* Classification (EU)[7,8]	*In Vitro* Classification	Reference
Acetaldehyde	75-07-0	100%	ORGANIC	Flammable liquid used in manufacture of acetic acid, perfumes, and flavors		Solution					SCNM[9]	Severe irritant	CEC (1991)
Acetic acid	**64-19-7**	**10%**	**CARBOXYLIC ACID**	**Food preservative and acidifier, Solvent, Manuf of acetates, acetyl compounds, cellulose acetate, rayon, plastics and rubber in tanning**		**Liquid**					**R41**	**Severe Irritant**	**CEC (1991)**
Acetone	**67-64-1**	**100%**	**KETONE**	**Solvent; Antiseptic; Chemical intermediate; Raw material**		**Liquid**	**99%**	**Category 2A**		**Category II**	**R36**	**Severe Irritant**	**Balls et al. (1995)**
Acetone (F33)	67-64-1	100%	KETONE	Solvent; Antiseptic; Chemical intermediate; Raw material		Liquid	99%	Category 2A		Category II	R36	Severe Irritant	Guerriero et al. (2004)
2-(Acetyloxy)-1-phenylethanone (F27)	**-**	**100%**	**KETONE, ESTER**	**Raw material**		**Solid**		**Nonirritant**		**Category III**	**Nonirritant**	**Nonsevere Irritant**	**Guerriero et al. (2004)**
Allyl alcohol (F34)	107-18-6	100%	ALCOHOL	Resins, Plasticizers, War gas, Allyl compounds		Liquid		NT[6]		NT	NT	Severe Irritant	Guerriero et al. (2004)
gamma-(Aminocarbonyl)-N-methyl N,N-bis(1-methylethyl)-gamma-phenyl-, iodide (F14)	**-**	**100%**	**ONIUM, AMIDE**	**Active pharmaceutical ingredient**		**Solid**		**Category 2A**		**Category II**	**R36**	**Nonsevere Irritant**	**Guerriero et al. (2004)**
1-(5-Amino-2-methoxyphenyl) piperazine hydrochloride (F20)	-	100%	HETEROCYCLE, AMINE	Chemical intermediate		Solid		Nonirritant		Category III	Nonirritant	Severe Irritant	Guerriero et al. (2004)
tetra-Aminopyrimidine sulfate	5392-28-9	100%	AMINE, HETEROCYCLE, SALT, INORGANIC	Developer		Solid	97%	Nonirritant		Category III	Nonirritant	Nonsevere Irritant	Balls et al. (1995)
Ammonium nitrate	6484-52-2	100%	SALT, INORGANIC, ONIUM	Fertilizer; Chemical intermediate; Industrial explosive		Solid	100%	Category 2B		Category III	R36	Nonsevere Irritant	Balls et al. (1995)
Ammonium nitrate (F36)	**6484-52-2**	**100%**	**SALT, INORGANIC, ONIUM**	**Fertilizer; Chemical intermediate; Industrial explosive**		**Solid**	**>99.9%**	**Category 2B**		**Category III**	**R36**	**Nonsevere Irritant**	**Guerriero et al. (2004)**
L-Aspartic acid	70-47-3	100%	AMINO ACID	Organic intermediate; Fungicides; Germicides		Solid	100%	SCNM[7]		SCNM	SCNM	Nonsevere Irritant	Balls et al. (1995)
Benzalkonium chloride	8001-54-5	100%	INORGANIC SALT, ONIUM	Surfactant (cationic), Bactericide, Fungicide, Preservative		Solution					R41	Severe Irritant	CEC (1991)
Benzalkonium chloride (1 %)	**8001-54-5**	**1%**	**ONIUM**	**Surfactant (cationic), Bactericide, Fungicide, Preservative**		**Solution**	**98%**	**Category 1**	**1**	**Category I**	**R41**	**Severe Irritant**	**Balls et al. (1995)**
Benzalkonium chloride (10%)	**8001-54-5**	**10%**	**ONIUM**	**Surfactant (cationic), Bactericide, Fungicide, Preservative**		**Solution**	**98%**	**Category 1**	**4**	**Category I**	**R41**	**Severe Irritant**	**Balls et al. (1995)**
Benzalkonium chloride (5%)	**8001-54-5**	**5%**	**ONIUM**	**Surfactant (cationic), Bactericide, Fungicide, Preservative**		**Solution**	**98%**	**Category 1**	**3**	**Category I**	**R41**	**Severe Irritant**	**Balls et al. (1995)**
3-((Benzylthio)methyl)-6-chloro-,1,1-dioxide (F29)	**-**	**100%**	**ETHER, SULFUR COMPOUND, ORGANIC**	**Active pharmaceutical ingredient**		**Solid**		**Nonirritant**		**Category IV**	**Nonirritant**	**Nonsevere Irritant**	**Guerriero et al. (2004)**
Brij 35	9002-92-0	100%	ALCOHOL	Detergent, Solubilizer, Emulsifier, Lubricant		Solution					Nonirritant	Nonsevere Irritant	CEC (1991)
Butanol	71-36-3	100%	ALCOHOL	Solvent; Chemical intermediate; Flavor ingredient		Liquid					Nonirritant	Severe Irritant	CEC (1991)
iso-Butanol	**78-83-1**	**100%**	**ALCOHOL**	**Solvent; Chemical intermediate; Flavor ingredient**		**Liquid**	**99.9%**	**Category 2A**		**Category II**	**R36**	**Severe Irritant**	**Balls et al. (1995)**
n-Butanol (F35)	**71-36-3**	**100%**	**ALCOHOL**	**Solvent; Chemical intermediate; Flavor ingredient**		**Liquid**	**99.9%**	**Category 2A**		**Category II**	**R36**	**Severe Irritant**	**Guerriero et al. (2004)**
2-Butoxyethyl acetate	112-07-2	100%	ESTER	Solvent, Textile dyeing and printing, Leather treatment, Production of plasticizers, Stabilizer		Liquid					Nonirritant	Nonsevere Irritant	CEC (1991)

Substance	CASRN[1]	Concentration Tested	Chemical Class	Product Class	pH	Form Tested	Purity	*In Vivo* Classification (GHS)[2,3]	Category 1 Subclass[4]	*In Vivo* Classification (EPA)[5,6]	*In Vivo* Classification (EU)[7,8]	*In Vitro* Classification	Reference
N-Butyl acetate	123-86-4	100%	ESTER	Solvent; Synthetic flavor ingredient		Liquid		Nonirritant		Category III	Nonirritant	Nonsevere Irritant	Balls et al. (1995)
n-Butyl acetate (F39)	**123-86-4**	**100%**	**ESTER**	**Solvent; Synthetic flavor ingredient**		**Liquid**	**99%**	**Nonirritant**		**Category III**	**Nonirritant**	**Severe Irritant**	**Guerriero et al. (2004)**
g-Butyrolactone	**96-48-0**	**100%**	**HETEROCYCLE, LACTONE**	**Synthetic intermediate; Solvent**		**Liquid**		**Category 2A**		**Category II**	**R36**	**Severe Irritant**	**Balls et al. (1995)**
Captan 90 concentrate	133-06-2	100%	IMIDE, SULFUR COMPOUND, ORGANIC	Pesticide		Solution	90%	Category 1	4	Category I	R41	Nonsevere Irritant	Balls et al. (1995)
4-Carboxybenzaldehyde	619-66-9	100%	CARBOXYLIC ACID, ALDEHYDE	Manufacturing impurity (polyester); Developer intermediate		Solid	>95%	Category 2A		Category II	R36	Nonsevere Irritant	Balls et al. (1995)
Cetylpyridium bromide (F37)	**140-72-7**	**100%**	**ONIUM, HETEROCYCLE**	**Surfactant (cationic), Germicide, Laboratory reagent**		**Solid**	**98%**	**Category 1**	**4**	**Category I**	**R41**	**Severe Irritant**	**Guerriero et al. (2004)**
Cetylpyridinium bromide (0.1%)	**140-72-7**	**0.1%**	**ONIUM, HETEROCYCLE**	**Surfactant (cationic), Germicide, Laboratory reagent**		**Solution**	**99%**	**Nonirritant**		**Category III**	**Nonirritant**	**Severe Irritant**	**Balls et al. (1995)**
Cetylpyridinium bromide (10%)	**140-72-7**	**10%**	**ONIUM, HETEROCYCLE**	**Surfactant (cationic), Germicide, Laboratory reagent**		**Solution**	**99%**	**Category 1**	**4**	**Category I**	**R41**	**Severe Irritant**	**Balls et al. (1995)**
Cetylpyridinium bromide (6%)	**140-72-7**	**6%**	**ONIUM, HETEROCYCLE**	**Surfactant (cationic), Germicide, Laboratory reagent**		**Solution**	**99%**	**Category 1**	**2**	**SCNM**	**R41**	**Severe Irritant**	**Balls et al. (1995)**
5-Chloro-2,4-disulfamoyl chloroacetanilide (F22)	**-**	**100%**	**AMIDE**	**Raw material**		**Solid**		**Nonirritant**		**Category IV**	**Nonirritant**	**Nonsevere Irritant**	**Guerriero et al. (2004)**
Chloroform	67-66-3	100%	HYDROCARBON, HALOGENATED COMPOUND, ORGANIC	Solvent		Liquid					SCNM	Nonsevere irritant	CEC (1991)
5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl chloride (F18)	**-**	**100%**	**SULFUR COMPOUND, ORGANIC**	**Raw material**		**Solid**		**Nonirritant**		**Category III**	**Nonirritant**	**Nonsevere Irritant**	**Guerriero et al. (2004)**
5-Chloro-N-[4-methoxy-3-(1-piperazinyl)phenyl]-3-methylbenzo[B]thiophene-2-sulfonamide monohydrochloride (F4)	**-**	**100%**	**HETEROCYCLE, ETHER, AMIDE**	**Active pharmaceutical ingredient**		**Solid**		**Category 1**	**4**	**Category I**	**R41**	**Severe Irritant**	**Guerriero et al. (2004)**
Chlorhexidine	**55-56-1**	**100%**	**AMIDINE**	**Disinfectant; Mouthwash; Anti-infective agent**		**Solid**		**Category 1**	**4**	**SCNM**	**SCNM**	**Severe Irritant**	**Balls et al. (1995)**
Cyclohexanol	**108-93-0**	**100%**	**ALCOHOL**	**Solvent; Chemical intermediate**		**Liquid**	**97%**	**Category 1**	**2**	**Category I**	**R41**	**Severe Irritant**	**Balls et al. (1995)**
Dibenzoyl-L-tartaric acid	2743-38-6	100%	CARBOXYLIC ACID	Optical resolution agent		Solid		Category 1	2	SCNM	R41	Nonsevere Irritant	Balls et al. (1995)
Dibenzyl phosphate	1623-08-1	100%	ESTER, ORGANOPHOSPHOROUS COMPOUND	Not classified		Solid	99%	Category 2A		Category II	R36	Nonsevere Irritant	Balls et al. (1995)
Dibutyltin chloride	**683-18-1**	**100%**	**ORGANOTIN COMPOUND**	**Molluscicide, Slime control in paper mills, Wood preservative, disinfectant, Biocide in cooling systems, Leather and textile processing**		**Solution**					**R41**	**Severe Irritant**	**CEC (1991)**
3,4-Dichloroaniline hydrochloride (F11)	**-**	**100%**		**Chemical intermediate**		**Solid**		**SCNM**		**SCNM**	**SCNM**	**Severe Irritant**	**Guerriero et al. (2004)**
2,6-Dichlorobenzenesulfonyl chloride (F1)	**6579-54-0**	**100%**		**Raw material**		**Solid**		**SCNM**		**SCNM**	**SCNM**	**Severe Irritant**	**Guerriero et al. (2004)**
2,6-Dichlorobenzoyl chloride	4659-45-4	100%	ACYL HALIDE	Anti-infective; Anti-fungal; Preservative		Liquid	99%	Category 2A		Category II	SCNM	Nonsevere Irritant	Balls et al. (1995)
2,6-Dichloro-5-fluoro-beta-oxo-3-pyridinepropanoate (F16)	**96568-04-6**	**100%**	**ESTER, KETONE, HETEROCYCLE**	**Chemical intermediate**		**Solid**		**Category 2B**		**Category III**	**Nonirritant**	**Nonsevere Irritant**	**Guerriero et al. (2004)**
1-(3,4-Dichlorophenyl)-5-isopropylbiguanide HCl (F6)	**537-21-3**	**100%**	**AMIDINE**	**Active pharmaceutical ingredient**		**Solid**		**Category 1**	**NC**	**Category I**	**R41**	**Severe Irritant**	**Guerriero et al. (2004)**
3,4-Dimethoxybenzaldehyde (F19)	**120-14-9**	**100%**	**ALDEHYDE**	**Raw material**		**Solid**		**Nonirritant**		**Category III**	**Nonirritant**	**Nonsevere Irritant**	**Guerriero et al. (2004)**
2,2-Dimethylbutanoic acid	595-37-9	100%	CARBOXYLIC ACID	Pharmaceutical metabolite		Liquid	96%	SCNM		Category I	SCNM	Severe Irritant	Balls et al. (1995)
Dimethyl carbonate (F30)	**616-38-6**	**100%**	**CARBOXYLIC ACID**	**Raw material**		**Solid**		**Nonirritant**		**Category III**	**Nonirritant**	**Severe Irritant**	**Guerriero et al. (2004)**

Substance	CASRN[1]	Concentration Tested	Chemical Class	Product Class	pH	Form Tested	Purity	*In Vivo* Classification (GHS)[2,3]	Category 1 Subclass[4]	*In Vivo* Classification (EPA)[5,6]	*In Vivo* Classification (EU)[7,8]	*In Vitro* Classification	Reference
2,5-Dimethylhexanediol	110-03-2	100%	ALCOHOL	Intermediate for pharmaceticals, pesticides, perfumes		Solid	99.5%	Category 1	1	Category I	R41	Nonsevere Irritant	Balls et al. (1995)
Dimethyl sulfoxide	67-68-5	100%	SULFUR COMPOUND	Solvent, Antifreeze, Paint and varnish remover,		Solution					Nonirritant	Nonsevere Irritant	CEC (1991)
Ethanol	**64-17-5**	**100%**	**ALCOHOL**	**Solvent; Beverages; Antifreeze agent**		**Liquid**	**100%**	**Category 2A**		**Category III**	**Nonirritant**	**Severe Irritant**	**Balls et al. (1995)**
Ethyl acetate	**141-78-6**	**100%**	**ESTER**	**Solvent; Synthetic flavoring**		**Liquid**	**99%**	**Nonirritant**		**Category III**	**Nonirritant**	**Severe Irritant**	**Balls et al. (1995)**
2-Ethyl-1-hexanol	104-76-7	100%	ALCOHOL	Solvent; Plasticizer		Liquid	99%	Category 2A		Category II	R36	Nonsevere Irritant	Balls et al. (1995)
Ethyl-2-methylacetoacetate	**609-14-3**	**100%**	**KETONE, ESTER**	**Not classified**		**Liquid**	**97%**	**Category 2B**		**Category III**	**Nonirritant**	**Severe Irritant**	**Balls et al. (1995)**
Ethyl trimethyl acetate	3938-95-2	100%	ESTER	Solvent		Liquid	99%	Nonirritant		Category III	Nonirritant	Nonsevere Irritant	Balls et al. (1995)
Fluorescein, sodium	518-47-8	100%	POLYCYCLIC COMPOUND, CYCLIC HYDROCARBON	Phthalic indicator dye; used to detect corneal lesions in ophthalmology		Solution					SCNM	Nonsevere irritant	CEC (1991)
p-Fluoraniline	**371-40-4**	**100%**	**AMINE**	**Intermediate for herbicides; Dyes**		**Liquid**	**99%**	**SCNM**		**SCNM**	**SCNM**	**Severe Irritant**	**Balls et al. (1995)**
Fomesafen, acid form (solid)	**72128-02-0**	**100%**	**IMIDE, ETHER, NITRO COMPOUND**	**Pesticide**		**Solid**	**97.5%**	**Nonirritant**		**Category III**	**Nonirritant**	**Severe Irritant**	**Balls et al. (1995)**
Glycerol	56-81-5	100%	ALCOHOL	Solvent; Plasticizer; Lubricant; Emollient; Drug vehicle		Liquid	>99.5%	Nonirritant		Category IV	Nonirritant	Nonsevere Irritant	Balls et al. (1995)
Glycerol	56-81-5	100%	ALCOHOL	Solvent; Plasticizer; Lubricant; Emollient; Drug vehicle		Solution					Nonirritant	Nonsevere Irritant	CEC (1991)
Glycerol (F41)	**56-81-5**	**100%**	**ALCOHOL**	**Solvent; Plasticizer; Lubricant; Emollient; Drug vehicle**		**Liquid**	**>99%**	**Nonirritant**		**Category IV**	**Nonirritant**	**Nonsevere Irritant**	**Guerriero et al. (2004)**
n-Hexane	110-54-3	100%	ACYCLIC HYDROCARBON	Solvent; Adhesive; Gasoline additive		Liquid					Nonirritant	Nonsevere Irritant	CEC (1991)
n-Hexanol	**111-27-3**	**100%**	**ALCOHOL**	**Solvent; Chemical intermediate; Synthetic flavor ingredient**		**Liquid**	**98%**	**Category 2A**		**Category II**	**R36**	**Severe Irritant**	**Balls et al. (1995)**
3-Hydroxy-2-phenyl-4-quinolinecarboxylic acid (F24)	**485-89-2**	**100%**	**HETEROCYCLE, CARBOXYLIC ACID, ALCOHOL**	**Chemical intermediate**		**Solid**		**Nonirritant**		**Category II**	**Nonirritant**	**Nonsevere Irritant**	**Guerriero et al. (2004)**
HZA-1	**-**	**Undiluted**	**FORMULATION**	**Shampoos, Hair care**		**Solution**		**Category 1**	**1**	**Category I**	**R41**	**Severe irritant**	**Gettings et al. (1996)**
HZB-1	**-**	**25%**	**FORMULATION**	**Soaps and surfactants**		**Solution**		**Category 1**	**1**	**Category I**	**R41**	**Severe irritant**	**Gettings et al. (1996)**
HZC-1	-	25%	FORMULATION	Shampoos, Hair care		Solution		Category 1	1	Category I	R41	Nonsevere irritant	Gettings et al. (1996)
HZD-1	-	25%	FORMULATION	Shampoos, Hair care		Solution		Category 2B		Category III	Nonirritant	Nonsevere irritant	Gettings et al. (1996)
HZE-1	-	Undiluted	FORMULATION	Soaps and surfactants		Solution		SCNM		Category I	SCNM	Nonsevere irritant	Gettings et al. (1996)
HZF-1	-	Undiluted	FORMULATION	Shampoos, Hair care		Solution		Category 1	1	Category I	R41	Nonsevere irritant	Gettings et al. (1996)
HZG-1	**-**	**25%**	**FORMULATION**	**Shampoos, Hair care**		**Solution**		**Category 1**	**1**	**Category I**	**R41**	**Severe irritant**	**Gettings et al. (1996)**
HZH-1	-	Undiluted	FORMULATION	Soaps and surfactants, cosmetics		Solution		Nonirritant		Category IV	Nonirritant	Nonsevere irritant	Gettings et al. (1996)
HZI-1	**-**	**Undiluted**	**FORMULATION**	**Soaps and surfactants**		**Solution**		**Category 1**	**1**	**Category I**	**R41**	**Severe irritant**	**Gettings et al. (1996)**
HZJ-1	-	Undiluted	FORMULATION	Shampoos, Hair care		Solution		Nonirritant		Category IV	Nonirritant	Nonsevere irritant	Gettings et al. (1996)
HZK-1	**-**	**Undiluted**	**FORMULATION**	**Soaps and surfactants**		**Solution**		**Category 1**	**1**	**Category I**	**R41**	**Severe irritant**	**Gettings et al. (1996)**
HZL-1	**-**	**Undiluted**	**FORMULATION**	**Soaps and surfactants**		**Solution**		**Category 1**	**1**	**Category I**	**R41**	**Severe irritant**	**Gettings et al. (1996)**
HZM-1	**-**	**25%**	**FORMULATION**	**Shampoos, Hair care**		**Solution**		**Category 1**	**1**	**Category I**	**R41**	**Severe irritant**	**Gettings et al. (1996)**
HZN-1	**-**	**25%**	**FORMULATION**	**Shampoos, Hair care**		**Solution**		**Category 1**	**1**	**Category I**	**R41**	**Severe irritant**	**Gettings et al. (1996)**
HZP-1	**-**	**Undiluted**	**FORMULATION**	**Shampoos, Hair care**		**Solution**		**Nonirritant**		**Category III**	**Nonirritant**	**Severe irritant**	**Gettings et al. (1996)**
HZQ-1	-	Undiluted	FORMULATION	Soaps and surfactants		Solution		Nonirritant		Category III	Nonirritant	Nonsevere irritant	Gettings et al. (1996)

Substance	CASRN[1]	Concentration Tested	Chemical Class	Product Class	pH	Form Tested	Purity	*In Vivo* Classification (GHS)[2,3]	Category 1 Subclass[4]	*In Vivo* Classification (EPA)[5,6]	*In Vivo* Classification (EU)[7,8]	*In Vitro* Classification	Reference
HZR-1	-	25%	FORMULATION	Soaps and surfactants		Solution		Category 1	1	Category I	R41	Nonsevere irritant	Gettings et al. (1996)
HZS-1	**-**	**Undiluted**	**FORMULATION**	**Soaps and surfactants**		**Solution**		**Category 1**	**1**	**Category I**	**R41**	**Severe irritant**	**Gettings et al. (1996)**
HZT-1	-	Undiluted	FORMULATION	Soaps and surfactants		Solution		Nonirritant		Category IV	Nonirritant	Nonsevere irritant	Gettings et al. (1996)
HZU-1	**-**	**25%**	**FORMULATION**	**Soaps and surfactants**		**Solution**		**Category 2B**		**Category III**	**R36**	**Severe irritant**	**Gettings et al. (1996)**
HZV-1	**-**	**25%**	**FORMULATION**	**Shampoos, Hair care**		**Solution**		**Category 1**	**1**	**Category I**	**R41**	**Severe irritant**	**Gettings et al. (1996)**
HZW-1	-	25%	FORMULATION	Soaps and surfactants		Solution		Category 1	1	Category I	R41	Nonsevere irritant	Gettings et al. (1996)
HZX-1	-	Undiluted	FORMULATION	Shampoos, Hair care		Solution		Category 1	1	Category I	R41	Nonsevere irritant	Gettings et al. (1996)
HZY-1	-	Undiluted	FORMULATION	Shampoos, Hair care		Solution		Category 1	1	Category I	R41	Nonsevere irritant	Gettings et al. (1996)
HZZ-1	-	Undiluted	FORMULATION	Soaps and surfactants		Solution		Nonirritant		Category IV	Nonirritant	Nonsevere irritant	Gettings et al. (1996)
Imidazole	**288-32-4**	**100%**	**HETEROCYCLE**	**Anti-fungal; Enzyme inhibitor**		**Solid**	**99%**	**Category 1**	**4**	**Category I**	**R41**	**Severe Irritant**	**Balls et al. (1995)**
1H-Indole-2,3-dione (F28)	**91-56-5**	**100%**	**HETEROCYCLE**	**Raw material**		**Solid**		**Nonirritant**		**Category IV**	**Nonirritant**	**Nonsevere Irritant**	**Guerriero et al. (2004)**
Iodine chloride with pyridine (1:1) (F10)	**6443-90-9**	**100%**	**HETEROCYCLE**	**Raw material**		**Solid**		**Category 1**	**NC**	**Category I**	**R41**	**Severe Irritant**	**Guerriero et al. (2004)**
di-Isopropyl aminoethyldiphenyl acetamide (F15)	**-**	**100%**	**AMINE, AMIDE**	**Raw material**		**Solid**		**Category 2B**		**Category III**	**R36**	**Nonsevere Irritant**	**Guerriero et al. (2004)**
Isopropyl dicyanamide (F9)	**35695-36-4**	**100%**	**AMINE, NITRILE**	**Chemical intermediate**		**Solid**		**Category 1**	**NC**	**Category I**	**R41**	**Severe Irritant**	**Guerriero et al. (2004)**
Maneb	**12427-38-2**	**100%**	**AMINE, SALT, ORGANIC, UREA**	**Pesticide**		**Solid**	**90% (approx)**	**SCNM**		**Category III**	**SCNM**	**Severe Irritant**	**Balls et al. (1995)**
Mebrophen hydramine HCl (F5)	**13977-28-1**	**100%**	**ETHER, AMINE, SLAT**	**Active pharmaceutical ingredient**		**Solid**		**Category 1**	**NC**	**Category I**	**R41**	**Severe Irritant**	**Guerriero et al. (2004)**
Mercuric chloride	7546-30-7	100%	INORGANIC	Topical antiseptic/disinfectant; corrosive agent		Solid		SCNM		SCNM	SCNM	Severe irritant	CEC (1991)
2-Methoxyethanol	**109-86-4**	**100%**	**ALCOHOL**	**Solvent**		**Liquid**					**Nonirritant**	**Severe Irritant**	**CEC (1991)**
1-(2-Methoxyphenyl)piperazine hydrogen sulfate (F2)	**-**	**100%**		**Raw material**		**Solid**		**SCNM**		**SCNM**	**SCNM**	**Severe Irritant**	**Guerriero et al. (2004)**
Methyl acetate	**79-20-9**	**100%**	**ESTER**	**Solvent; Chemical intermediate; Synthetic flavor ingredient**		**Liquid**	**98%**	**Category 2A**		**Category II**	**R36**	**Severe Irritant**	**Balls et al. (1995)**
6-(Methylamino)-2-pyridine ethanol formate (1:1) (salt) (F17)	**-**	**100%**	**HETEROCYCLE, AMINE, CARBOXYLIC ACID, SALT**	**Chemical intermediate**		**Solid**		**Nonirritant**		**Category III**	**Nonirritant**	**Severe Irritant**	**Guerriero et al. (2004)**
Methyl cyanoacetate	105-34-0	100%	ESTER, NITRILE	Adhesive; Pharmaceutical intermediate		Liquid	99%	Category 2A		Category II	R36	Nonsevere Irritant	Balls et al. (1995)
Methylcyclopentane	96-37-7	100%	HYDROCARBONS, CYCLIC	Solvent		Liquid	>99%	Nonirritant		Category III	Nonirritant	Nonsevere Irritant	Balls et al. (1995)
4,4'-Methylenebis-(2,6-di-tert-butylphenol) (F43)	**118-82-3**	**100%**	**SULFUR COMPOUND, ORGANIC**	**Raw material**		**Solid**		**Nonirritant**		**Category III**	**Nonirritant**	**Nonsevere Irritant**	**Guerriero et al. (2004)**
Methyl ethyl ketone	78-93-3	100%	KETONE	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals		Liquid	99%	Category 2A		Category III	R36	Severe Irritant	Balls et al. (1995)
Methyl ethyl ketone (F38)	**78-93-3**	**100%**	**KETONE**	**Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals**		**Liquid**	**99%**	**Nonirritant**		**Category III**	**Nonirritant**	**Severe Irritant**	**Guerriero et al. (2004)**
Methyl isobutyl ketone	**108-10-1**	**100%**	**KETONE**	**Solvent; Synthetic flavor; Drycleaning**		**Liquid**	**98%**	**Nonirritant**		**Category III**	**Nonirritant**	**Severe Irritant**	**Balls et al. (1995)**
1-Naphthalene acetic acid	86-87-3	100%	CARBOXYLIC ACID, POLYCYCLIC COMPOUND	Pesticide		Solid	96%	Category 1	NC	Category I	SCNM	Nonsevere Irritant	Balls et al. (1995)

Substance	CASRN[1]	Concentration Tested	Chemical Class	Product Class	pH	Form Tested	Purity	*In Vivo* Classification (GHS)[2,3]	Category 1 Subclass[4]	*In Vivo* Classification (EPA)[5,6]	*In Vivo* Classification (EU)[7,8]	*In Vitro* Classification	Reference
1-Naphthalene acetic acid, Na salt	**61-31-4**	**100%**	**SALT, ORGANIC, POLYCYCLIC COMPOUND, CARBOXYLIC ACID, SALT**	**Pesticide**		**Solid**	**95%**	**Category 1**	**1**	**Category I**	**R41**	**Severe Irritant**	**Balls et al. (1995)**
2-Nitro-4-propoxyaniline (F23)	**-**	**100%**	**NITRO COMPOUND, AMINE, ETHER**	**Chemical intermediate**		**Solid**		**Nonirritant**		**Category III**	**Nonirritant**	**Nonsevere Irritant**	**Guerriero et al. (2004)**
2-Nitro-4-thiocyanoaniline (F7)	**54029-45-7**	**100%**	**NITRO COMPOUND,AMINE,SULFUR COMPOUND, ORGANIC**	**Chemical intermediate**		**Solid**		**Category 1**	**NC**	**Category I**	**R41**	**Severe Irritant**	**Guerriero et al. (2004)**
2-Nitro-4-thio-N-propylaniline (F21)	**54393-89-4**	**100%**	**AMINE,NITRO COMPOUND,SULFUR COMPOUND, ORGANIC**	**Chemical intermediate**		**Solid**		**Nonirritant**		**Category III**	**Nonirritant**	**Severe Irritant**	**Guerriero et al. (2004)**
***n*-Octanol**	**111-87-5**	**100%**	**ALCOHOL**	**Solvent; Fragrance**		**Liquid**	**>99%**	**Category 2A**		**Category II**	**R36**	**Severe Irritant**	**Balls et al. (1995)**
tetra-N-Octylammonium bromide (F8)	**14866-33-2**	**100%**	**ONIUM**	**Raw material**		**Solid**		**Category 1**	**NC**	**Category I**	**R41**	**Severe Irritant**	**Guerriero et al. (2004)**
2-(4-Oxopentyl)-1H-isoindole-1,3 (2H)-dione (F26)	**3197-25-9**	**100%**	**HETEROCYCLE**	**Chemical intermediate**		**Solid**		**Nonirritant**		**Category III**	**Nonirritant**	**Nonsevere Irritant**	**Guerriero et al. (2004)**
(S)-1-Phenyl-N-propylamine (F13)	**3789-59-1**	**100%**		**Raw material**		**Liquid**		**SCNM**		**SCNM**	**SCNM**	**Severe Irritant**	**Guerriero et al. (2004)**
Polyethylene glycol 400	25322-68-3	100%	ALCOHOL, ETHER	Surfactant (nonionic), Lubricant, Plasticizer, Solvent		Liquid		Nonirritant		Category IV	Nonirritant	Severe Irritant	Balls et al. (1995)
Polyethylene glycol 400 (F44)	**25322-68-3**	**100%**	**ALCOHOL, ETHER**	**Surfactant (nonionic), Lubricant, Plasticizer, Solvent**		**Liquid**		**Nonirritant**		**Category IV**	**Nonirritant**	**Nonsevere Irritant**	**Guerriero et al. (2004)**
Potassium cyanate	590-28-3	100%	SALT, INORGANIC	Herbicide; Pharmaceutical intermdiate		Solid	97%	SCNM		SCNM	SCNM	Nonsevere Irritant	Balls et al. (1995)
Promethazine HCl	**58-33-3**	**100%**	**AMINE, HETEROCYCLE, SULFUR COMPOUND, ORGANIC**	**Antihistamine; Anti-nausea drug**		**Solid**	**98%**	**Category 1**	**3**	**Category I**	**R41**	**Severe Irritant**	**Balls et al. (1995)**
iso-Propanol	**67-63-0**	**100%**	**ALCOHOL**	**Solvent; Aerosol formulations (ingredient)**		**Liquid**	**99.9%**	**Category 2A**		**Category III**	**SCNM**	**Severe Irritant**	**Balls et al. (1995)**
Propylene glycol (F42)	**57-55-6**	**100%**	**ALCOHOL**	**Antifreeze, Solvent, Emulsifier, Resins, Inhibitor of fermentation and mold growth**		**Liquid**		**Nonirritant**		**Category IV**	**Nonirritant**	**Nonsevere Irritant**	**Guerriero et al. (2004)**
Pyridine	**110-86-1**	**100%**	**HETEROCYCLE**	**Solvent; Intermediate for pharmaceuticals, dyes, pesticides**		**Liquid**	**99.9+%**	**Category 1**	**3**	**Category I**	**R41**	**Severe Irritant**	**Balls et al. (1995)**
4,4'-Pyridylpiperidine (F12)	**-**	**100%**		**Raw material**		**Solid**		**SCNM**		**SCNM**	**SCNM**	**Severe Irritant**	**Guerriero et al. (2004)**
Quinacrine	69-05-6	100%	AMINE, HETEROCYCLE, POLYCYCLIC COMPOUND	Anti-infective (anti-helmentic)		Solid		Category 1	3	Category I	R41	Nonsevere Irritant	Balls et al. (1995)
Silver nitrate	7761-88-8	3% in water	INORGANIC	Germicide		Solution		SCNM		SCNM	SCNM	Nonsevere irritant	CEC (1991)
Sodium dicyanamide (F3)	**-**	**100%**	**AMIDE**	**Raw material**		**Solid**		**Category 1**	**NC**	**Category I**	**R41**	**Severe Irritant**	**Guerriero et al. (2004)**
Sodium dodecyl sulfate	**151-21-3**	**100%**	**ORGANIC SALT, CARBOXYLIC ACID SALT**	**Anionic detergent, Emulsifier, Lubricant, Solubilizer**		**Solution**					**R41**	**Severe Irritant**	**CEC (1991)**
Sodium hydroxide	1310-73-2	1% in water	INORGANIC, ALKALi	Acid neutralizer; caustic agent		Solution					SCNM	Severe irritant	CEC (1991)
Sodium hydroxide (1%)	**1310-73-2**	**1%**	**ALKALI**	**Caustic agent**		**Solution**	**Reagent grade**	**Category 2B**		**Category III**	**R36**	**Severe Irritant**	**Balls et al. (1995)**
Sodium hydroxide (10%)	1310-73-2	10%	ALKALI	Caustic agent		Solution	Reagent grade	Category 1	4	Category I	R41	Severe Irritant	Balls et al. (1995)
Sodium hydroxide (F31)	**1310-73-2**	**10%**	**ALKALI**	**Caustic agent**		**Liquid**	**Reagent grade**	**Category 1**	**4**	**Category I**	**R41**	**Severe Irritant**	**Guerriero et al. (2004)**

Substance	CASRN[1]	Concentration Tested	Chemical Class	Product Class	pH	Form Tested	Purity	*In Vivo* Classification (GHS)[2,3]	Category 1 Subclass[4]	*In Vivo* Classification (EPA)[5,6]	*In Vivo* Classification (EU)[7,8]	*In Vitro* Classification	Reference
Sodium lauryl sulfate (15 %)	151-21-3	15%	SALT, ORGANIC, CARBOXYLIC ACID, SALT	Surfactant (anionic), Detergent		Solution	98%	Category 1	NC	Category I	SCNM	Nonsevere Irritant	Balls et al. (1995)
Sodium lauryl sulfate (3 %)	151-21-3	3%	SALT, ORGANIC, CARBOXYLIC ACID, SALT	Surfactant (anionic), Detergent		Solution	98%	Nonirritant		Category III	Nonirritant	Nonsevere Irritant	Balls et al. (1995)
Sodium oxalate	62-76-0	100%	SALT, ORGANIC, CARBOXYLIC ACID, SALT	Textile finishing; Pyrotechnic, Industrial byproduct		Solid	>99%	Category 1	4	Category I	R41	Nonsevere Irritant	Balls et al. (1995)
Sodium perborate tetrahydrate	10486-00-7	100%	SALT, INORGANIC, BORON CONTAINING COMPOUND	Household cleaner; Detergent		Solid	98.6%	Category 1	4	Category I	R41	Nonsevere Irritant	Balls et al. (1995)
4,4`-Sulfonylbisbenzenamine (F25)	**80-08-0**	**100%**	**SULFUR COMPOUND, ORGANIC**	**Active pharmaceutical ingredient**		**Solid**		**Nonirritant**		**Category IV**	**Nonirritant**	**Nonsevere Irritant**	**Guerriero et al. (2004)**
Toluene	108-88-3	100%	CYCLIC HYDROCARBON	Solvent; Gasoline additive; Manufacture of benzene derivatives, medicines, dyes, perfumes		Liquid	99%	Nonirritant		Category III	Nonirritant	Severe Irritant	Balls et al. (1995)
Toluene	108-88-3	100%	CYCLIC HYDROCARBON	Solvent; Gasoline additive; Manufacture of benzene derivatives, medicines, dyes, perfumes		Liquid					Nonirritant	Nonsevere Irritant	CEC (1991)
Toluene (F40)	**108-88-3**	**100%**	**CYCLIC HYDROCARBON**	**Solvent; Gasoline additive; Manufacture of benzene derivatives, medicines, dyes, perfumes**		**Liquid**	**99%**	**Nonirritant**		**Category III**	**Nonirritant**	**Nonsevere Irritant**	**Guerriero et al. (2004)**
Triacetin	102-76-1	100%	ESTER	Solvent, Fixative		Solution					Nonirritant	Nonsevere Irritant	CEC (1991)
Tributyltin chloride	**688-73-3**	**100%**	**ORGANOTIN COMPOUND**	**Molluscicide, Slime control in paper mills, Wood preservative, disinfectant, Biocide in cooling systems, Leather and textile processing**		**Solution**					**R41**	**Severe Irritant**	**CEC (1991)**
Trichloroacetic acid (3%)	76-03-9	3%	CARBOXYLIC ACID	Caustic agent; Fixative; Herbicide		Solution	Reagent grade	Nonirritant		Category III	Nonirritant	Nonsevere Irritant	Balls et al. (1995)
Trichloroacetic acid (30%)	76-03-9	30%	CARBOXYLIC ACID	Caustic agent; Fixative; Herbicide		Solution	Reagent grade	Category 1	4	Category I	R41	Severe Irritant	Balls et al. (1995)
Trichloroacetic acid (F32)	**76-03-9**	**30%**	**CARBOXYLIC ACID**	**Caustic agent; Fixative; Herbicide**		**Liquid**	**Reagent grade**	**Category 1**	**4**	**Category I**	**R41**	**Severe Irritant**	**Guerriero et al. (2004)**
Triethanolamine	102-71-6	100%	AMINE, ALCOHOL	Chemical intermediate, Cosmetic ingredient, Vulcanization acelerator		Solution					Nonirritant	Nonsevere Irritant	CEC (1991)
Triton X-100 (10 %)	**9002-93-1**	**10%**	**ETHER**	**Surfactant (nonionic), Detergent, Emulsifier**		**Solution**	**98%**	**Category 1**	**NC**	**Category II**	**R41**	**Severe Irritant**	**Balls et al. (1995)**
Triton X-100 (5 %)	**9002-93-1**	**5%**	**ETHER**	**Surfactant (nonionic), Detergent, Emulsifier**		**Solution**	**98%**	**Category 2A**		**Category III**	**R36**	**Severe Irritant**	**Balls et al. (1995)**
Tween 20	9005-64-5	100%	ESTER, ETHER	Surfactant (nonionic), Detergent		Solution	98%	Nonirritant		Category III	Nonirritant	Nonsevere Irritant	Balls et al. (1995)

Substances in bold indicate those that were included in the "Expanded data set" analyses described in the text.

[1]CASRN=Chemical Abstracts Service Registry Number.

[2]GHS=Globally Harmonized System (UN [2003]).

[3]Eye Irritant Category 1 = irreversible effects on the eye/serious damage to the eye; Category 2A = reversible effects on the eye/irritating to the eyes; Category 2B = reversible effects on the eye/mildly irritating to the eyes; Nonirritant = not an eye irritant

[4]NICEATM-defined subgroups assigned based on the lesions that drove classification of a GHS Category 1 substance. 1: based on lesions that are persistent; 2: based on lesions that are severe (not including corneal opacity score equal to 4); 3: based on lesions that are severe (not including corneal opacity score equal to 4) and persistent; 4: corneal opacity score equal to 4 at any time; NC: No subclassification could be made based on the data.

Substance	CASRN[1]	Concentration Tested	Chemical Class	Product Class	pH	Form Tested	Purity	*In Vivo* Classification (GHS)[2,3]	Category 1 Subclass[4]	*In Vivo* Classification (EPA)[5,6]	*In Vivo* Classification (EU)[7,8]	*In Vitro* Classification	Reference

[5]EPA=U.S. Enviromental Protection Agency (EPA [1996]).

[6]Toxicity Category I for the Primary Eye Irritation Study = Corrosive, or corneal involvement or irritation not reversible within 21 days; Category II = Corneal involvement or irritation clearing in 8-21 days; Category III = Corneal involvement or irritation clearing in 7 days or less; Category IV = Minimal effects clearing within 24 hr.

[7]EU=European Union (EU [2001]).

[8]Risk phrase R41 = risk of serious damage to the eyes; R36 = irritating to the eyes; nonirritant = not an eye irritant.

[9]SCNM=Study Criteria Not Met.

[10]NT=Not tested.

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SECTION II

ISOLATED CHICKEN EYE (ICE) TEST METHOD ACCURACY AND RELIABILITY REANALYSIS

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1.0 INTRODUCTION

On November 1, 2004, NICEATM released draft BRDs on the current status of four *in vitro* test methods for detecting ocular corrosives and severe irritants (see http://iccvam.niehs.nih.gov/methods/ocudocs/ocu_brd.htm). The test methods reviewed were the BCOP, the HET-CAM, the IRE, and the ICE assays. On January 11-12, 2005, ICCVAM convened an Expert Panel to independently evaluate the validation status of these four *in vitro* test methods for identifying ocular corrosives or severe irritants. The Expert Panel Report, *Evaluation of the Current Validation Status of In Vitro Test Methods for Identifying Ocular Corrosives and Severe Irritants*, can be obtained by contacting NICEATM or electronically from http://iccvam.niehs.nih.gov/methods/eyeirrit.htm. Public comments at the meeting revealed that additional data could be made available that had not yet been provided in response to earlier requests for data. The Expert Panel subsequently recommended that the additional data be requested and that a reanalysis of the accuracy and reliability of each test method be conducted, to the extent possible.

In response to this recommendation, a second *FR* notice was published on February 28, 2005 (*FR* Vol. 70, No. 38, pp. 9661-9662; http://iccvam.niehs.nih.gov/methods/eyeirrit.htm) requesting all available *in vitro* data on these four *in vitro* ocular irritancy test methods and corresponding *in vivo* rabbit eye test method data, as well as any human exposure data (either via ethical human studies or accidental exposure). The first *FR* notice requesting these data had been published on March 24, 2004 (*FR* Vol. 69, No. 57, pp. 13859-13861; http://iccvam.niehs.nih.gov/methods/eyeirrit.htm). Also, a request for relevant data was re-sent directly to the primary developers or users of each test method and sent to other scientists who participated in or attended the Expert Panel Meeting on January 11-12, 2005 and who had indicated a desire to provide additional data. No human exposure data was obtained for the substances evaluated in the ICE test method, and therefore no calculations could be made on the accuracy of the ICE test method for predicting human severe ocular irritancy.

Other factors also necessitated a reanalysis of the accuracy of the ICE test method for detecting ocular corrosives and severe irritants. First, clarification regarding the rules for classification of severe irritants was obtained subsequent to the release of the four BRDs that resulted in changes to the hazard classification of some of the substances used in the original analysis. For the original analysis, reversibility of ocular effects for the EU and GHS hazard classification systems was considered to be achieved if, by post-exposure day 21, the endpoint scores fell below the threshold that resulted in a test substance being classified as a severe irritant (EU [2001]; UN [2003]). The new information obtained indicated that reversibility of ocular effects is achieved only when all scores reach zero by post-exposure day 21. This change resulted in one substance previously classified as non-severe GHS irritants now being classified as a GHS severe irritant.

Second, the chemical classes assigned to each test substance were revised to reflect a standardized classification scheme (based on MeSH [http://www.nlm.nih.gov/mesh]) that would ensure consistency in classifying substances among all *in vitro* ocular test methods under consideration. This resulted in some chemicals being reclassified. The accuracy of the

ICE test method, by chemical class and using the GHS classification system (UN [2003]), has been reanalyzed to reflect these changes.

Finally, an additional accuracy analysis was conducted. In this analysis, the accuracy of each *in vitro* ocular irritancy test method for detecting ocular corrosives or severe irritants, depending on whether the classification was based on the severity of the response and/or its persistence to day 21 post-treatment, was determined.

For the ICE test method, the changes to the existing database that resulted from using the appropriate persistence classification criteria and any new data and/or information received subsequent to the release of the draft BRD are summarized in **Table II-1**. Additional ICE test method data and corresponding *in vivo* rabbit eye test data were submitted by the Netherlands Organisation for Applied Scientific Research (TNO) Nutrition and Food Institute for the 44 substances tested in Prinsen (1996) and for an additional 50 substances (Prinsen [2005]).

Also, the TNO Nutrition and Food Institute provided replicate ICE test data and the corresponding *in vivo* EU hazard classification for four substances (Prinsen [2000]). The efforts of Mr. Menk Prinsen and the TNO Nutrition and Food Institute in providing additional data and/or information are gratefully acknowledged.

2.0 ACCURACY OF THE ICE TEST METHOD - REANALYSIS

The ability of the ICE test method to correctly identify ocular corrosives and severe irritants, as defined by the GHS, EPA, and EU classification systems (EPA [1996]; EU [2001]; UN [2003])[1], was evaluated. The three regulatory ocular hazard classification systems considered during this analysis use different classification systems and decision criteria to identify ocular corrosives and severe irritants based on *in vivo* rabbit eye test results. All three classification systems are based on individual animal data in terms of the magnitude of the response and on the extent to which induced ocular lesions fail to reverse by day 21. However, there are differences among the three classification systems in regard to their criteria used by NICEATM for distinguishing between a severe and a non-severe response (see **Appendix A**). Thus, to evaluate the accuracy of the IRE test method for identifying ocular corrosives and severe irritants, individual rabbit data collected at the different observation times was needed for each substance.

The ability of the ICE test method to correctly identify ocular corrosives and severe irritants, as defined by the GHS, EPA, and EU classification systems (EPA [1996]; EU [2001]; UN [2003]), was evaluated using two approaches. In the first approach, the accuracy of ICE was assessed separately for each *in vitro-in vivo* comparative study (i.e., publication) reviewed in Sections 4.0 and 5.0 of the draft ICE BRD. In the second approach, an overall analysis of ICE test method accuracy was conducted by combining results from each study, and then an

[1] For the purposes of this analysis, an ocular corrosive or severe irritant was defined as a substance that would be classified as Category 1 according to the GHS classification system (UN [2003]), as Category I according to the EPA classification system (EPA [1996]), or as R41 according to the EU classification system (EU [2001]).

992 **Table II-1. Summary of ICE Database Changes**
993

Data Source	Data Set	Number of Available Substances	Number of Acceptable Substances by Ocular Irritancy Classification System			Comments
			EPA[1]	EU[2]	GHS[3]	
			Cat[4] I/Total[5]	R41/Total[4]	Cat 1/Total[4]	
Prinsen and Koëter (1993)	New[6]	21	2/10	7/21	2/10	The decrease in the number of corrosive/severe irritants is due to the reclassification of one substance from a severe ocular irritant/corrosive to a moderate ocular irritatnt.
	Old[6]	21	3/10	8/21	3/10	
Balls et al. (1995)	New	59	19/51	19/50	22/54	The decrease in the total number of usable substances is due to excluding substances from consideration due to insufficient rabbit eye test data for classification (See **Appendix A)**.
	Old	59	20/54	21/59	22/56	
Prinsen (1996)	New	44	2/36	2/36	2/36	The *in vivo* data that corresponded to the substances tested were received, which allowed for an evaluation of all three regulatory hazard classification systems for this study (previously, the analysis of severe irritants was limited to the published EU classification for these substances). The published EU classification for four severe irritants was based only on dermal corrosivity (no rabbit eye test was performed). Therefore, these substances were excluded from the revised analysis.
	Old	44	0/29	6/44	0/29	
Prinsen (2000)	New	4	-	1/4	-	This is new information received subsequent to the original analysis. Because the corresponding *in vivo* rabbit test data were not submitted, the analysis was based on the provided EU classification only.
Prinsen (2005)	New	50	4/46	4/46	4/46	This is new information received subsequent to the original analysis. Four of these substances were classified based only on dermal corrosivity (no *in vivo* rabbit eye test was performed); these substances were excluded from the analysis.

994 [1]EPA = U.S. Environmental Protection Agency (EPA [1996]).
995 [2]EU = European Union (EU [2001]).
996 [3]GHS = Globally Harmonized System (UN [2003]).

997 [4]Cat = Category.
998 [5]First number (before forward slash) refers to the number of substances in each study that were classified as a severe irritant according to each classification
999 system (EPA, EU, and GHS). The second number (after the forward slash) refers to the number of substances that were classified, based on animal data, for
1000 each classification system (EPA, EU, GHS).
1001 [6]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on the previous analysis included in the draft ICE BRD.

overall ocular irritancy classification was assigned for each substance. When the same substance was evaluated in multiple laboratories, the overall ICE ocular irritancy classification was based on the majority of calls among all of the studies. When there was an equal number of different irritancy classifications for substances (e.g., two tests classified a substance as a nonsevere irritant and two tests classified a substance as a severe irritant), the more severe irritancy classification was used for the overall classification for the substance (severe irritant, in this case).

Based on the revisions made to the ICE test method database, which included the addition of 46 to 50 new substances, a revised accuracy analysis has been conducted. The calculations were performed as described in Section 6.0 of the draft ICE BRD. To allow for a comparison of the results obtained in the revised analysis relative to those obtained previously, the data tables below include accuracy statistics from both analyses. However, the discussion of the results in the sections that follow relate to the revised analysis only.

2.1 GHS Ocular Hazard Classification System

The four studies (Prinsen and Koëter [1993]; Balls et al. [1995]; Prinsen [1996]; Prinsen [2005]) contained ICE test data on 171 substances, 144 of which had sufficient *in vivo* data to be assigned an ocular irritancy classification as defined by the GHS classification system (UN [2003])[2] (see **Appendix II-A**). Based on results from *in vivo* rabbit eye experiments, 30[3] of the 144 substances were classified as severe irritants (i.e., Category 1), the other 114 substances were classified as nonsevere irritants (either Category 2A, 2B) or nonirritants. The 27 substances that could not be classified according to the GHS classification system due to the lack of adequate animal data are so noted in **Appendix II-A**.

2.1.1 Prinsen and Koëter (1993)

Based on the available *in vivo* rabbit eye data, 10 of the 21 substances tested in this study could be assigned a GHS classification (**Table II-2**). The remaining 11 substances had inadequate *in vivo* data for assigning a classification according to the GHS system (UN [2003]). For the 10 substances that could be evaluated, the ICE test method has an accuracy of 80% (8/10), a sensitivity of 100% (2/2), a specificity of 75% (6/8), a false positive rate of 25% (2/8), and a false negative rate of 0% (0/2).

2.1.2 Balls et al (1995)

Based on the available *in vivo* rabbit eye data, 54 of the 59 substances tested in this study could be assigned a GHS classification (**Table II-2**). The remaining five substances had inadequate *in vivo* data for assigning a classification according to the GHS system (UN [2003]). For the 54 substances assigned a GHS classification, the ICE test method has an

[2] For the purpose of this accuracy analysis, *in vivo* rabbit study results were used to identify GHS Category 1 irritants (i.e., severe irritants); substances classified as GHS Category 2A and 2B irritants were identified as nonsevere irritants.

[3] One chemical (benzalkonium chloride, 1%) was tested *in vivo* twice in the same laboratory. The results were discordant with respect to GHS classification. According to one test, the classification was Category 1, while results from the other test yielded a Category 2B classification. The accuracy analysis was performed with the substance classified as Category 1.

Table II-2. Evaluation of the Performance of the ICE Test Method In Predicting Ocular Corrosives and Severe Irritants Compared to the *In Vivo* Rabbit Eye Test Method, as Defined by the GHS[1] Classification System, by Study and Overall

Data Source	N[2]	Accuracy		Sensitivity		Specificity		Positive Predictivity		Negative Predictivity		False Positive Rate		False Negative Rate	
		%	No.[3]	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Prinsen and Koëter (1993) (new)[4]	10/21	80	8/10	100	2/2	75	6/8	50/2/4	3/4	100	6/6	25	2/8	0	0/2
Prinsen and Koëter (1993) (old)[4]	10/21	80	8/10	100	3/3	86	6/7	75	3/4	100	6/6	17	1/7	0	0/3
Balls et al. (1995)[5,6] (new)	54/59	69	37/54	50	11/22	81	26/32	65	11/17	70	26/37	19	6/32	50	11/22
Balls et al. (1995)[5,6] (old)	56/59	71	40/56	55	12/22	82	28/34	67	12/18	74	28/38	18	6/34	46	10/22
Prinsen (1996) (new)	36/44	97	35/36	50	1/2	100	34/34	100	1/1	97	34/35	0	0/34	50	1/2
Prinsen (1996) (old)	29/44	100	29/29	-	0/0	100	29/29	-	0/0	100	29/29	0	0/29	-	0/0
Prinsen (2005) (new)	46/50	89	41/46	0	0/4	98	41/42	0	0/1	91	41/45	2	1/42	100	4/4
Entire Data Set[6,7] (new)	144/171	83	120/144	50	15/30	92	105/114	63	15/24	88	105/120	8	9/114	50	15/30
Entire Data Set[6,7] (old)	92/121	82	75/92	60	15/25	90	60/67	68	15/22	86	60/70	10	7/67	40	10/25

[1]GHS = Globally Harmonized System (UN [2003]).
[2]N = Number of substances included in this analysis/the total number of substances in the study.
[3]No. = Data used to calculate the percentage.
[4]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on the previous analysis included in the draft ICE BRD.
[5]One chemical (benzalkonium chloride, 1%) was tested *in vivo* twice within the same laboratory. The results were discordant with respect to GHS classification; the analysis was performed assuming Category 1 classification.
[6]Performance calculated using the overall *in vitro* classification based on the majority and/or most severe classification among the four laboratories.
[7]Includes the data from Balls et al. (1995) using the overall *in vitro* classification based on the majority and/or most severe classification among the four laboratories.

accuracy of 69% (37/54), a sensitivity of 50% (11/22), a specificity of 81% (26/32), a false positive rate of 19% (6/32), and a false negative rate of 50% (11/22).

2.1.3 Prinsen (1996)

Based on the *in vivo* rabbit eye data obtained subsequent to the original ICE test method analysis, 36 of the 44 substances tested in this study could be assigned a GHS classification (**Table II-2**). The remaining eight substances had inadequate *in vivo* data for assigning a classification according to the GHS system (UN [2003]). For the 36 substances that could be evaluated, the ICE test method has an accuracy of 97% (35/36), a sensitivity of 50% (1/2), a specificity of 100% (34/34), a false positive rate of 0% (0/34), and a false negative rate of 50% (1/2).

2.1.4 Prinsen (2005)

Subsequent to the original ICE test method accuracy analysis, data were submitted on 50 substances. Based on the available *in vivo* rabbit eye data provided in this submission, 46 of the 50 substances tested in this study could be assigned a GHS classification (**Table II-2**). The remaining four substances had inadequate *in vivo* data for assigning a classification according to the GHS system. For the 46 substances that could be evaluated, the ICE test method has an accuracy of 89% (41/46), a sensitivity of 0% (0/4), a specificity of 98% (41/42), a false positive rate of 2% (1/42), and a false negative rate of 100% (4/4).

2.1.5 Entire Data Set

A total of 144 substances had sufficient *in vivo* data among the four studies to perform an accuracy analysis, based on the GHS classification system (**Table II-2**). Twenty-two substances lacked sufficient *in vivo* information on which to assign a GHS classification. Based on these 144 substances, the ICE test method has an accuracy of 83% (120/144), a sensitivity of 50% (15/30), a specificity of 92% (105/114), a false positive rate of 8% (9/114), and a false negative rate of 50% (15/30).

2.2 EPA Ocular Hazard Classification System

The four studies (Prinsen and Koëter [1993]; Balls et al. [1995]; Prinsen [1996]; Prinsen [2005]) contained ICE test method data on 171 substances, 145 of which had sufficient *in vivo* data to be assigned an ocular irritancy classification according to the EPA classification system (EPA 1996)[4] (see **Appendix II-A**). Based on results from the *in vivo* rabbit eye test, 29 of these 145 substances were classified as severe irritants (i.e., Category I), while the other 116 substances were classified as nonsevere irritants or nonirritants (Categories II, III, or IV). The 26 substances that could not be classified according to the EPA classification system are so noted in **Appendix II-A**.

[4] For the purpose of this accuracy analysis, *in vivo* rabbit study results were used to identify EPA Category I irritants (i.e., severe irritants); substances classified as EPA Category II, III, or IV irritants were defined as nonsevere irritants.

2.2.1 Prinsen and Koëter (1993)

Based on the available *in vivo* rabbit eye data, 10 of the 21 substances tested in this study could be assigned an EPA classification (**Table II-3**). The remaining 11 substances had inadequate *in vivo* data for assigning a classification according to the EPA system (EPA 1996). For the 10 substances that could be evaluated, the ICE test method has an accuracy of 80% (8/10), a sensitivity of 100% (2/2), a specificity of 75% (6/8), a false positive rate of 25% (2/8), and a false negative rate of 0% (0/2).

2.2.2 Balls et al. (1995)

Based on the available *in vivo* rabbit eye data, 53 of the 59 substances tested in this study could be assigned an EPA classification (**Table II-3**). The remaining six substances had inadequate *in vivo* data for assigning a classification according to the EPA system (1996). For the 53 substances assigned an EPA classification, the ICE test method has an accuracy of 72% (38/53), sensitivity of 53% (10/19), a specificity of 82% (28/34), a false positive rate of 18% (6/34), and a false negative rate of 47% (9/19).

2.2.3 Prinsen (1996)

Based on the *in vivo* rabbit eye data obtained subsequent to the original ICE test method analysis, 36 of the 44 substances tested in this study could be assigned an EPA classification (**Table II-3**). The remaining eight substances had inadequate *in vivo* data for assigning a classification according to the EPA system (1996). For the 36 substances that could be evaluated, the ICE test method has an accuracy of 97% (35/36), a sensitivity of 50% (1/2), a specificity of 100% (34/34), a false positive rate of 0% (0/34), and a false negative rate of 50% (1/2).

2.2.4 Prinsen (2005)

Subsequent to the original ICE test method accuracy analysis, data were submitted on 50 substances. Based on the available *in vivo* rabbit eye data provided in this submission, 46 of the 50 substances tested in this study could be assigned an EPA classification (**Table II-3**). The remaining four substances had inadequate *in vivo* data for assigning a classification according to the EPA system (1996). For the 46 substances that could be evaluated, the ICE test method has an accuracy of 89% (41/46), a sensitivity of 0% (0/4), a specificity of 98% (41/42), a false positive rate of 2% (1/42), and a false negative rate of 100% (4/4).

2.2.5 Entire Data Set

A total of 145 substances had sufficient *in vivo* data among the four studies to perform an accuracy analysis, based on the EPA classification system (**Table II-3**). Twenty-six substances lacked sufficient *in vivo* information on which to assign an EPA classification (EPA [1996]). Based on these 145 substances, the ICE test method has an accuracy of 84% (122/145), a sensitivity of 52% (15/29), a specificity of 92% (107/116), a false positive rate of 8% (9/116) and a false negative rate of 48% (14/29).

Table II-3. Evaluation of the Performance of the ICE Test Method In Predicting Ocular Corrosives and Severe Irritants Compared to the *In Vivo* Rabbit Eye Test Method, as Defined by the EPA[1] Classification System, by Study and Overall

Data Source	N[2]	Accuracy		Sensitivity		Specificity		Positive Predictivity		Negative Predictivity		False Positive Rate		False Negative Rate	
		%	No.[3]	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Prinsen and Koëter (1993) (new)[4]	10/21	80	8/10	100	2/2	75	6/8	50	2/4	100	6/6	25	2/8	0	0/2
Prinsen and Koëter (1993) (old)[4]	10/21	80	8/10	100	3/3	86	6/7	75	3/4	100	6/6	17	1/6	0	0/5
Balls et al. (1995)[5,6] (new)	53/59	72	38/53	53	10/19	82	28/34	63	10/16	76	28/37	18	6/34	47	9/19
Balls et al. (1995)[5,6] (old)	54/59	72	39/54	55	11/20	82	28/34	65	11/17	76	28/37	18	6/34	45	9/20
Prinsen (1996) (new)	36/44	97	35/36	50	1/2	100	34/34	100	1/1	97	34/35	0	0/34	50	1/2
Prinsen (1996) (old)	29/44	100	29/29	-	0/0	100	29/29	-	0/0	100	29/29	0	0/29	-	0/0
Prinsen (2005) (new)	46/50	89	41/46	0	0/4	98	41/42	0	0/1	91	41/45	2	1/42	100	4/4
Entire Data Set[6,7] (new)	145/171	84	122/145	52	15/29	92	107/116	63	15/24	89	107/121	8	9/116	48	14/29
Entire Data Set[6,7](old)	90/121	82	74/90	61	14/23	90	60/67	67	14/21	87	60/69	10	7/67	39	9/23

[1]EPA = U.S. Environmental Protection Agency (EPA [1996]).
[2]N = Number of substances included in this analysis/the total number of substances in the study.
[3]Data used to calculate the percentage.
[4]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on the previous analysis included in the draft ICE BRD.
[5]One chemical (benzalkonium chloride, 1%) was tested *in vivo* twice within the same laboratory. The results were discordant with respect to EPA classification; the analysis was performed assuming Category I classification.
[6]Performance calculated using the overall *in vitro* classification based on the majority and/or most severe classification among the four laboratories.
[7]Includes the data from Balls et al. (1995) using the overall *in vitro* classification based on the majority and/or most severe classification among the four laboratories.

2.3 EU Ocular Hazard Classification System

The five studies (Prinsen and Koëter [1993]; Balls et al. [1995]; Prinsen [1996]; Prinsen [2000]; Prinsen [2005]) contained ICE test method data on 175 substances, 154 of which had sufficient *in vivo* data to be assigned an ocular irritancy classification according the EU classification system (EU [2001])[5] (see **Appendix II-A**). Based on results from the *in vivo* rabbit eye test, 32[6] of the 154 substances were classified as severe irritants (i.e., R41) and the other 122 substances were classified as nonsevere irritants (either R36) or nonirritants. The 21 substances that could not be classified according to the EU classification system are so noted in **Appendix II-A**.

2.3.1 Prinsen and Koëter (1993)

All 21 substances tested in this study were included in an analysis of accuracy (**Table II-4**). Based on the available *in vivo* rabbit eye data or the EU ocular irritancy classification for each substance provided in the published study (individual rabbit eye test data was not available for all of the substances), the ICE test method has an accuracy of 95% (20/21), a sensitivity of 100% (7/7), a specificity of 93% (13/14), a false positive rate of 7% (1/14), and a false negative rate of 0% (0/7).

2.3.2 Balls et al. (1995)

Based on the available *in vivo* rabbit eye data, 50 of the 59 substances tested in this study could be assigned an EU classification (**Table II-4**). Nine substances lacked sufficient *in vivo* information on which to assign an EU classification (2001). For the 50 substances assigned an EU classification, the ICE test method has an accuracy of 72% (36/50), sensitivity of 53% (10/19), a specificity of 84% (26/31), a false positive rate of 16% (5/31), and a false negative rate of 47% (9/19).

2.3.3 Prinsen (1996)

Based on the *in vivo* rabbit eye data obtained subsequent to the original ICE test method analysis, 36 of the 44 substances tested in this study could be assigned an EU classification (**Table II-4**). Eight substances lacked sufficient *in vivo* information on which to assign an EU classification (2001). For the 36 substances that could be evaluated, the ICE test method has an accuracy of 97% (35/36), a sensitivity of 50% (1/2), a specificity of 100% (34/34), a false positive rate of 0% (0/34), and a false negative rate of 50% (1/2).

2.3.4 Prinsen (2000)

Subsequent to the original ICE test method accuracy analysis, data were submitted on four substances. The EU classifications were provided by the author for all four of these substances that were used for the accuracy analysis (**Table II-4**). For these substances, the

[5] For the purpose of this accuracy analysis, *in vivo* rabbit study results were used to identify R41 irritants (i.e., severe irritants); substances classified as R36 were defined as nonsevere irritants.

[6] One chemical (benzalkonium chloride, 1%) was tested *in vivo* twice in the same laboratory. The results were discordant with respect to EU classification. According to one test, the classification was R41, while results from the other test yielded an R36 classification. The accuracy analysis was performed with the substance classified as R41.

Table II-4. Evaluation of the Performance of the ICE Test Method In Predicting Ocular Corrosives and Severe Irritants Compared to the *In Vivo* Rabbit Eye Test Method, as Defined by the EU[1] Classification System, by Study and Overall

Data Source	N[2]	Accuracy		Sensitivity		Specificity		Positive Predictivity		Negative Predictivity		False Positive Rate		False Negative Rate	
		%	No.[3]	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Prinsen and Koëter (1993) (new)[4]	21/21	95	20/21	100	7/7	93	13/14	88	7/8	100	13/13	7	1/14	0	0/7
Prinsen and Koëter (1993) (old)[4]	21/21	100	21/21	100	8/8	100	13/13	100	8/8	100	13/13	0	0/13	0	0/8
Balls et al. (1995)[5,6] (new)	50/59	72	36/50	53	10/19	84	26/31	67	10/15	74	26/35	16	5/31	47	9/19
Balls et al. (1995)[5,6] (old)	59/59	73	43/59	57	12/21	82	31/38	63	12/19	78	31/40	18	7/38	43	9/21
Prinsen (1996) (new)	36/44	97	35/36	50	1/2	100	34/34	100	1/1	97	34/35	0	0/34	50	1/2
Prinsen (1996) (old)	44/44	96	42/44	100	6/6	95	36/38	75	6/8	100	36/36	5	2/38	0	0/6
Prinsen (2000) (new)	4/4	100	4/4	100	1/1	100	3/3	100	1/1	100	3/3	0	0/3	0	0/1
Prinsen (2005) (new)	46/50	89	41/46	0	0/4	98	41/42	0	0/1	91	41/45	2	1/42	100	4/4
Entire Data Set[6,7] (new)	154/175	87	134/154	59	19/32	94	115/122	73	19/26	90	115/128	6	7/122	41	13/32
Entire Data Set[6,7] (old)	121/121	85	103/121	70	26/37	92	77/84	79	26/33	88	77/88	8	7/84	30	11/37

[1]EU = European Union (EU [2001]).
[2]N = Number of substances included in this analysis/the total number of substances in the study.
[3]Data used to calculate the percentage.
[4]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on the previous analysis included in the draft ICE BRD.
[5]One chemical (benzalkonium chloride, 1%) was tested in vivo twice within the same laboratory. The results were discordant with respect to EU classification; the analysis was performed assuming Category 1 classification.
[6]Performance calculated using the overall *in vitro* classification based on the majority and/or most severe classification among the four laboratories.

[7]Includes the data from Balls et al. (1995) using the overall *in vitro* classification based on the majority and/or most severe classification among the four laboratories.

ICE test method has an accuracy (4/4), sensitivity (1/1), and specificity (3/3) of 100%, and false positive (0/3) and false negative (0/1) rates of 0%.

2.3.5 Prinsen (2005)

Subsequent to the original ICE test method accuracy analysis, data were submitted on 50 substances. Based on the available *in vivo* rabbit eye data provided in this submission, 46 of the 50 substances tested in this study could be assigned an EPA classification (**Table II-4**). The remaining four substances had inadequate *in vivo* data for assigning a classification according to the EU system. For the 46 substances that could be evaluated, the ICE test method has an accuracy of 89% (41/46), a sensitivity of 0% (0/4), a specificity of 98% (41/42), a false positive rate of 2% (1/42), and a false negative rate of 100% (4/4).

2.3.6 Entire Data Set

A total of 154 substances had sufficient *in vivo* data among the three studies to perform an accuracy analysis, based on the EU classification system (**Table II-4**). For these 154 substances, the ICE test method has an accuracy of 87% (134/154), a sensitivity of 59% (19/32), a specificity of 94% (115/122), a false positive rate of 6% (7/122), and a false negative rate of 41% (13/32).

2.4 Accuracy of the ICE Test Method for the GHS Ocular Hazard Classification System, by Chemical Class and Property of Interest – Reanalysis

In order to further evaluate discordant responses of the ICE test method relative to the *in vivo* hazard classification, several accuracy sub-analyses were performed. These included specific classes of chemicals with sufficiently robust numbers of substances ($n \geq 5$), as well as certain properties of interest considered relevant to ocular toxicity testing (e.g., pesticides, surfactants, pH, physical form). Because the international community will soon adopt the GHS classification system for hazard labeling (UN [2003]), and considering that there were only modest differences in overall ICE test method accuracy among the three regulatory classification systems (i.e., EPA, EU, GHS), these sub-analyses focused on the GHS system only. As indicated in **Table II-5**, there were some notable trends in the performance of the ICE test method among these subgroups of substances. The chemical class of substances that was most consistently overpredicted according the GHS classification system (i.e., were false positives) by the ICE test method is alcohols. Five out the nine overpredicted substances were alcohols. The remaining chemical classes represented among the overpredicted substances were alkalis (1), esters (1), ketones (1), and one unclassified coded substance. With regard to physical form of the substances overpredicted by the ICE test method, all nine were liquids.

There were no chemical classes that were prominently represented among the 15 substances that were underpredicted (i.e., were false negatives) by the ICE test method according to the GHS classification system (see **Appendix II-A**). Five of the 15 substances were unclassified coded substances, and three were carboxylic acids. No other chemical classes were represented more than twice. These included heterocycles (2), onium compounds (2), polycyclics (2), alcohols (1), amines/amidines (1), imides (1), inorganic chemicals (1), and polyethers (1). However, five of the 15 unpredicted substances were labeled as surfactants,

Table II-5. False Negative and False Positive Rates of the ICE Test Method, by Chemical Class and Properties of Interest, for the GHS[1] Classification System

Category	N[2]	False Positive Rate[3]		False Negative Rate[4]	
		%	No.[5]	%	No.
Overall	144	8	9/114	50	15/30
Chemical Class[6]					
Alcohol	12	50	5/10	50	1/2
Amine/Amidine	5	0	0/2	33	1/3
Carboxylic acid	10	0	0/3	43	3/7
Ester	9	13	1/8	0	0/1
Heterocycle	9	0	0/3	33	2/6
Onium compound	8	0	0/2	33	2/6
Properties of Interest					
Liquids	108	10	9/90	44	8/18
Solids	36	0	0/24	58	7/12
Pesticide	11	0	0/6	60	3/5
Surfactant – Total	21	0	0/12	56	5/9
-nonionic	4	0	0/3	100	1/1
-anionic	2	0	0/1	100	1/1
-cationic	7	0	0/1	33	2/6
pH – Total[7]	20	-	-	40	8/20
- acidic (pH < 7.0)	12	-	-	33	4/12
- basic (pH > 7.0)	8	-	-	50	4/8
Category 1 Subgroup[8]					
- Total	30	-	-	50	15/30
- 4 (CO=4 at any time)	13	-	-	39	5/13
- 3 (severity/persistence)	1	-	-	0	0/1
- 2 (severity)	6	-	-	50	3/6
- 2-4 combined[9]	*20*	-	-	*45*	*9/20*
- 1 (persistence)	10	-	-	70	7/10

[1]GHS =- Globally Harmonized System (UN [2003]).
[2]N = number of substances.
[3]False Negative Rate = the proportion of all positive substances that are falsely identified as negative *in vitro*;
[4]False Positive Rate = the proportion of all negative substances that are falsely identified as positive *in vitro*; n = number of substances.
[5]Data used to calculate the percentage.
[6]Chemical classes included in this table are represented by at least five substances tested in the ICE test method and assignments are based on the MeSH categories (www.nlm.nih.gov/mesh) as defined in **Appendix B**.
[7]Total number of GHS Category 1 substances for which pH information was obtained.
[8]NICEATM-defined subgroups assigned based on the lesions that drove classification of a GHS Category 1 substance. 1: based on lesions that are persistent; 2: based on lesions that are severe (not including CO=4); 3: based on lesions that are severe (not including CO=4) and persistent; 4: corneal opacity (CO) = 4 at any time.
[9]Subcategories 2 to 4 combined to allow for a direct comparison of GHS Category 1 substances classified *in vivo* based on some lesion severity component and those classified based on persistent lesions alone.

which included anionic (1), cationic (2), and nonionic (1) surfactants (the remaining substance was coded, but described as a surfactant). Another three of the underpredicted substances were labeled as pesticides. With regard to physical form of the substances tested, eight of the fifteen underpredicted substances were liquids while seven were solids. However, considering the proportion of the total database, solids (36/144; 25%) appear more likely than liquids (108/144; 75%) to be underpredicted by the ICE test method. Similarly, among the eight underpredicted substances for which pH information was available, four were acidic (pH < 7.0) and four were basic (pH > 7.0), although basic substances appear more likely to be underpredicted (8/20; 40% vs. 12/20; 60%), given their relative proportionality in the total database. Finally, the fifteen underpredicted substances were more likely to be substances classified *in vivo* based on persistent lesions, rather than on severe lesions, as evidenced by an analysis of NICEATM-defined GHS Category 1 sub-groupings (**Table II-5**).

2.5 Accuracy of the ICE Test Method for Identifying Ocular Corrosives and Severe Irritants – Summary of Reanalysis

As detailed in **Section II-1.0** of the ICE addendum, additional or new relevant ICE test method data was received after the Expert Panel meeting on January 11 and 12, 2005 that increased the size of the comparative ICE: *in vivo* rabbit eye test database from 92 to 144 substances for the GHS classification system (UN [2003]), 90 to 145 for the EPA classification system (EPA [1996]), and 121 to 154 for the EU classification system (EU [2001]). As can be seen in **Tables II-2** through **II-4**, the overall accuracy of the ICE test method changed from 82-85% (old) to 83-87% (reanalysis) depending on the classification system used), the false positive rate was reduced from 8-10% (old) to 6-8% (reanalysis), while the false negative rate was increased from 30-40% (old) to 41-50% (reanalysis).

Similar to the original analysis, the revised analysis indicated that alcohols are overpredicted (50% [5/10] false positive rate) in the ICE test method. Carboxylic acids were shown to have a false negative rate of 43% (3/7).

The total database for surfactants was increased from 13 to 21 substances. However, given the stability of the false negative rate (old analysis: 57% [4/7]; new analysis 56% [5/9]), these substances still appear to be underpredicted by the ICE test method. With the additional data, it was now possible to evaluate the accuracy of the ICE test method for pesticides. While the false positive rate for these substances was 0% (0/6), the false negative rate (60% [3/5]) suggests that these substances may be underpredicted by the ICE test method.

As noted in **Section II-2.4**, eight of the fifteen underpredicted substances were liquids while seven were solids. However, considering that the total number of solids (36) in the database is much smaller than the number of liquids (108), solids appear more likely to be underpredicted (58%) than liquids (44%) by the ICE test method. In comparison to the original analysis, the false negative rate of solid substances changed from 55% (6/11) to 58% (7/12). However, the false negative rate for liquids was increased in the revised analysis from 29% (4/14) to 44% (8/18).

Using the expanded database, an analysis was conducted of the ability of the ICE test method to identify ocular corrosives and severe irritants, depending on the nature of the *in vivo* ocular lesions (i.e., severity and/or persistence) responsible for classification of a substance as an ocular corrosive/severe irritant. As indicated in **Table II-5**, the fifteen underpredicted substances were more likely to be substances classified *in vivo* based on persistent lesions (false negative rate = 70% [7/10]), rather than on severe lesions (false negative rate = 45% [9/20]).

A new analysis not included originally was an evaluation of accuracy related to acidic or basic pH. Among the eight underpredicted substances for which pH information was available, four were acidic (pH < 7.0) and four were basic (pH > 7.0). Again, basic substances (8) occupy a smaller proportion of the total database than acidic substances (12), and were more often underpredicted (50% vs. 33%). However, it is noted that pH information was obtained for only 20 of the 30 total Category 1 substances.

Table II-6 provides a summary of the revised analysis of the overall performance of the ICE test method defined by the GHS classification system (UN [2003]). As noted from this analysis, the false positive substances were mild to moderate ocular irritants (i.e., GHS Category 2A or 2B). No nonirritating substances were classified as severe irritants. However, the mild irritants (Category 2B; n = 1/12) were less likely to be overpredicted as severe irritants/ocular corrosives than the moderate irritants (Category 2A, n = 8/23). The false negative substances were predominantly confined to those classified, based on ICE test results as Category 2A (n=4) or Category 2B (n=10), although one false negative substance was classified as a nonirritant.

Table II-6. Overall Accuracy of the ICE Test Method in the Predicting the Irritancy of a Substance as Defined by the GHS[1] Classification System

		***In Vitro* Classification**				
		1	**2A**	**2B**	**Nonirritant**	**TOTAL**
***In Vivo* Classification[2]**	**1**	***15***	***4***	***10***	***1***	**30**
	2A	***8***	9	4	2	**23**
	2B	***1***	2	8	1	**12**
	Nonirritant	***0***	6	22	51	**79**
	TOTAL	**24**	**21**	**44**	**55**	**144**

[1]GHS = Globally Harmonized System (UN [2003]).
[2]Twenty-seven substances included in **Appendix II-A** had insufficient data with which to assign a precise GHS classification and therefore were not included in this table.

Compared to the overall underprediction rate of the ICE test method (15/30; 50%), the undeprediction rate for pesticides is 60% (3/5), for surfactants is 56% (5/9), and for solids is

58% (7/12). Compared to the overall overprediction rate of the ICE test method (8%; 9/114), the overprediction rate of the ICE test method for alcohols is 50% (5/10).

3.0 RELIABILITY OF THE ICE TEST METHOD - REANALYSIS

An assessment of test method reliability (intralaboratory repeatability and intra- and inter-laboratory reproducibility) is an essential element of any evaluation of the performance of an alternative test method (ICCVAM [2003]). Repeatability refers to the closeness of agreement between test results obtained within a single laboratory when the procedure is performed on the same substance under identical conditions within a given time period (ICCVAM [1997, 2003]). Intralaboratory reproducibility refers to the determination of the extent to which qualified personnel within the same laboratory can replicate results using a specific test protocol at different times. Interlaboratory reproducibility refers to the determination of the extent to which different laboratories can replicate results using the same protocol and test chemicals, and indicates the extent to which a test method can be transferred successfully among laboratories. A reliability assessment includes reviewing the rationale for selecting the substances used to evaluate test method reliability, a discussion of the extent to which the substances tested represent the range of possible test outcomes, the properties of the various substances for which the test method is proposed for use, and a quantitative and/or qualitative analysis of repeatability and intra- and inter-laboratory reproducibility. In addition, measures of central tendency and variation are summarized for historical control data (negative, vehicle, positive), where applicable.

3.1 Substances Used to Re-evaluate the Reliability of the ICE Test Method

While intralaboratory repeatability and reproducibility were not originally evaluated due to a lack of appropriate data, subsequent to the original analysis, additional data were received for four substances (two surfactants and two siloxanes). This unpublished study (Prinsen [2000]) provided data from a single laboratory, which tested each of these substances in four to five separate experiments, and therefore allowed for such an evaluation. The only source of data for conducting an assessment of ICE test method interlaboratory reproducibility was Balls et al. (1995). This study evaluated the performance and reproducibility of the ICE test method using 60 substances (i.e., there were 52 different substances with four substances tested at two different concentrations and two substances tested at three different concentrations, for a total of 60 possible ocular irritation outcomes). One substance (thiourea) was tested *in vitro* in the ICE assay but, due to its excessive toxicity *in vivo*, was excluded from the comparison of *in vitro* and *in vivo* test results.

3.2 Reanalysis of ICE Test Method Intralaboratory Repeatability

Generally, analyses of intralaboratory repeatability have included approaches such as:

- a CV analysis, which is a statistical measure of the deviation of a variable from its mean (e.g., Holzhütter et al. [1996])
- ANOVA methods (e.g., Holzhütter et al. [1996]; ASTM [1999]).

Due to the lack of available ICE test data for replicate enucleated chicken eyes within individual experiments and for experiments conducted on the same substance under identical conditions, an evaluation of the intralaboratory repeatability of the ICE test method could not previously be conducted. As noted above, additional data were received for four substances from a single laboratory, which tested each of these substances in four to five separate experiments. Each experiment used three eyes. A CV analysis was performed on within-experiment ICE test method data, using scores for each of the test method endpoints (i.e., corneal thickness/swelling, corneal opacity, fluorescein retention) along with the ICE Irritation Index for each test substance (**Table II-7**). These CV values are not very informative given the nature of the data (0 means and standard deviations for some test substances, limited ranges of possible values for corneal opacity or fluorescein retention). However, the analysis of intralaboratory repeatability indicates that the corneal thickness measurement was generally repeatable when results were compared within experiments, as evidenced by the range of %CV values (0.9 to 6.1). The other endpoints evaluated produced somewhat more variable responses, most prominent with the nonirritating substance (SP-1). However, this could be an exaggeration of variability given the relatively small values that were produced from the nonirritating substance relative to the irritating and corrosive substances (i.e., corneal swelling values of 2, 0, and 3 yield a much higher % CV than values of 11, 14, and 18, but may not be indicative of truly increased variability). A similar discussion can also be applied to the variability among the qualitative endpoints (i.e., corneal opacity and fluorescein retention) given the small dynamic range of their scores (0-4 or 0-3, respectively).

3.3 Reanalysis of ICE Test Method Intralaboratory Reproducibility

Generally, analyses of intralaboratory reproducibilitity have included approaches such as:

- a CV analysis, which is a statistical measure of the deviation of a variable from its mean (e.g., Holzhütter et al. [1996])
- ANOVA methods (e.g., Holzhütter et al. [1996]; ASTM [1999]).

Due to the lack of available ICE test data for experiments conducted multiple times on the same substance in the same laboratory, an evaluation of ICE test method intralaboratory reproducibility could not previously be conducted. However, the data from Prinsen (2000) could also be used to perform a CV analysis on between-experiment values for each of the test method endpoints (i.e., corneal thickness/swelling, corneal opacity, fluorescein retention) along with the ICE Irritation Index for each test substance (**Table II-8**). Results similar to those obtained from an analysis of intralaboratory repeatability were obtained from this analysis. The corneal thickness measurement was again generally reproducible (%CV = 1.8 to 6.3), but the %CV values for the remaining endpoints had a much larger range (e.g., corneal swelling %CV = 13.9 to 138.7). However, if the nonirritating substance is removed, the range of %CV values is reduced (e.g., corneal swelling %CV = 13.9 to 22.4).

Table II-7. Intralaboratory Repeatability of ICE Test Method Endpoints – Prinsen (2000)

Substance (Experiment No.[1])	EU[2] Class[3]	CT[4] (mean[5])	CT (%CV[6])	CS[7] (mean)	CS (%CV)	CO[8] (mean)	CO (%CV)	FR[9] (mean)	FR (%CV)	Index[10] (mean)	Index (%CV)
SP-1 (1)[11]	NI	60	3.3	0.7	346.4	0.3	86.6	0.3	86.6	15	41.6
SP-1 (2)	NI	63.3	3.3	1.7	91.6	0.3	86.6	0.5	0	18.3	39.4
SP-1 (3)	NI	62.3	2.4	2.3	24.7	0.5	0	0	-	12.3	4.7
SP-1 (4)	NI	61.7	0.9	-1.3	-86.6	0	-	0	-	-1.3	-86.6
SP-1 (5)	NI	63.3	0.9	2	0	0	-	0	-	2	0
SP-4 (1)	R36	68.7	3.0	14.3	24.5	3	0	2	0	114.3	3.1
SP-4 (2)	R36	69.3	3.0	13.3	40.0	2	0	2	0	93.3	5.3
SP-4 (3)	R36	75.7	3.3	21	23.8	2.7	21.6	2	0	114.3	14.0
SP-4 (4)	R36	69.7	4.4	14	49.5	2.7	21.6	2	0	107.3	15.1
SP-5 (5)	R36	70	3.8	12.7	27.7	2	0	2	0	92.7	3.8
SU-4 (1)	R36	72	2.4	13.7	18.4	0.7	43.3	1	0	47	16.9
SU-4 (2)	R36	68.7	3.4	14	12.4	0.7	43.3	1	0	47.3	8.5
SU-4 (3)	R36	67.7	6.0	13	15.4	0.7	43.3	1	0	46.3	9.0
SU-4 (4)	R36	66.7	3.5	11	31.5	0.8	34.6	1	0	47.7	10.6
SU-4 (5)	R36	67.7	2.2	9.7	15.8	0.7	43.3	1	0	43	16.3
SU-5 (1)	R41	77.7	1.5	23	24.2	2	0	2	0	103	5.4
SU-5 (2)	R41	74.7	4.7	20.7	19.6	2	0	2	0	100.7	4.0
SU-5 (3)	R41	75.3	6.1	21	9.5	2	0	2	0	101	2.0
SU-5 (4)	R41	76.7	2.0	16.3	25.5	1.7	34.6	2	0	89.7	16.4

[1]No. = Number.
[2]EU = European Union (EU [2001]).
[3]Class. = Classification (EU [2001]).

[4]CT = Corneal thickness.
[5]Mean values calculated with scores from three eyes.
[6]%CV = % coefficient of variation.
[7]CS = Corneal swelling.
[8]CO = Corneal opacity.
[9]FR = fluorescein retention.
[10]Index = ICE Irritation Index (= CS x [CO x 20] + FR x 20]); No. = number.
[11]*In vivo* animal data were not provided for these substances, and therefore the EU classification that was provided by testing laboratory is presented here.

Table II-8. Intralaboratory Reproducibility of ICE Test Method Endpoints – Prinsen (2000)

Substance (Experimental Replicates)	EU[1] Class[2]	CT[3] (mean[4])	CT (%CV[5])	CS[6] (mean)	CS (%CV)	CO[7] (mean)	CO (%CV)	FR[8] (mean)	FR (%CV)	Index[9] (mean)	Index (%CV)
SP-1 (5)[10]	NI	62.1	2.2	1.1	138.7	0.2	95.8	0.2	141.4	9.3	91.8
SP-4 (5)	R36	70.7	4.0	15.1	22.4	2.5	18.1	2	0	104.4	10.3
SU-4 (5)	R36	70.5	6.3	12.3	15.2	0.7	10.6	1	0	46.3	4.1
SU-5 (4)	R41	76.1	1.8	20.2	13.9	1.9	8.7	2	0	98.6	6.1

[1]EU = European Union (EU [2001]).
[2]Class. = Classification (EU [2001]).
[3]CT = Corneal thickness.
[4]Mean values calculated with scores from three eyes.
[5]%CV = % coefficient of variation.
[6]CS = Corneal swelling.
[7]CO = Corneal opacity.
[8]FR = fluorescein retention.
[9]Index = ICE Irritation Index (= CS x [CO x 20] + FR x 20]); No. = number.
[10]*In vivo* animal data were not provided for these substances, and therefore the EU classification that was provided by testing laboratory is presented here.

3.4 Reanalysis of ICE Test Method Interlaboratory Reproducibility

Generally, analyses of interlaboratory variability have included approaches such as:

- the extent of concordance among laboratories in assigning the same regulatory classification for a particular substance (e.g., Holzhütter et al. [1996])
- a CV analysis, which is a statistical measure of the deviation of a variable from its mean (e.g., Holzhütter et al. [1996])
- ANOVA methods (e.g., Holzhütter et al. [1996]; ASTM [1999])
- bivariant scatter diagrams/correlation analyses for pairs of laboratories to assess the extent possibility of divergence (e.g., Holzhütter et al. [1996])

In the EC/HO study reported by Balls et al. (1995), ICE test data for an assessment of interlaboratory reproducibility was provided for four laboratories. While the draft BRD contained the same analysis as detailed below, new information regarding *in vivo* classification of substances according to the three regulatory classification schemes was provided, which resulted in changes to the classification of some substances. Therefore, a revised analysis was conducted to reflect the updated classifications. As previously stated in the draft ICE BRD, 19 of the 59 substances tested in this study were assigned an overall *in vitro* classification of corrosive/severe irritant and 40 substances were assigned an overall classification of nonsevere irritant (i.e., irritants other than severe or nonirritant). For an assessment of interlaboratory reproducibility, substances classified as corrosive/severe irritants or nonsevere irritants/nonirritants were further classified within the GHS, EPA, and EU classification schemes (EPA [1996]; EU [2001]; UN [2003]) by their *in vivo* rabbit eye test results. Because the focus of this assessment is on the interlaboratory reproducibility of the ICE test method in identifying corrosives/severe irritants versus nonsevere irritants/nonirritants, considerable variability could exist among laboratories in their classification of substances as nonsevere irritants or nonirritants (e.g., three laboratories could classify a substance as a nonirritant and one laboratory could classify the same substance as a moderate irritant; for the purpose of the analysis, this would be considered 100% agreement between laboratories).

3.4.1 Qualitative Reanalysis of Interlaboratory Reproducibility

3.4.1.1 *GHS Ocular Hazard Classification System*

The four participating laboratories were in 100% agreement in regard to the ocular irritancy classification (corrosive/severe irritant or nonsevere irritant/nonirritant) of 44 (75%) of the 59 substances tested. As shown in **Table II-9:**

- All four participating laboratories agreed on the classification of seven (64%) of the 11 substances that were GHS corrosives/severe irritants[7]. Three of the four laboratories were in agreement for the three (27%) substances with discordant *in vitro* classification results among the four participating

[7] The overall *in vitro* classification for each substance was determined based on the most frequent individual laboratory classification, or in the case of an even number of discordant responses, the most severe classification. For one chemical (trichloroacetic acid, 30%), scores for fluorescein retention and corneal swelling were not provided from one laboratory. Therefore, this chemical was classified based on the results from only three laboratories.

laboratories for three substances (5% benzalkonium chloride, cyclohexanol, promethazine HCl). The discordant laboratory was never the same for these three substances. In addition, two of the four laboratories were in agreement for one (9%) substance (dibenzoyl-L-tartaric acid).

- Nine (82%) of the 11 substances classified according to the GHS based on *in vivo* rabbit eye data as corrosives/severe irritants were incorrectly classified by the four participating laboratories as nonsevere irritants (i.e., Category 2A and 2B irritants) or nonirritants. Of the two substances (18%) with discordant *in vitro* classification results among the four laboratories, three of the four laboratories were in agreement for both substances (10% cetylpyridinium bromide, 2,5-dimethylhexanediol). The discordant laboratory for these two substances was not the same laboratory.
- One (17%) of the six substances (isobutanol) classified according to the GHS based on *in vivo* rabbit eye data as a nonsevere irritant/nonirritant was incorrectly classified by the four laboratories as a corrosive/severe irritant. Of the five substances (83%) with discordant *in vitro* classification results among the four laboratories, two of the four laboratories were in agreement for all five substances (ethanol, n-hexanol, isopropanol, methyl acetate, methyl ethyl ketone). The discordant laboratories for these five substances were not consistently the same two laboratories.
- All four laboratories agreed on the classification of 22 (85%) of the 26 substances classified as GHS nonsevere irritants/nonirritants (UN [2003]). Three of the four laboratories were in agreement for the four substances (15%) with discordant classification results (n-butyl acetate, 4-carboxybenzaldehyde, dibenzyl phosphate, methyl isobutyl ketone). The discordant laboratory for three of these four substances was always the same laboratory.
- Due to the lack of appropriate *in vivo* data (e.g., studies were terminated too early to assess reversibility of effects), five (8%) of the 59 test substances could not be classified according to the GHS classification scheme (UN [2003]). Among these five substances, all four laboratories were in agreement with the classification of three substances as nonsevere irritants/nonirritants and two substances as corrosive/severe irritants.

Table II-9. Interlaboratory Variability of Balls et al. (1995) for Substances Classified as Ocular Corrosives/Severe Irritants or Nonsevere Irritants/Nonirritants Using the GHS[1] Classification System

Classification (*in vivo*/ *in vitro*)[2]	Data Set	Number of Substances	Number of Testing Labs[3]	Substances with 100% Agreement Among Labs	Substances with 75% Agreement Among Labs	Substances with 50% Agreement Among Labs
+/+	New[4]	11	4[3]	7 (64%)	3 (27%)	1 (9%)
	Old[4]	12	4[3]	8 (67%)	3 (25%)	1 (8%)
+/-	New	11	4	9 (82%)	2 (18%)	0 (0%)
	Old	10	4	8 (80%)	2 (20%)	0 (0%)
-/+	New	6	4	1 (17%)	0 (0%)	5 (83%)
	Old	6	4	1 (17%)	0 (0%)	5 (82%)
-/-	New	26	4	22 (85%)	4 (15%)	0 (0%)
	Old	28	4	24 (86%)	4 (14%)	0 (0%)
?/-	New	3	4	3 (100%)	0 (0%)	0 (0%)
	Old	2	4	2 (100%)	0 (0%)	0 (0%)
?/+	New	2	4	2 (100%)	0 (0%)	0 (0%)
	Old	1	4	1 (100%)	0 (0%)	0 (0%)
TOTAL	New	59	4[3]	44 (75%)	9 (15%)	6 (10%)
	Old	59	4[3]	44 (75%)	9 (15%)	6 (10%)

[1]GHS = Globally Harmonized System (UN [2003]).

[2]A "+" indicates that the substance was assigned an overall classification of corrosive or a severe irritant (Category 1); a "-" indicates that the substance was assigned an overall classification of nonsevere irritant (Category 2A, 2B) or nonirritant; a "?" indicates that, due to the lack of appropriate *in vivo* data (e.g., studies were terminated too early to assess reversibility of effects), a GHS classification could not be made. See **Section II-2.0** for a description of the rules followed to classify the ocular irritancy of test substances tested multiple times *in vitro*.

[3]Scores for fluorescein retention and corneal swelling were not provided from one laboratory for one substance (trichloroacetic acid, 30%), and therefore this substance was classified based on results from only three laboratories.

[4]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on the previous analysis included in the draft ICE BRD.

3.4.1.2 *EPA Ocular Hazard Classification System*

The four participating laboratories were in 100% agreement for the ocular irritancy classification (corrosive/severe irritant or nonsevere irritant/nonirritant) of 44 (75%) of the 59 substances tested. As shown in **Table II-10:**

- All four participating laboratories agreed on the classification of seven (70%) of the 10 substances that were EPA corrosives/severe irritants[8]. Three of the four laboratories were in agreement for the three (30%) substances with

[8] As described in **Section II-2.0**, the overall *in vitro* classification for each substance was determined based on the most frequent individual laboratory classification, or in the case of an even number of discordant responses, the most severe classification. For one chemical (trichloroacetic acid, 30%), scores for fluorescein retention and corneal swelling were not provided from one laboratory. Therefore, this chemical was classified based on the results from only three laboratories.

discordant *in vitro* classification results among the four participating laboratories (benzalkonium chloride, 5%, cyclohexanol, promethazine HCl). The discordant laboratory was never the same for these three substances.

- Seven (78%) of the nine substances classified according to the EPA based on *in vivo* rabbit eye data as corrosives/severe irritants were incorrectly classified by the four participating laboratories as nonsevere irritants/nonirritants. Of the two substances (22%) with discordant *in vitro* classification results among the four participating laboratories, both substances (10% cetylpyridinium bromide, 2,5-dimethylhexanediol) were incorrectly classified by three of the four laboratories. The discordant laboratory for these two substances was not the same laboratory.
- One (17%) of the six substances (isobutanol) classified according to the EPA based on *in vivo* rabbit eye data as a nonsevere irritant/nonirritant was incorrectly classified by the four participating laboratories as a corrosive/severe irritant. Of the five substances (83%) with discordant *in vitro* classification results among the four participating laboratories, all five substances (ethanol, n-hexanol, isopropanol, methyl acetate, methyl ethyl ketone) were incorrectly classified by two of the four laboratories. The discordant laboratories for these five substances were not consistently the same two laboratories.
- All four laboratories agreed on the classification of 24 (86%) of the 28 substances that were EPA nonsevere irritants/nonirritants. Three of the four laboratories were in agreement for the four substances (14%) with discordant classification results (n-butyl acetate, 4-carboxybenzaldehyde, dibenzyl phosphate, methyl isobutyl ketone). The discordant laboratory for three of these four substances was always the same laboratory.
- Due to the lack of appropriate *in vivo* data (e.g., studies were terminated too early to assess reversibility of effects), six (10%) of the 59 test substances could not be classified according to the EPA classification scheme. Among these six substances, three substances were classified as nonsevere irritants/nonirritants by all four laboratories. In addition, two substances were classified as a corrosive/severe irritant by all four laboratories and one substance was classified as a corrosive/severe irritant by two of the four laboratories.

Table II-10. Interlaboratory Variability of Balls et al. (1995) for Substances Classified as Ocular Corrosives/Severe Irritants or Nonsevere Irritants/Nonirritants Using the EPA[1] Classification System

Classification (*in vivo*/ *in vitro*)[2]	Data Set	Number of Substances	Number of Testing Labs[3]	Substances with 100% Agreement Among Labs	Substances with 75% Agreement Among Labs	Substances with 50% Agreement Among Labs
+/+	New[4]	10	4[3]	7 (70%)	3 (30%)	0 (0%)
	Old[4]	11	4[3]	8 (73%)	3 (27%)	0 (0%)
+/-	New	9	4	7 (78%)	2 (22%)	0 (0%)
	Old	9	4	7 (78%)	2 (22%)	0 (0%)
-/+	New	6	4	1 (17%)	0 (0%)	5 (83%)
	Old	6	4	1 (17%)	0 (0%)	5 (83%)
-/-	New	28	4	24 (86%)	4 (14%)	0 (0%)
	Old	28	4	24 (86%)	4 (14%)	0 (0%)
?/-	New	3	4	3 (100%)	0 (0%)	0 (0%)
	Old	3	4	3 (100%)	0 (0%)	0 (0%)
?/+	New	3	4	2 (67%)	0 (0%)	1 (33%)
	Old	2	4	1 (50%)	0 (0%)	1 (50%)
TOTAL	New	59	4[3]	44 (75%)	9 (15%)	6 (10%)
	Old[2]	59	4[3]	44 (75%)	9 (15%)	6 (10%)

[1]EPA = U.S. Environmental Protection Agency (EPA [1996]).
[2]A "+" indicates that the substance was assigned an overall classification of corrosive or a severe irritant (Category I); a "-" indicates that the substance was assigned an overall classification of nonsevere irritant (Category II, III) or nonirritant (category IV); a "?" indicates that, due to the lack of appropriate *in vivo* data (e.g., studies were terminated too early to assess reversibility of effects), an EPA classification could not be made. See **Section II-2.0** for a description of the rules followed to classify the ocular irritancy of test substances tested multiple times *in vitro*.
[3]Scores for fluorescein retention and corneal swelling were not provided from one laboratory for one substance (trichloroacetic acid, 30%), and therefore this substance was classified based on results from only three laboratories.
[4]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on the previous analysis included in the draft ICE BRD.

3.4.1.3 *EU Ocular Hazard Classification System*

The participating laboratories were in 100% agreement in regard to the ocular irritancy classification (corrosive/severe irritant or nonsevere irritant/nonirritant) of 45 (76%) of the 59 substances tested. As shown in **Table II-11**:

- All four participating laboratories agreed on the classification of six (60%) of the 10 substances that were EU (2001) corrosives/severe irritants[9]. Three of

[9] As described in **Section II-2.0**, the overall *in vitro* classification for each substance was determined based on the most frequent individual laboratory classification, or in the case of an even number of discordant responses, the most severe classification. For one chemical (trichloroacetic acid, 30%), scores for fluorescein retention and corneal swelling were not provided from one laboratory. Therefore, this chemical was classified based on the results from only three laboratories.

the four laboratories were in agreement for the three (30%) substances with discordant *in vitro* classification results among the four participating laboratories (5% benzalkonium chloride, cyclohexanol, promethazine HCl). The discordant laboratory was never the same for these three substances. In addition, one (10%) substance (dibenzoyl-L-tartaric acid) was correctly classified by two of the four laboratories.

- Seven (78%) of the nine substances classified according to the EU (2001) based on *in vivo* rabbit eye data as corrosives/severe irritants were incorrectly classified by the four participating laboratories as nonsevere irritants/nonirritants. Of the two substances (22%) with discordant *in vitro* classification results among the four participating laboratories, both substances (10% cetylpyridinium bromide, 2,5-dimethylhexanediol) were incorrectly classified by three of the four laboratories. The discordant laboratory for these two substances was not the same laboratory.
- One (20%) of the five substances classified according to the EU (2001) based on *in vivo* rabbit eye data as a nonsevere irritant/nonirritant was incorrectly classified by the four participating laboratories as a corrosive/severe irritant. Of the four substances (80%) with discordant *in vitro* classification results among the four participating laboratories, all four substances (ethanol, n-hexanol, methyl acetate, methyl ethyl ketone) were incorrectly classified by two of the four laboratories. The discordant laboratories for these five substances were not consistently the same two laboratories.
- All four laboratories agreed on the classification of 23 (88%) of the 26 substances classified as EU (2001) nonsevere irritants/nonirritants the four participating laboratories. Three of the four laboratories were in agreement for the three substances (12%) with discordant classification results (n-butyl acetate, 4-carboxybenzaldehyde, methyl isobutyl ketone). The discordant laboratory for these three substances was always the same laboratory.

3.4.2 Quantitative Reanalysis of Interlaboratory Reproducibility

As detailed in the draft BRD, to provide a quantitative assessment of interlaboratory variability, individual laboratory ICE test results were used to calculate a mean, standard deviation, and the %CV for corneal opacity, fluorescein retention, corneal swelling, and the irritation index for each of the 59 substances tested in the Balls et al. (1995) study. Mean and median %CV values were calculated to provide an assessment of overall variability. This analysis was not affected by the information received subsequent to the release of the draft BRD on November 1, 2004, and therefore is not presented here.

3.4.3 Additional Reanalyses of Interlaboratory Reproducibility

The draft BRD also contains a description of the analysis performed by Balls et al. (1995) in which they determined the interlaboratory correlation between ICE test method endpoint data generated by each laboratory for all substances tested, as well as for subsets of test substances (water-soluble, water-insoluble, surfactants, solids, solutions, and liquids). This analysis was not affected by the information received subsequent to the release of the draft BRD on November 1, 2004, and therefore is not presented here.

Table II-11. Interlaboratory Variability of Balls et al. (1995) for Substances Classified as Ocular Corrosives/Severe Irritants or Nonsevere Irritants/Nonirritants Using the EU[1] Classification System

Classification (*in vivo*/ *in vitro*)[2]	Data Set	Number of Substances	Number of Testing Labs[3]	Substances with 100% Agreement Among Labs	Substances with 75% Agreement Among Labs	Substances with 50% Agreement Among Labs
+/+	New[4]	10	4[3]	6 (60%)	3 (30%)	1 (10%)
	Old[4]	12	4[3]	9 (67%)	3 (25%)	1 (8%)
+/-	New	9	4	7 (78%)	2 (22%)	0 (0%)
	Old	9	4	7 (78%)	2 (22%)	0 (0%)
-/+	New	5	4	1 (20%)	0 (0%)	4 (80%)
	Old	7	4	2 (29%)	0 (0%)	5 (71%)
-/-	New	26	4	23 (88%)	3 (12%)	0 (0%)
	Old	31	4	28 (90%)	3 (10%)	0 (0%)
?/-	New	5	4	5 (100%)	0 (0%)	0 (0%)
	Old	0	4	0 (0%)	0 (0%)	0 (0%)
?/+	New	4	4	3 (75%)	0 (0%)	1 (25%)
	Old	0	4	0 (0%)	0 (0%)	0 (0%)
TOTAL	New	59	4[3]	45 (76%)	8 (14%)	6 (10%)
	Old	59	4[3]	45 (76%)	8 (14%)	6 (10%)

[1]EU = European Union (EU [2001]).
[2]A "+" indicates that the substance was assigned an overall classification of corrosive or severe irritant (Category R41); a "-" indicates that the substance was assigned an overall classification of nonsevere irritant (Category R36) or nonirritant; a "?" indicates that, due to the lack of appropriate *in vivo* data, an EU classification could not be made. See **Section II-2.0** for a description of the rules followed to classify the ocular irritancy of test substances tested multiple times *in vitro*.
[3]Scores for fluorescein retention and corneal swelling were not provided from one laboratory for one substance (trichloroacetic acid, 30%), and therefore this substance was classified based on results from only three laboratories.
[4]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on the previous analysis included in the draft ICE BRD.

3.5 ICE Test Method Historical Positive and Negative Control Data - Reanalysis

Concurrent positive control substances have not been employed in the ICE test method, and therefore, an evaluation of historical positive control data is not possible. One eye is traditionally included in each study as a negative/vehicle controls (isotonic saline). However, irritancy data for this control eye were not available for inclusion in the original analysis. Subsequent to the original analysis, individual eye data were obtained from negative control eyes that could be used to perform a CV analysis on between-experiment values for each of the test method endpoints (i.e., corneal thickness/swelling, corneal opacity, fluorescein retention) along with the ICE Irritation Index for each test substance (**Table II-12**). This analysis revealed that responses in the negative control eye remain relatively consistent.

Table II-12. Intralaboratory Reproducibility of ICE Test Method Endpoints – Negative Control (Isotonic Saline) Data

Substance (Experiment No.[1])	Max[2] Corneal Thickness	Max Corneal Swelling (%)	Max Corneal Opacity	Max Fluorescein Retention	Irritation Index[3]
Negative Control[4] (1)	63	0	0	0	0
Negative Control (2)	61	-2	0	0	-2
Negative Control (3)	63	-2	0	0	-2
Negative Control (4)	60	0	0	0	0
Negative Control (5)	62	0	0	0	0
Negative Control (6)	61	-2	0	0	-2
Negative Control (7)	62	0	0	0	0
Negative Control (8)	65	0	0	0	0
Negative Control (9)	62	-2	0	0	-2
Negative Control (10)	62	0	0	0	0
Negative Control (11)	64	2	0	0	2
Negative Control (12)	61	0	0	0	0
Negative Control (13)	64	0	0	0	0
Negative Control (14)	64	0	0	0	0
Negative Control (15)	67	2	0	0	2
Negative Control (16)	60	2	0	0	2
Mean	62.6	-0.1	0	0	-0.1
SD[5]	1.9	1.4	0	0	1.4
%CV[6]	3.0	-1088.1	-	-	-1088.1

[1]No. = Number.
[2]Max = Maximum.
[3]Index = ICE Irritation Index (= CS x [CO x 20] + FR x 20]).
[4]Isotonic saline.
[5]SD = Standard deviation.
[6]CV = coefficient of variation (%CV = [standard deviation/mean] x 100); FR = fluorescein retention

3.6 Reliability of the ICE Test Method for Identifying Ocular Corrosives and Severe Irritants – Summary of Reanalysis

Previously, an evaluation of the intralaboratory repeatability and reproducibility of the ICE test method could not be conducted. However, subsequent to the original reliability analysis

(see draft ICE BRD, November 1, 2004), replicate data received allowed for a quantitative analysis of intralaboratory repeatability and reproducibility of ICE test method endpoints.

The range of %CV values for the corneal thickness measurement, when results were compared within experiments, was from 0.9 to 6.1. The other endpoints evaluated produced ranges of %CV values that were larger, with variability most prominent with the nonirritating substance (SP-1). However, this could be an exaggeration of variability given the relatively small values that were produced from the nonirritating substance relative to the irritating and corrosive substances (i.e., corneal swelling values of 2, 0, and 3 yield a higher % CV than values of 11, 14, and 18). A similar discussion can also be applied to the variability among the qualitative endpoints (i.e., corneal opacity and fluorescein retention) given the small dynamic range of their scores (0-4 or 0-3, respectively).

The range of %CV values for the corneal thickness measurement, when results were compared across labs, was from 1.8 to 6.3. The %CV values for the remaining endpoints had a larger range (e.g., corneal swelling %CV = 13.9 to 138.7). However, if the nonirritating substance is removed, the range of %CV values is reduced (e.g., corneal swelling %CV = 13.9 to 22.4).

The previous analysis also included an evaluation of interlaboratory reproducibility using both qualitative and quantitative approaches. While the quantitative analysis was unaffected by the new information that was received, the qualitative analysis (correct classification as an ocular corrosive/severe irritant or as a non-corrosive/non-severe irritant) of the individual laboratory test results obtained for the EC/HO validation study (Balls et al., [1995]) mandated that this analysis be repeated. However, the results obtained in the revised analysis were not different from the original analysis (see **Tables II-9** to **II-11**).

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APPENDIX II-A

SUBSTANCES USED IN THE ICE TEST METHOD REANALYSIS

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Substances Used in the ICE Test Method Reanalysis

Substance	CASRN[1]	Concentration Tested	Chemical Class	Product Class	pH	Form Tested	Water Solubility[2]	*In Vitro* Classification (GHS)[3,4]	*In Vivo* Classification (GHS)[4]	Category 1 Subclass[5]	*In Vitro* Classification (EPA)[6,7]	*In Vivo* Classification (EPA)[7]	*In Vitro* Classification (EU)[8,9]	*In Vivo* Classification (EU)[9]	Reference
Acetone	67-64-1	100%	Ketone	Solvent; Antiseptic; Chemical intermediate; Raw material		liquid	S	2A	2A		II	II	R36	R36	Balls et al. (1995)
Ammonium nitrate	6484-52-2	100%	Inorganic salt, Onium compound	Fertilizer; Chemical intermediate; Industrial explosive		solid	S	2B	2B		III	III	NI	R36	Balls et al. (1995)
L-Aspartic acid	70-47-3	100%	Amino acid	Organic intermediate; Fungicides; Germicides		solid	S	2A	SCNM[10]		II	SCNM	R36	SCNM	Balls et al. (1995)
Benzalkonium chloride (1%)	8001-54-5	1%	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative		liquid	S	2A	1	1	II	I	R36	R41	Balls et al. (1995)
Benzalkonium chloride (10%)	8001-54-5	10%	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	3.10	liquid	S	1	1	4	I	I	R41	R41	Balls et al. (1995)
Benzalkonium chloride (5%)	8001-54-5	5%	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	3.23	liquid	S	1	1	2	I	I	R41	R41	Balls et al. (1995)
n-Butyl acetate	123-86-4	100%	Ester	Solvent; Synthetic flavor ingredient		liquid	I *	2A	NI		II	III	R36	NI	Balls et al. (1995)
Gammabutyrolactone	96-48-0	100%	Heterocyclic, Lactone	Synthetic intermediate; Solvent		liquid	S	2A	2A		II	II	R36	R36	Balls et al. (1995)
Captan 90 concentrate	133-06-2	100%	Imide, Organic sulfur compound	Pesticide	7.95	solid	S	2B	1	4	III	I	NI	R41	Balls et al. (1995)
4-Carboxybenzaldehyde	619-66-9	100%	Carboxylic acid, Aldehyde	Manufacturing impurity (polyester); Developer intermediate		solid	I*	NI	2A		IV	II	NI	R36	Balls et al. (1995)
Cetylpyridinium bromide (0.1%)	140-72-7	0.1%	Heterocyclic, Onium compound	Surfactant (cationic), Germicide, Laboratory reagent		liquid	Sf	2B	NI		III	III	NI	NI	Balls et al. (1995)
Cetylpyridinium bromide (10%)	140-72-7	10%	Heterocyclic, Onium compound	Surfactant (cationic), Germicide, Laboratory reagent	4.81	liquid	Sf	2A	1	4	II	I	R36	R41	Balls et al. (1995)
Chlorhexidine	55-56-1	100%	Amine/Amidine	Disinfectant; Mouthwash; Anti-infective agent	10.12	solid	I*	1	1	4	I	SCNM	R41	SCNM	Balls et al. (1995)
Cyclohexanol	108-93-0	100%	Alcohol	Solvent; Chemical intermediate	4.54	liquid	S	1	1	2	I	I	R41	R41	Balls et al. (1995)
Dibenzoyl-L-tartaric acid	2743-38-6	100%	Carboxylic acid, Ester	Optical resolution agent	2.39	solid	I	1	1	2	I	SCNM	R41	R41	Balls et al. (1995)
Dibenzyl phosphate	1623-08-1	100%	Ester, Organophosphorus compound	Not classified		solid	I*	2A/2B	2A		II/III	II	R36	R36	Balls et al. (1995)
2,6-Dichlorobenzoyl chloride	4659-45-4	100%	Acyl halide	Anti-infective; Anti-fungal; Preservative		liquid	I*	2A	2A		II	II	R36	SCNM	Balls et al. (1995)
2,2-Dimethylbutanoic acid	595-37-9	100%	Carboxylic acid	Pharmaceutical metabolite		liquid	I	1	SCNM		I	I	R41	SCNM	Balls et al. (1995)
2,5-Dimethylohexanediol	110-03-2	100%	Alcohol	Intermediate for pharmaceticals, pesticides, perfumes	5.72	solid	I	2B	1	1	III	I	R36	R41	Balls et al. (1995)
Ethanol	64-17-5	100%	Alcohol	Solvent; Beverages; Antifreeze agent		liquid	S	1	2A		I	III	R41	NI	Balls et al. (1995)
Ethyl acetate	141-78-6	100%	Ester	Solvent; Synthetic flavoring		liquid	S	2A	NI		II	III	R36	NI	Balls et al. (1995)
2-Ethyl-1-hexanol	104-76-7	100%	Alcohol	Solvent; Plasticizer		liquid	S	2A	2A		II	II	R36	R36	Balls et al. (1995)
Ethyl-2-methylacetoacetate	609-14-3	100%	Ketone, Ester	Not classified		liquid	S*	2B	2B		III	III	NI	NI	Balls et al. (1995)
Ethyl trimethyl acetate	3938-95-2	100%	Ester	Solvent		liquid	I*	2B	NI		III	III	NI	NI	Balls et al. (1995)
Fomesafen	72128-02-0	100%	Imide, Ether, Nitro compound	Pesticide		solid	S	2B	NI		III	III	NI	NI	Balls et al. (1995)
Glycerol	56-81-5	100%	Alcohol	Solvent; Plasticizer; Lubricant; Emollient; Drug vehicle		liquid	S	2B	NI		III	IV	NI	NI	Balls et al. (1995)
n-Hexanol	111-27-3	100%	Alcohol	Solvent; Chemical intermediate; Synthetic flavor ingredient		liquid	I*	1	2A		I	II	R41	R36	Balls et al. (1995)
Imidazole	288-32-4	100%	Heterocyclic	Anti-fungal; Enzyme inhibitor	10.32	solid	S	1	1	4	I	I	R41	R41	Balls et al. (1995)
Isobutanol	78-83-1	100%	Alcohol	Solvent; Chemical intermediate; Flavor ingredient		liquid	I*	1	2A		I	II	R41	R36	Balls et al. (1995)
Isopropanol	67-63-0	100%	Alcohol	Solvent; Aerosol formulations (ingredient)		liquid	S	1	2A		I	III	R41	SCNM	Balls et al. (1995)
Maneb	12427-38-2	100%	Amine/Amidine, Organic salt, Urea compound	Pesticide		solid	S	NI	SCNM		IV	III	NI	SCNM	Balls et al. (1995)
Methyl acetate	79-20-9	100%	Ester	Solvent; Chemical intermediate; Synthetic flavor ingredient		liquid	S	1	2A		I	II	R41	R36	Balls et al. (1995)

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Methyl cyanoacetate	105-34-0	100%	Ester, Nitrile compound	Adhesive; Pharmaceutical intermediate		liquid	S*	NI	2A		IV	II	NI	R36	Balls et al. (1995)
Methylcyclopentane	96-37-7	100%	Hydrocarbon (cyclic)	Solvent		liquid	I*	NI	NI		IV	III	NI	NI	Balls et al. (1995)
Methyl ethyl ketone	78-93-3	100%	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals		liquid	S	1	2A		I	III	R41	R36	Balls et al. (1995)
Methyl isobutyl ketone	108-10-1	100%	Ketone	Solvent; Synthetic flavor; Drycleaning		liquid	I*	2A	NI		II	III	R36	NI	Balls et al. (1995)
1-Napthaleneacetic acid	86-87-3	100%	Carboxylic acid, Polycyclic compound	Pesticide	3.34	solid	I*	2B	1	NC	III	I	R36	SCNM	Balls et al. (1995)
1-Napthaleneacetic acid, sodium salt	61-31-4	100%	Carboxylic acid (salt), Polycyclic compound	Pesticide		solid	S*	1	1	1	I	I	R41	R41	Balls et al. (1995)
n-Octanol	111-87-5	100%	Alcohol	Solvent; Fragrance		liquid	I*	2A	2B		II	II	R36	R36	Balls et al. (1995)
Parafluoroaniline	371-40-4	100%	Amine/Amidine	Intermediate for herbicides; Dyes		liquid	I	1	SCNM		I	SCNM	R41	SCNM	Balls et al. (1995)
Polyethylene glycol 400	25322-68-3	100%	Alcohol, Polyether	Surfactant (nonionic), Lubricant, Plasticizer, Solvent		liquid	S	2B	NI		III	IV	R36	NI	Balls et al. (1995)
Potassium cyanate	590-28-3	100%	Inorganic salt	Herbicide; Pharmaceutical intermdiate		solid	S	2B	SCNM		III	SCNM	R36	SCNM	Balls et al. (1995)
Promethazine HCl	58-33-3	100%	Amine/Amidine, Heterocyclic, Organic sulfur compound	Antihistamine; Anti-nausea drug	4.50	solid	S*	1	1	3	I	I	R41	R41	Balls et al. (1995)
Pyridine	110-86-1	100%	Heterocyclic	Solvent; Intermediate for pharmaceuticals, dyes, pesticides	9.85	liquid	S	1	1	4	I	I	R41	R41	Balls et al. (1995)
Quinacrine	69-05-6	100%	Amine/Amidine, Heterocyclic, Polycyclic compound	Anti-infective (anti-helmentic)	3.77	solid	S*	2B	1	3	III	I	NI	R41	Balls et al. (1995)
Sodium hydroxide (1%)	1310-73-2	1%	Alkali	Caustic agent		liquid	S	2A	2B		II	III	R36	R36	Balls et al. (1995)
Sodium hydroxide (10%)	1310-73-2	10%	Alkali	Caustic agent	12.66	liquid	S	1	1	4	I	I	R41	R41	Balls et al. (1995)
Sodium lauryl sulfate (15%)	151-21-3	15%	Carboxylic acid (salt)	Surfactant (anionic), Detergent		liquid	Sf	2B	1	NC	III	I	R36	R36	Balls et al. (1995)
Sodium lauryl sulfate (3%)	151-21-3	3%	Carboxylic acid (salt)	Surfactant (anionic), Detergent	6.57	liquid	Sf	2B	NI		III	III	NI	NI	Balls et al. (1995)
Sodium oxalate	62-76-0	100%	Carboxylic acid (salt)	Textile finishing; Pyrotechnic, Industrial byproduct	9.40	solid	S	2B	1	4	III	I	NI	R41	Balls et al. (1995)
Sodiumperborate, $4H_2O$	10486-00-7	100%	Inorganic salt, Boron compound	Household cleaner; Detergent	9.98	solid	S	2B	1	4	III	I	NI	R41	Balls et al. (1995)
Tetraaminopyrimidine sulfate	5392-28-9	100%	Amine/Amidine, Heterocyclic	Developer		solid	I*	2B	NI		III	III	NI	NI	Balls et al. (1995)
Toluene	108-88-3	100%	Hydrocarbon (cyclic)	Solvent; Gasoline additive; Manufacture of benzene derivatives, medicines, dyes, perfumes		liquid	I *	2A	NI		II	III	R36	NI	Balls et al. (1995)
Trichloroacetic acid (3%)	76-03-9	3%	Carboxylic acid	Caustic agent; Fixative; Herbicide		liquid	S	2A	NI		II	III	R36	NI	Balls et al. (1995)
Trichloroacetic acid (30%)	76-03-9	30%	Carboxylic acid	Caustic agent; Fixative; Herbicide	0.69	liquid	S	1	1	4	I	I	R41	R41	Balls et al. (1995)
Triton X-100 (10%)	9002-93-1	10%	Polyether	Surfactant (nonionic), Detergent, Emulsifier	7.18	liquid	Sf	2A/2B	1	NC	II/III	II	R36	R41	Balls et al. (1995)
Triton X-100 (5%)	9002-93-1	5%	Polyether	Surfactant (nonionic), Detergent, Emulsifier		liquid	Sf	2A	2A		II	III	R36	NI	Balls et al. (1995)
Tween 20	9005-64-5	100%	Ester, Polyether	Surfactant (nonionic), Detergent	3.84	liquid	Sf	2B	NI		III	III	NI	NI	Balls et al. (1995)
TNO-41 (Amidosulfonic acid)	5329-14-6	100%	Acid	Herbicide; Flame retardant; Metal cleaning; Acid dye		solid	n.p.[11]	1	-		I	-	R41	R41 (SC)	Prinsen (1996)
TNO-04 (Detergent-1[12])	n.p.	undiluted	Not classified	Soaps; Surfactants		liquid	n.p.	2B	2A		III	III	NI	NI	Prinsen (1996)
TNO-34 (Detergent-2)	n.p.	undiluted	Not classified	Soaps; Surfactants		liquid	n.p.	1	SCNM		I	SCNM	R41	SCNM	Prinsen (1996)
TNO-39 (Detergent-3)	n.p.	undiluted	Not classified	Soaps; Surfactants		liquid	n.p.	NI	NI		IV	IV	NI	NI	Prinsen (1996)
TNO-44 (Didecyldimethylammoniumchloride [23% in propyl glycol])	7173-51-5	23%	Not classified	Household cleaner (disinfectant)		liquid	n.p.	1	-		I	-	R41	R41 (SC)	Prinsen (1996)
TNO-36 (Ethylhexyl lactate)	6283-86-9	undiluted	Acid; Ester	Solvent; Wetting agent		liquid	n.p.	2A	SCNM		II	II	R36	SCNM	Prinsen (1996)
TNO-01 (Formulation-1)	n.p.	undiluted	Not classified	Not classified		liquid	n.p.	NI	NI		IV	IV	NI	NI	Prinsen (1996)
TNO-02 (Formulation-2)	n.p.	undiluted	Not classified	Not classified		liquid	n.p.	2A	2A		II	II	R36	R36	Prinsen (1996)
TNO-12 (Formulation-3)	n.p.	undiluted	Not classified	Not classified		paste	n.p.	2A	NI		II	SCNM	R36	R36	Prinsen (1996)
TNO-42 (Glycolbromoacetate)	3785-34-0	85%	Acetate	Not classified		liquid	n.p.	1	-		I	-	R41	R41 (SC)	Prinsen (1996)
TNO-40 (Glycolbromoacetate form.)	n.p.	undiluted	Not classified	Not classified		liquid	n.p.	1	-		I	-	R41	R41 (SC)	Prinsen (1996)
TNO-07 (Ink-1)	n.p.	undiluted	Not classified	Dyes		liquid	n.p.	NI	NI		IV	IV	NI	NI	Prinsen (1996)
TNO-08 (Ink-2)	n.p.	undiluted	Not classified	Dyes		liquid	n.p.	NI	NI		IV	IV	NI	NI	Prinsen (1996)
TNO-26 (Ink-3)	n.p.	undiluted	Not classified	Dyes		liquid	n.p.	NI	NI		IV	IV	NI	NI	Prinsen (1996)
TNO-32 (Ink-4)	n.p.	undiluted	Not classified	Dyes		liquid	n.p.	2B	NI		III	IV	NI	NI	Prinsen (1996)
TNO-16 (Liquid nylon product)	n.p.	undiluted	Not classified	Industrial formulation		liquid	n.p.	NI	NI		IV	IV	NI	NI	Prinsen (1996)

Substance	CASRN[1]	Concentration Tested	Chemical Class	Product Class	pH	Form Tested	Water Solubility[2]	*In Vitro* Classification (GHS)[3,4]	*In Vivo* Classification (GHS)[4]	Category 1 Subclass[5]	*In Vitro* Classification (EPA)[6,7]	*In Vivo* Classification (EPA)[7]	*In Vitro* Classification (EU)[8,9]	*In Vivo* Classification (EU)[9]	Reference
TNO-06 (Lubricant)	n.p.	undiluted	Not classified	Not classified		gel	n.p.	NI	NI		IV	IV	NI	NI	Prinsen (1996)
TNO-43 (Monobromoacetic acid)	79-08-3	undiluted	Acid	Chlorination byproduct		solid	S	1	-		I	-	R41	R41 (SC)	Prinsen (1996)
TNO-09 (Paint)	n.p.	undiluted	Not classified	Paint		liquid	n.p.	NI	NI		IV	II	NI	NI	Prinsen (1996)
TNO-03 (Pesticide-1)	n.p.	undiluted	Not classified	Pesticide		liquid	n.p.	NI	NI		IV	III	NI	NI	Prinsen (1996)
TNO-13 (Pesticide-2)	n.p.	undiluted	Not classified	Pesticide		solid	n.p.	NI	NI		IV	IV	NI	NI	Prinsen (1996)
TNO-30 (Pesticide-3)	n.p.	undiluted	Not classified	Pesticide		solid	n.p.	2B	NI		III	IV	NI	NI	Prinsen (1996)
TNO-37 (Pesticide-4)	n.p.	undiluted	Not classified	Pesticide		solid	n.p.	2B	2B		III	III	NI	NI	Prinsen (1996)
TNO-14 (Polydisaccharide)	n.p.	14.5%	Carbohydrate	Not classified		liquid	n.p.	NI	NI		IV	IV	NI	NI	Prinsen (1996)
TNO-15 (Polydisaccharide)	n.p.	50%	Carbohydrate	Not classified		liquid	n.p.	NI	NI		IV	IV	NI	NI	Prinsen (1996)
TNO-35 (Propyl-lactate)	616-09-1	undiluted	Acid	Food additive; Solvent		liquid	S	1	1	1	I	I	R41	R41	Prinsen (1996)
TNO-05 (Silicone powder-1)	n.p.	undiluted	Not classified	Not classified		solid	I	NI	NI		IV	IV	NI	NI	Prinsen (1996)
TNO-10 (Silicone powder-2)	n.p.	undiluted	Not classified	Not classified		solid	I	NI	NI		IV	IV	NI	NI	Prinsen (1996)
TNO-11 (Sodium p-styrene sulfonate)	2695-37-6	undiluted	Hydrocarbon; Acid	Industrial chemical		solid	n.p.	2A	SCNM		II	SCNM	R36	SCNM	Prinsen (1996)
TNO-17 (Solvent-1)	n.p.	undiluted	Not classified	Solvent		liquid	n.p.	NI	NI		IV	IV	NI	NI	Prinsen (1996)
TNO-38 (Solvent-10)	n.p.	undiluted	Not classified	Solvent		liquid	n.p.	NI	NI		IV	IV	NI	NI	Prinsen (1996)
TNO-18 (Solvent-2)	n.p.	undiluted	Not classified	Solvent		liquid	n.p.	NI	NI		IV	IV	NI	NI	Prinsen (1996)
TNO-19 (Solvent-3)	n.p.	undiluted	Not classified	Solvent		liquid	n.p.	NI	NI		IV	IV	NI	NI	Prinsen (1996)
TNO-20 (Solvent-4)	n.p.	undiluted	Not classified	Solvent		liquid	n.p.	NI	NI		IV	IV	NI	NI	Prinsen (1996)
TNO-21 (Solvent-5)	n.p.	undiluted	Not classified	Solvent		liquid	n.p.	NI	NI		IV	IV	NI	NI	Prinsen (1996)
TNO-22 (Solvent-6)	n.p.	undiluted	Not classified	Solvent		liquid	n.p.	NI	NI		IV	IV	NI	NI	Prinsen (1996)
TNO-23 (Solvent-7)	n.p.	undiluted	Not classified	Solvent		liquid	n.p.	NI	NI		IV	IV	NI	NI	Prinsen (1996)
TNO-24 (Solvent-8)	n.p.	undiluted	Not classified	Solvent		liquid	n.p.	NI	NI		IV	IV	NI	NI	Prinsen (1996)
TNO-25 (Solvent-9)	n.p.	undiluted	Not classified	Solvent		liquid	n.p.	NI	NI		IV	IV	NI	NI	Prinsen (1996)
TNO-31 (Sulfur)	7704-34-9	undiluted	Inorganic chemical	Industrial chemical		solid	I	NI	NI		IV	III	NI	NI	Prinsen (1996)
TNO-27 (Thermal paper coating-1)	n.p.	undiluted	Not classified	Industrial chemical		liquid	n.p.	2B	2B		III	III	NI	NI	Prinsen (1996)
TNO-33 (Thermal paper coating-2)	n.p.	undiluted	Not classified	Industrial chemical		liquid	n.p.	2B	NI		III	IV	NI	NI	Prinsen (1996)
TNO-28 (Toilet cleaner-1)	n.p.	undiluted	Not classified	Household cleaner		liquid	n.p.	2B	1	NC	III	I	NI	R41	Prinsen (1996)
TNO-29 (Toilet cleaner-2)	n.p.	undiluted	Not classified	Household cleaner		liquid	n.p.	2B	2A		III	III	NI	R36	Prinsen (1996)
Cetylpyridinium bromide (6%)	140-72-7	6%	Heterocyclic, Onium compound	Surfactant (cationic), Germicide, Laboratory reagent	6.37	liquid	n.p.	1	1	2	I	SCNM	R41	R41	Prinsen (2000)
cyclohexylamino-functional PMS			Organosilicon compound			liquid	n.p.	2A	-		II	-	R36	R36	Prinsen (2000)
decamethylcyclopentasiloxane			Organosilicon compound			liquid	n.p.	NI	-		NI	-	NI	NI	Prinsen (2000)
Triton X-500 (5%)			Polyether	Surfactant (nonionic), Detergent, Emulsifier		liquid	n.p.	2B	-		III	-	NI	R36	Prinsen (2000)
TNO-45 (Aqueous framing solution)	n.p.	undiluted	Not classified	Not classified		liquid	n.p.	NI	NI		NI	IV	NI	NI	Prinsen (2005)
TNO-46 (Raw material powder)	n.p.	undiluted	Not classified	Raw material		solid	n.p.	NI	NI		NI	IV	NI	NI	Prinsen (2005)
TNO-47 (Ferro powder)	n.p.	undiluted	Not classified	Not classified		solid	n.p.	NI	NI		NI	IV	NI	NI	Prinsen (2005)
TNO-48 (Corrosion inhibitor liquid)	n.p.	undiluted	Not classified	Not classified		liquid	n.p.	2A	-		II	-	R36	R41 (SC)	Prinsen (2005)
TNO-49 (Wood impregnator liquid)	n.p.	undiluted	Not classified	Not classified		liquid	n.p.	1	-		I	-	R41	R41 (SC)	Prinsen (2005)
TNO-50 (Sodium hypochlorite-containing formulation)	n.p.	undiluted	Not classified	Disinfectant		n.p.	n.p.	1	-		I	-	R41	R41 (SC)	Prinsen (2005)
TNO-51 (Disinfectant)	n.p.	undiluted	Not classified	Disinfectant		n.p.	n.p.	1	-		I	-	R41	R41 (SC)	Prinsen (2005)
TNO-52 (Pesticide liquid)	n.p.	undiluted	Not classified	Pesticide		liquid	n.p.	2B	2A		III	III	NI	R36	Prinsen (2005)
TNO-53 (Ink formulation)	n.p.	undiluted	Not classified	Dyes		liquid	n.p.	NI	NI		NI	IV	NI	NI	Prinsen (2005)
TNO-54 (Raw material powder)	n.p.	undiluted	Not classified	Raw material		solid	n.p.	2B	2B		III	III	NI	NI	Prinsen (2005)
TNO-55 (Elastomer liquid)	n.p.	undiluted	Not classified	Elastomer		liquid	n.p.	2B	2A		III	III	R36	R36	Prinsen (2005)
TNO-56 (Elastomer liquid)	n.p.	undiluted	Not classified	Elastomer		liquid	n.p.	2B	2B		III	III	R36	NI	Prinsen (2005)
TNO-57 (Epoxy resin liquid)	n.p.	undiluted	Not classified	Resin		liquid	n.p.	2B	NI		III	IV	NI	NI	Prinsen (2005)
TNO-58 (Styrene resin powder)	n.p.	undiluted	Not classified	Resin		solid	n.p.	NI	NI		NI	IV	NI	NI	Prinsen (2005)
TNO-59 (Ferro powder)	n.p.	undiluted	Not classified	Not classified		solid	n.p.	NI	NI		NI	IV	NI	NI	Prinsen (2005)
TNO-60 (Fungicide paint)	n.p.	undiluted	Not classified	Paint		liquid	n.p.	NI	NI		NI	IV	NI	NI	Prinsen (2005)
TNO-61 (Silver thiosulfate liquid)	n.p.	undiluted	Not classified	Not classified		liquid	n.p.	NI	NI		NI	IV	NI	NI	Prinsen (2005)
TNO-62 (Lactate liquid)	n.p.	undiluted	Not classified	Not classified		liquid	n.p.	2B	NI		III	III	R36	NI	Prinsen (2005)
TNO-63 (Copolymer powder)	n.p.	undiluted	Not classified	Copolymer		solid	n.p.	NI	NI		IV	III	NI	NI	Prinsen (2005)
TNO-64 (Fluoroallyl acrylate copolymer)	n.p.	undiluted	Not classified	Copolymer		emulsion	n.p.	2B	NI		III	IV	NI	NI	Prinsen (2005)
TNO-65 (Fluoroallyl acrylate copolymer)	n.p.	undiluted	Not classified	Copolymer		emulsion	n.p.	NI	NI		NI	IV	NI	NI	Prinsen (2005)
TNO-66 (Raw material powder)	n.p.	undiluted	Not classified	Raw material		solid	n.p.	NI	NI		NI	IV	NI	NI	Prinsen (2005)
TNO-67 (Ink formulation)	n.p.	undiluted	Not classified	Dyes		liquid	n.p.	2B	NI		III	IV	NI	NI	Prinsen (2005)
TNO-68 (Cleaning product)	n.p.	undiluted	Not classified	Cleaner		liquid	n.p.	2A	2A		II	II	R36	R36	Prinsen (2005)
TNO-69 (Cleaning product)	n.p.	2%	Not classified	Not classified		liquid	n.p.	NI	NI		NI	IV	NI	NI	Prinsen (2005)
TNO-70 (Fluoroallyl acrylate copolymer)	n.p.	undiluted	Not classified	Copolymer		emulsion	n.p.	2A	2A		II	III	R36	R36	Prinsen (2005)
TNO-71 (Fluoroallyl acrylate copolymer)	n.p.	undiluted	Not classified	Copolymer		emulsion	n.p.	2B	NI		III	IV	NI	NI	Prinsen (2005)
TNO-72 (fluoroallyl acrylate copolymer)	n.p.	undiluted	Not classified	Copolymer		emulsion	n.p.	NI	NI		NI	IV	NI	NI	Prinsen (2005)
TNO-73 (fluoroallyl acrylate copolymer)	n.p.	undiluted	Not classified	Copolymer		emulsion	n.p.	1	2A		I	II	R41	R36	Prinsen (2005)
TNO-74 (Raw material powder)	n.p.	undiluted	Not classified	Raw material		solid	n.p.	NI	NI		IV	III	NI	NI	Prinsen (2005)
TNO-75 (Fluoroallyl acrylate copolymer)	n.p.	undiluted	Not classified	Copolymer		liquid	n.p.	NI	NI		NI	IV	NI	NI	Prinsen (2005)

Substance	CASRN[1]	Concentration Tested	Chemical Class	Product Class	pH	Form Tested	Water Solubility[2]	*In Vitro* Classification (GHS)[3,4]	*In Vivo* Classification (GHS)[4]	Category 1 Subclass[5]	*In Vitro* Classification (EPA)[6,7]	*In Vivo* Classification (EPA)[7]	*In Vitro* Classification (EU)[8,9]	*In Vivo* Classification (EU)[9]	Reference
TNO-76 (Ferro powder)	n.p.	undiluted	Not classified	Not classified		solid	n.p.	NI	NI		NI	IV	NI	NI	Prinsen (2005)
TNO-77 (Raw material liquid)	n.p.	undiluted	Not classified	Raw material		liquid	n.p.	2B	NI		III	IV	NI	NI	Prinsen (2005)
TNO-78 (Raw material liquid)	n.p.	undiluted	Not classified	Raw material		liquid	n.p.	2B	2B		III	III	NI	NI	Prinsen (2005)
TNO-79 (Silicon resin powder)	n.p.	undiluted	Not classified	Silicone resin		solid	n.p.	2B	NI		III	IV	NI	NI	Prinsen (2005)
TNO-80 (Raw material powder)	n.p.	undiluted	Not classified	Raw material		solid	n.p.	NI	NI		NI	IV	NI	NI	Prinsen (2005)
TNO-81 (Surfactant liquid)	n.p.	undiluted	Not classified	Soaps; Surfactants		liquid	n.p.	NI	NI		NI	IV	NI	NI	Prinsen (2005)
TNO-82 (Surfactant liquid)	n.p.	undiluted	Not classified	Soaps; Surfactants		liquid	n.p.	NI	NI		NI	IV	NI	NI	Prinsen (2005)
TNO-83 (Surfactant liquid)	n.p.	undiluted	Not classified	Soaps; Surfactants		liquid	n.p.	2B	2B		III	III	NI	R36	Prinsen (2005)
TNO-84 (Surfactant liquid)	n.p.	undiluted	Not classified	Soaps; Surfactants		liquid	n.p.	2B	NI		III	IV	NI	NI	Prinsen (2005)
TNO-85 (Surfactant liquid)	n.p.	undiluted	Not classified	Soaps; Surfactants		liquid	n.p.	2B	1	1	III	I	R36	R41	Prinsen (2005)
TNO-86 (Surfactant liquid)	n.p.	undiluted	Not classified	Soaps; Surfactants		liquid	n.p.	2B	NI		III	IV	NI	NI	Prinsen (2005)
TNO-87 (Enzyme liquid)	n.p.	undiluted	Not classified	Enzyme solution		liquid	n.p.	2B	NI		III	IV	NI	NI	Prinsen (2005)
TNO-88 (Miscellaneous liquid)	n.p.	undiluted	Not classified	Not classified		liquid	n.p.	NI	NI		NI	IV	NI	NI	Prinsen (2005)
TNO-89 (Ferro powder)	n.p.	undiluted	Not classified	Not classified		solid	n.p.	NI	NI		NI	IV	NI	NI	Prinsen (2005)
TNO-90 (Enzyme solution)	n.p.	undiluted	Not classified	Enzyme solution		liquid	n.p.	NI	NI		NI	IV	NI	NI	Prinsen (2005)
TNO-91 (Enzyme solution)	n.p.	undiluted	Not classified	Enzyme solution		liquid	n.p.	NI	NI		NI	IV	NI	NI	Prinsen (2005)
TNO-92 (Raw material powder)	n.p.	undiluted	Not classified	Raw material		solid	n.p.	2B	1	NC	III	I	R36	R41	Prinsen (2005)
TNO-93 (Antifouling paint)	n.p.	undiluted	Not classified	Paint		emulsion	n.p.	2A	1	NC	II	I	R36	R41	Prinsen (2005)
TNO-94 (Antifouling paint)	n.p.	undiluted	Not classified	Paint		liquid	n.p.	NI	1	NC	NI	I	NI	R41	Prinsen (2005)
Acetaldehyde	75-07-0	100%	Aldehyde	Manufacture of acetic acid, perfumes, and flavors; Narcotic		liquid	S	2A	-		II	-	R36	R36	Prinsen and Koëter (1993)
Acetic acid	64-19-7	10%	Carboxylic acid	Reagent; Indicator	2.40	liquid	S	1	1	4	I	I	R41	R41	Prinsen and Koëter (1993)
Benzalkonium chloride (100%)	8001-54-5	100%	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative		liquid	S	1	1	4	I	I	R41	R41	Prinsen and Koëter (1993)
Brij 35	9002-92-0	100%	Alcohol	Solvent; Excipient; Surfactant		n.p.	S	NI	-		IV	-	NI	NI	Prinsen and Koëter (1993)
Butanol	71-36-3	100%	Alcohol	Ingredient of spray paint, nail polish		liquid	S	1	2A		I	II	R41	R41	Prinsen and Koëter (1993)
2-Butoxyethyl acetate	112-07-2	100%	Alcohol	Cleaner; Polish; Sealant		liquid	n.p.	2B	-		III	-	NI	NI	Prinsen and Koëter (1993)
Chloroform	67-66-3	100%	Hydrocarbon (halogenated)	Solvent; Cleaner		liquid	I*	2A	-		II	-	R36	R36	Prinsen and Koëter (1993)
Dibutyltin dichloride	683-18-1	100%	Organometallic compound	Industrial chemical; Immunosuppressive agent		solid	S	1	-		I	-	R41	R41	Prinsen and Koëter (1993)
Dimethyl sulfoxide	67-68-5	100%	Organic sulfur compound	Solvent; Cryoprotective agent		liquid	S	NI	2B		IV	III	NI	NI	Prinsen and Koëter (1993)
n-Hexane	110-54-3	100%	Hydrocarbon (acyclic)	Solvent; Adhesive; Gasoline additive		liquid	I	NI	NI		IV	IV	NI	NI	Prinsen and Koëter (1993)
Mercury (II) chloride	7487-94-7	100%	Inorganic chloride compound	Antiseptic; Disinfectant		solid	I	1	-		I	-	R41	R41	Prinsen and Koëter (1993)
2-Methoxyethanol	109-86-4	100%	Alcohol	Solvent		liquid	S	2A	-		II	-	R36	R36	Prinsen and Koëter (1993)
Silver (I) nitrate	7761-88-8	3%	Inorganic silver/nitrogen compound	Aniti-infective; Diagnostic agent		solid	S	2B	-		III	-	NI	NI	Prinsen and Koëter (1993)
Sodium dodecyl sulfate	151-21-3	100%	Carboxylic acid (salt)	Surfactant (anionic), Detergent		solid	Sf	2B	-		III	-	R41	R41	Prinsen and Koëter (1993)
Sodium fluorescein	518-47-8	20%	Polycyclic	Stain; Dye		liquid	S	NI	-		IV	-	NI	NI	Prinsen and Koëter (1993)
Sodium hydroxide (1%)	1310-73-2	1%	Alkali	Caustic agent		liquid	S	1	2B		I	III	R41	R36	Prinsen and Koëter (1993)
Triacetin	102-76-1	100%	Lipid	Anti-fungal		liquid	I*	NI	NI		IV	IV	NI	NI	Prinsen and Koëter (1993)
Tributyltin chloride	1461-22-9	100%	Organometallic compound, Heavy metal	Pesticide; Preservative		liquid	n.p.	1	-		I	-	R41	R41	Prinsen and Koëter (1993)
Triethanolamine	102-71-6	100%	Amine/Amidine, Alcohol	Cleaner; Cosmetic ingredient; Intermediate for herbicides, waxes, cutting oils		liquid	S	2B	NI		III	III	NI	NI	Prinsen and Koëter (1993)

[1]CASRN=Chemical Abstracts Service Registry Number.

[2]I=Insoluble, S=Soluble, Sf=Surfactant, *=solubility uncertain.

[3]GHS=Globally Harmonized System (UN [2003]).

[4]Eye Irritant Category 1 = irreversible effects on the eye/serious damage to the eye; Category 2A = reversible effects on the eye/irritating to the eyes; Category 2B = reversible effects on the eye/mildly irritating to the eyes; Nonirritant = not an eye irritant

Substance	CASRN[1]	Concentration Tested	Chemical Class	Product Class	pH	Form Tested	Water Solubility[2]	*In Vitro* Classification (GHS)[3,4]	*In Vivo* Classification (GHS)[4]	Category 1 Subclass[5]	*In Vitro* Classification (EPA)[6,7]	*In Vivo* Classification (EPA)[7]	*In Vitro* Classification (EU)[8,9]	*In Vivo* Classification (EU)[9]	Reference

[5]NICEATM-defined subgroups assigned based on the lesions that drove classification of a GHS Category 1 substance. 1: based on lesions that are persistent; 2: based on lesions that are severe (not including corneal opacity score equal to 4); 3: based on lesions that are severe (not including corneal opacity score equal to 4) and persistent; 4: corneal opacity score equal to 4 at any time; NC: No subclassification could be made based on the data.

[6]EPA=U.S. Enviromental Protection Agency (EPA [1996]).

[7]Toxicity Category I for the Primary Eye Irritation Study = Corrosive, or corneal involvement or irritation not reversible within 21 days; Category II = Corneal involvement or irritation clearing in 8-21 days; Category III = Corneal involvement or irritation clearing in 7 days or less; Category IV = Minimal effects clearing within 24 hr.

[8]EU=European Union (EU [2001]).

[9]Risk phrase R41 = risk of serious damage to the eyes; R36 = irritating to the eyes; nonirritant = not an eye irritant.

[10]SCNM=Study Criteria Not Met

[11]n.p.=not provided

[12]numbering assigned based on order of appearance in Table 3 of Prinsen (1996)

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SECTION III

BOVINE CORNEAL OPACITY AND PERMEABILITY (BCOP) TEST METHOD ACCURACY AND RELIABILITY REANALYSIS

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1.0 INTRODUCTION

On November 1, 2004, NICEATM released draft BRDs on the current status of four *in vitro* test methods for detecting ocular corrosives and severe irritants (see http://iccvam.niehs.nih.gov/methods/ocudocs/ocu_brd.htm). The test methods reviewed were the BCOP, the HET-CAM, the IRE, and the ICE assays. On January 11-12, 2005, ICCVAM convened an Expert Panel to independently evaluate the validation status of the four *in vitro* test methods for identifying ocular corrosives or severe irritants. The Expert Panel Report, *Evaluation of the Current Validation Status of In Vitro Test Methods for Identifying Ocular Corrosives and Severe Irritants*, can be obtained by contacting NICEATM or electronically from http://iccvam.niehs.nih.gov/methods/eyeirrit.htm. Public comments at the meeting revealed that additional data could be made available that had not yet been provided in response to earlier requests for data. The Expert Panel subsequently recommended that the additional data be requested and that a reanalysis of the accuracy and reliability of each test method be conducted, to the extent possible.

In response to this recommendation, a second *FR* notice was published on February 28, 2005 (*FR* Vol. 70, No. 38, pp. 9661-9662; http://iccvam.niehs.nih.gov/methods/eyeirrit.htm) requesting all available *in vitro* data on these four *in vitro* ocular irritancy test methods and corresponding *in vivo* rabbit eye test method data, as well as any human exposure data (either via ethical human studies or accidental exposure). The first *FR* notice requesting these data had been published on March 24, 2004 (*FR* Vol. 69, No. 57, pp. 13859-13861; http://iccvam.niehs.nih.gov/methods/eyeirrit.htm). Also, a request for relevant data was re-sent directly to the primary developers or users of each test method, and sent to other scientists who participated in or attended the Expert Panel Meeting on January 11-12, 2005 and who had indicated a desire to provide additional data. No human exposure data was obtained for the substances evaluated in the BCOP test method, and therefore no calculations could be made on the accuracy of the BCOP test method for predicting human severe ocular irritancy.

Other factors also necessitated a reanalysis of the accuracy of BCOP for detecting ocular corrosives and severe irritants. First, clarification regarding the rules for classification of severe irritants was obtained subsequent to the release of the four BRDs that resulted in changes to the hazard classification of some of the substances used in the original analysis. For the original analysis, reversibility of ocular effects for all EU (EU [2001]) and GHS ([UN 2003]) hazard classification systems was considered to be achieved if, by post-exposure day 21, the endpoint scores fell below the threshold that resulted in a test substance being classified as a severe irritant. The new information obtained indicated that reversibility of ocular effects is achieved only when all scores reach zero by post-exposure day 21. This change resulted in a small number of substances previously classified as non-severe irritants now being classified as severe irritants.

Second, the chemical classes assigned to each test substance were revised to reflect a standardized classification scheme (based on MeSH; [http://www.nlm.nih.gov/mesh]) that would ensure consistency in classifying substances among all *in vitro* ocular test methods under consideration. This resulted in some chemicals being re-classified into other chemical

classes. The accuracy of the BCOP test method, by chemical class and using the GHS classification system (UN [2003]), has been reanalyzed to reflect these changes.

Finally, an additional accuracy analysis was conducted. In this analysis, the accuracy of each *in vitro* ocular irritancy test method for detecting ocular corrosives or severe irritants, depending on whether the classification was based on the severity of the response and/or its persistence to day 21 post-treatment, was determined.

For the BCOP test method, the changes to the existing database that resulted from using the appropriate persistence classification criteria and any new data and/or information received subsequent to the release of the draft BRD are summarized in Table III-1. At the Expert Panel meeting, the *in vivo* rabbit eye test data that corresponded to the substances tested in BCOP in the Gautheron et al. (1994) study were received from Johnson & Johnson Pharmaceutical R&D. Individual cornea data from the BCOP tests evaluating these 52 substances also were provided subsequent to the meeting. Johnson & Johnson Pharmaceutical R&D also provided individual cornea data for 20 substances evaluated in the BCOP test method, comparing results achieved using corneas from adult animals (>24 months) versus those from young animals (6 - 8 months). The efforts of Drs. Freddy Van Goethem and Philippe Vanparys that provided this additional data are gratefully acknowledged.

2.0 ACCURACY OF THE BCOP TEST METHOD – REANLYSIS

The ability of the BCOP test method to correctly identify ocular corrosives and severe irritants, as defined by the GHS, EPA, and EU classification systems (EPA [1996]; EU [2001]; UN [2003])[1], was evaluated. The three regulatory ocular hazard classification systems considered during this analysis use different classification systems and decision criteria to identify ocular corrosives and severe irritants based on *in vivo* rabbit eye test results. All three classification systems are based on individual animal data in terms of the magnitude of the response and on the extent to which induced ocular lesions fail to reverse by day 21. However, there are differences among the three classifications systems with regard to the criteria used by NICEATM for distinguishing between a severe and a nonsevere response (See **Appendix A**). Thus, to evaluate the accuracy of the HET-CAM test method for identifying ocular corrosives and severe irritants, individual rabbit data collected at the different observation times was needed for each substance.

The ability of the BCOP test method to correctly identify ocular corrosives and severe irritants, as defined by the GHS, EPA, and EU classification systems (EPA [1996]; EU [2001]; UN [2003]), was evaluated using two approaches. In the first approach, the accuracy of BCOP was assessed separately for each *in vitro-in vivo* comparative study (i.e., publication) reviewed in Sections 4.0 and 5.0 of the draft BCOP BRD. In the second approach, an overall analysis of BCOP test method accuracy was conducted by combining

[1] For the purposes of this analysis, an ocular corrosive or severe irritant was defined as a substance that would be classified as Category 1 according to the GHS classification system (UN [2003]), as Category I according to the EPA classification system (EPA [1996]), or as R41 according to the EU classification system (EU [2001]).

1882 **Table III-1. Summary of BCOP Database Changes**
1883

Data Source	Data Base	Number of Available Substances	Number of Acceptable Substances by Ocular Irritancy Classification System			*Comments*
			EPA[1]	EU[2]	GHS[3]	
			Cat[4] I/Total[5]	R41/Total	Cat 1/Total	
Gautheron (1994)	New[6]	51	7/48	7/48	7/47	Additional *in vivo* animal data were received subsequent to the original analysis that allowed for classification according to all three classification systems.
	Old[6]	51	6/12	8/51	7/13	
Balls et al. (1995)	New	59	18/53	19/50	22/54	The decrease in the total number of usable substances is due to excluding substances from consideration due to insufficient *in vivo* rabbit eye test data for classification (See **Appendix A**).
	Old	59	20/55	21/59	22/57	
Swanson et al. (1995)	New	20	6/8	6/9	6/8	The decrease in the total number of usable substances is due to excluding substances from consideration due to insufficient *in vivo* rabbit eye test data for classification (See **Appendix A**). The increase in the number of corrosive/severe irritants is due to the reclassification of substances.
	Old	20	6/9	5/9	6/9	
Casterton (1996)	New	97	27/56	25/54	27/55	The decrease in the total number of usable substances is due to excluding substances from consideration due to insufficient *in vivo* rabbit eye test data for classification (See **Appendix A**). The increase in the number of corrosive/severe irritants is due to the reclassification of substances.
	Old	97	26/55	24/60	26/56	
Gettings (1996)	New	25	10/25	8/23	8/23	The decrease in the total number of usable substances is due to excluding substances from consideration due to insufficient *in vivo* rabbit eye test data for classification
	Old	25	10/25	6/25	8/25	

Data Source	Data Base	Number of Available Substances	Number of Acceptable Substances by Ocular Irritancy Classification System			*Comments*
			EPA[1]	EU[2]	GHS[3]	
			Cat[4] I/Total[5]	R41/Total	Cat 1/Total	
						(See **Appendix A**). The increase in the number of corrosive/severe irritants is due to the reclassification of substances.
Southee (1998)	New	16	5/14	6/14	7/15	The decrease in the total number of usable substances is due to excluding substances from consideration due to insufficient *in vivo* rabbit eye test data for classification (See **Appendix A**). The change in the number of corrosive/severe irritants is due to the reclassification of substances.
	Old	16	6/14	5/15	6/14	
Swanson and Harbell (2000)	New	13	4/9	1/9	1/9	
	Old	13	4/9	1/9	1/9	
Bailey (2004)	New	16	1/13	3/13	3/14	The decrease in the total number of usable substances is due to excluding substances from consideration due to insufficient *in vivo* rabbit eye test data for classification (See **Appendix A**). The change in the number of corrosive/severe irritants is due to the reclassification of substances.
	Old	16	3/16	3/16	3/16	

[1]EPA = U.S. Environmental Protection Agency (EPA [1996]).
[2]EU = European Union (EU [2001]).
[3]GHS = Globally Harmonized System (UN [2003]).
[4]Cat = Category.
[5]First number (before forward slash) refers to the number of substances in each study that were classified as a severe irritant according to each classification system (EPA, EU, and GHS). The second number (after the forward slash) refers to the number of substances in were classified, based on animal data, for each classification system (EPA, EU, GHS).
[6]New = accuracy statistics based on revised analysis; New = accuracy statistics based on the previous analysis included in the draft BCOP BRD.

results from each study, and then assigning an overall ocular irritancy classification for each substance. When the same substance was evaluated in multiple laboratories, the overall BCOP ocular irritancy classification was based on the majority of calls among all of the studies. When there was an even number of different irritancy classifications for substances (e.g., two tests classified a substance as a nonsevere irritant and two tests classified a substance as a severe irritant), the more severe irritancy classification was used for the overall classification for the substance (severe irritant, in this case).

Based on the revisions made to the BCOP test method database, a revised accuracy analysis has been conducted. The calculations were performed as described previously in Section 6.0 of the draft BRD. To allow for a comparison of the results obtained in the revised analysis relative to those obtained previously, the data tables below include accuracy statistics from both analyses. However, the discussion of the results in the sections that follow relate to the revised analysis only.

2.1 GHS Ocular Hazard Classification System

The eight studies (Gautheron et al. [1994]; Balls et al. [1995]; Swanson et al. [1995]; Casterton et al. [1996]; Gettings et al. [1996]; Southee [1998]; Swanson and Harbell [2000]; Bailey et al. [2004]) contained BCOP test data on 203 substances, 161 of which had sufficient *in vivo* data to be assigned an ocular irritancy classification as defined by the GHS classification system (UN [2003])[2] (see **Appendix III-A**). Based on results from *in vivo* rabbit eye experiments, 53[3] of the 161 substances were classified as severe irritants (i.e., Category 1), the other 108 substances were classified as nonsevere irritants (either Category 2A, 2B) or nonirritants. The 42 substances that could not be classified according to the GHS classification system due to the lack of adequate animal data are so noted in **Appendix III-A**.

Based on the data provided in the eight studies, and when results across multiply tested substances were combined to generate a single consensus call per test substance, the BCOP test method has an accuracy of 70% to 93%, a sensitivity of 57% to 100%, a specificity of 66% to 100%, a false positive rate of 0% to 34%, and a false negative rate of 0% to 52% (**Table III-2**).

In terms of an overall accuracy analysis, combining the data from Gautheron et al. (1994), Balls et al. (1995), Swanson et al. (1995), Gettings et al. (1996), Southee (1998), Swanson and Harbell (2000), and Bailey et al. (2004), the BCOP test method has an accuracy of 81% (119/147), a sensitivity of 84% (36/43), a specificity of 80% (83/104), a false positive rate of 20% (21/104), and a false negative rate of 16% (7/43). The performance characteristics for the pooled studies are provided in **Table III-2**. Similar to the original accuracy analysis, data from Casterton et al. (1996) were not included in the overall accuracy analysis since the

[2] For the purpose of this accuracy analysis, *in vivo* rabbit study results were used to identify GHS Category 1 irritants (i.e., severe irritants); substances classified as GHS Category 2A and 2B irritants were identified as nonsevere irritants.

[3] One chemical (benzalkonium chloride, 1%) was tested *in vivo* twice in the same laboratory. The results were discordant with respect to GHS classification. According to one test, the classification was Category 1, while results from the other test yielded a Category 2A classification. The accuracy analysis was performed with the substance classified as Category 1.

Table III-2. Evaluation of the Performance of the BCOP Test Method In Predicting Ocular Corrosives and Severe Irritants Compared to the *In Vivo* Rabbit Eye Test Method, as Defined by the GHS[1] Classification System, by Study and Overall

Data Source	Anal.[2]	N[3]	Accuracy		Sensitivity		Specificity		Positive Predictivity		Negative Predictivity		False Positive Rate		False Negative Rate	
			%	No.[4]	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Gautheron et al. 1994 (new)[5]	IVIS	47/52	74[6]	35/47	71	5/7	75	30/40	33	5/15	94	30/32	25	11/40	29	2/7
Gautheron et al. 1994 (old)[5]	IVIS	13/52	77[6]	10/13	71	5/7	83	5/6	83	5/6	71	5/7	17	1/6	29	2/7
Balls et al. 1995 (new)[7]	IVIS	54/59	70[6]	38/54	77	17/22	66	21/32	61	17/28	81	21/26	34	11/32	23	5/22
Balls et al. 1995 (old)	IVIS	57/59	70[6]	40/57	77	17/22	66	23/35	59	17/29	82	23/28	34	12/35	23	5/22
Swanson et al. 1995 (new)	IVIS	8/20	100	8/8	100	6/6	100	2/2	100	6/6	100	2/2	0	0/2	0	0/6
Swanson et al. 1995 (old)	IVIS	9/20	89	8/9	100	6/6	67	2/3	86	6/7	100	2/2	33	1/3	0	0/6
Gettings et al. 1996 (new)	Perm	23/25	87	20/23	75	6/8	93	14/15	86	6/7	88	14/16	7	1/15	25	2/8
Gettings et al. 1996 (old)	Perm	25/25	88	22/25	75	6/8	94	16/17	86	6/7	89	16/18	6	1/17	25	2/8
Casterton et al. 1996 (new)	O/P	55/97	67	37/55	48	13/27	86	24/48	76	13/17	63	24/38	14	4/28	52	14/27
Casterton et al. 1996 (old)	O/P	56/97	66	37/56	46	12/26	83	25/30	71	12/17	64	25/39	17	5/30	54	14/26
Southee 1998 (new)	IVIS	15/16	73	11/15	57	4/7	88	7/8	80	4/5	70	7/10	12	1/8	43	3/7
Southee 1998 (old)	IVIS	14/16	64[6]	9/14	50	3/6	75	6/8	40	2/5	67	6/9	25	2/8	50	3/6
Swanson & Harbell 2000 (new)	IVIS	9/13	78	7/9	100	1/1	75	6/8	33	1/3	100	6/6	25	2/8	0	0/1
Swanson & Harbell 2000 (old)	IVIS	9/13	78	7/9	100	1/1	75	6/8	33	1/3	100	6/6	25	2/8	0	0/1

Data Source	Anal[2]	N[3]	Accuracy		Sensitivity		Specificity		Positive Predictivity		Negative Predictivity		False Positive Rate		False Negative Rate	
			%	No.[4]	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Bailey et al. 2004 (new)	IVIS	14/16	93	13/14	67	2/3	100	11/11	100	2/2	92	11/12	0	0/11	33	1/3
Bailey et al. 2004 (old)	IVIS	16/16	94	15/16	67	2/3	100	13/13	100	2/2	93	13/14	0	0/13	33	1/3
Entire Data Set[8] (new)		147/203	81	119/147	84	36/43	80	83/104	63	36/57	92	83/90	20	21/104	16	7/43
Entire Data Set (old)		120/200	79	95/120	76	32/42	81	63/78	69	34/49	86	61/71	19	15/78	24	10/42

[1]GHS = Globally Harmonized System (UN [2003]).

[2]Anal. = Analytical method used to transform the sample data into BCOP classification. IVIS = *In Vitro* Irritancy Score developed by Gautheron et al. (1994). Perm = Permeability value only used to classify *in vitro* ocular irritancy in the BCOP assay; an OD_{490} value >0.600 was considered a severe irritant. O/P = irritation class based on the endpoint (opacity or permeability) with the highest score for its respective range (Casterton et al. [1996]).

[3]N = Number of substances included in this analysis/the total number of substances evaluated in the study.

[4]Data used to calculate the percentage.

[5]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on the previous analysis included in the draft BCOP BRD.

[6]Performance calculated using the overall *in vitro* classification based on the majority and/or most severe classification among the multiple testing laboratories and tests (for substances tested multiple times in a laboratory).

[7]The test substance 1% benzalkonium chloride was tested in two different *in vivo* studies, producing discordant results with respect to GHS classification; the analysis was performed using the Category 1 classification.

[8]Data from Gautheron et al. (1994), Balls et al. (1995), Swanson et al. (1995), Gettings et al. (1996), Southee (1998), Swanson and Harbell (2000), and Bailey et al. (2004) were pooled together and an overall *in vitro* classification was assigned for each test substance based on the majority and/or most severe classification obtained across tests and testing laboratories. Data from Casterton et al. (1996) were not included in this analysis since the protocol used to generate BCOP data differed considerably from the other studies (e.g., a spectrophotometer was used to measure opacity instead of an opacitometer, and solids were applied neat instead of as a 20% solution or suspension).

protocol used to generate BCOP data differed considerably from the other studies (e.g., a spectrophotometer was used to measure opacity instead of an opacitometer; solids were applied neat instead of as a 20% solution or suspension).

2.2 EPA Ocular Hazard Classification System

The eight studies (Gautheron et al. [1994]; Balls et al. [1995]; Swanson et al. [1995]; Casterton et al. [1996]; Gettings et al. [1996]; Southee [1998]; Swanson and Harbell [2000]; Bailey et al. [2004]) contained BCOP test data on 203 substances, 160 of which had sufficient *in vivo* data to be assigned an ocular irritancy classification as defined by the EPA classification system (EPA [1996])[4] (see **Appendix III-A**). Based on results from *in vivo* rabbit eye experiments, 50 of the 160 substances were classified as severe irritants (i.e., Category I), the other 110 substances were classified as nonsevere irritants (either Category II, III, or IV). The 43 substances that could not be classified according to the EPA classification system due to the lack of adequate animal data are so noted in **Appendix III-A**.

Based on the data provided in the eight studies, and when results across multiply tested substances were combined to generate a single consensus call per test substance, the BCOP test method has an accuracy of 62% to 92%, a sensitivity of 0% to 100%, a specificity of 50% to 100%, a false positive rate of 0% to 50%, and a false negative rate of 0% to 100% (**Table III-3**).

In terms of an overall accuracy analysis, combining the data from Gautheron et al. (1994), Balls et al. (1995), Swanson et al. (1995), Gettings et al. (1996), Southee (1998), Swanson and Harbell (2000), and Bailey et al. (2004), the BCOP test method has an accuracy of 79% (113/143), a sensitivity of 75% (30/40), a specificity of 81% (83/103), a false positive rate of 19% (20/103), and a false negative rate of 25% (10/40). The performance characteristics for the pooled studies are provided in **Table III-3**. Data from Casterton et al. (1996) were not included in the overall accuracy analysis since the protocol used to generate BCOP data differed considerably from the other studies (e.g., a spectrophotometer was used to measure opacity instead of an opacitometer; solids were applied neat instead of as a 20% solution or suspension).

2.3 EU Ocular Hazard Classification System

The eight studies (Gautheron et al. [1994]; Balls et al. [1995]; Swanson et al. [1995]; Casterton et al. [1996]; Gettings et al. [1996]; Southee [1998]; Swanson and Harbell [2000], and Bailey et al. [2004]) contained BCOP test data on 203 substances, 158 of which had sufficient *in vivo* data to be assigned an ocular irritancy classification as defined by the EU classification system (EU [2001])[5] (see **Appendix III-A**). Based on results from *in vivo*

[4] For the purpose of this accuracy analysis, *in vivo* rabbit study results were used to identify EPA Category I irritants (i.e., severe irritants); substances classified as EPA Category II, III, or IV were identified as nonsevere irritants.

[5] For the purpose of this accuracy analysis, *in vivo* rabbit study results were used to identify EU R41 irritants (i.e., severe irritants); substances classified as EU R36 or not classified were identified as nonsevere irritants.

Table III-3. Evaluation of the Performance of the BCOP Test Method In Predicting Ocular Corrosives and Severe Irritants Compared to the *In Vivo* Rabbit Eye Test Method, as Defined by the EPA[1] Classification System, by Study and Overall

Data Source	Anal.[2]	N[3]	Accuracy		Sensitivity		Specificity		Positive Predictivity		Negative Predictivity		False Positive Rate		False Negative Rate	
			%	No.[4]	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Gautheron et al. 1994 (new)[5]	IVIS	48/52	73[6]	35/48	71	5/7	73	30/41	31	5/16	94	30/32	27	11/41	29	2/7
Gautheron et al. 1994 (old)[5]	IVIS	12/52	75[6]	9/12	67	4/6	83	5/6	80	4/5	71	5/7	17	1/6	33	2/6
Balls et al. 1995 (new)[7]	IVIS	53/59	66[6]	35/53	72	13/18	63	22/35	50	13/26	82	22/27	37	13/35	28	5/18
Balls et al. 1995 (old)	IVIS	55/59	69[6]	38/55	75	15/20	66	23/35	56	15/27	82	23/28	34	12/35	25	5/20
Swanson et al. 1995 (new)	IVIS	8/20	88	7/8	100	6/6	50	1/2	86	6/7	100	1/1	50	1/2	0	0/6
Swanson et al. 1995 (old)	IVIS	9/20	89	8/9	100	6/6	67	2/3	86	6/7	100	2/2	33	1/3	0	0/6
Gettings et al. 1996 (new)	Perm	25/25	80	20/25	60	6/10	93	14/15	86	6/7	78	14/18	7	1/15	40	4/10
Gettings et al. 1996 (old)	Perm	25/25	80	20/25	60	6/10	93	14/15	86	6/7	78	14/18	7	1/15	40	4/10
Casterton et al. 1996 (new)	O/P	56/97	62	35/56	41	11/27	83	24/49	69	11/16	60	24/40	17	5/29	59	14/27
Casterton et al. 1996 (old)	O/P	55/97	64	35/55	42	11/26	83	24/49	69	11/16	62	24/39	17	5/29	58	15/26
Southee 1998 (new)	IVIS	14/16	64[6]	9/14	40	2/5	78	7/9	50	2/4	70	7/10	22	2/9	60	3/5
Southee 1998 (old)	IVIS	14/16	64[6]	9/14	50	3/6	75	6/8	60	3/5	67	6/9	25	2/8	50	3/6
Swanson & Harbell 2000 (new)[7]	IVIS	9/13	89	8/9	75	3/4	100	5/5	100	3/3	83	5/6	0	0/5	25	1/4
Swanson & Harbell 2000 (old)	IVIS	9/13	89	8/9	75	3/4	100	5/5	100	3/3	83	5/6	0	0/5	25	1/4

1997

Data Source	Anal.[2]	N[3]	Accuracy		Sensitivity		Specificity		Positive Predictivity		Negative Predictivity		False Positive Rate		False Negative Rate	
			%	No.[4]	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Bailey et al. 2004 (new)	IVIS	13/16	92	12/13	0	0/1	100	12/12	-	0/0	92	12/13	0	0/12	100	1/1
Bailey et al. 2004 (old)	IVIS	16/16	94	15/16	67	2/3	100	13/13	100	2/2	93	13/14	0	0/13	33	1/3
Entire Data Set[8] (new)		143/203	79	113/143	75	30/40	81	83/103	60	30/50	89	83/93	19	20/103	25	10/40
Entire Data Set (old)		117/200	80	93/117	73	33/45	83	60/72	74	35/47	83	58/70	17	12/72	27	12/45

1998 [1]EPA = U.S. Environmental Protection Agency (EPA [1996]).
1999 [2]Anal. = Analytical method used to transform the sample data into BCOP classification. IVIS = *In Vitro* Irritancy Score developed by Gautheron et al.
2000 (1994). Perm = Permeability value only used to classify *in vitro* ocular irritancy in the BCOP assay; an OD_{490} value >0.600 was considered a severe irritant.
2001 O/P = irritation class based on the endpoint (opacity or permeability) with the highest score for its respective range (Casterton et al. 1996).
2002 [3]N = Number of substances included in this analysis/the total number of substances in the study.
2003 [4]Data used to calculate the percentage.
2004 [5]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on the previous analysis included in the draft BCOP BRD.
2005 [6]Performance calculated using the overall *in vitro* classification based on the majority and/or most severe classification among the multiple testing
2006 laboratories and tests (for substances tested multiple times in a laboratory).
2007 [7]The test substance ethanol was evaluated in two different *in vivo* studies (ECETOC [1998]; Swanson and Harbell [2000]), producing discordant results with
2008 respect to EPA classification; the analysis was performed using the Category I classification.
2009 [8]Data from Gautheron et al. (1994), Balls et al. (1995), Swanson et al. (1995), Gettings et al. (1996), Southee (1998), Swanson and Harbell (2000), and
2010 Bailey et al. (2004) were pooled together and an overall *in vitro* classification was assigned for each test substance based on the majority and/or most severe
2011 classification obtained across tests and testing laboratories. Data from Casterton et al. (1996) were not included in this analysis since the protocol used to
2012 generate BCOP data differed considerably from the other studies (e.g., a spectrophotometer was used to measure opacity instead of an opacitometer, and
2013 solids were applied neat instead of as a 20% solution or suspension).

rabbit eye experiments, 49 of the 158 substances were classified as severe irritants (i.e., Category I), the other 109 substances were classified as nonsevere irritants (either Category R36 or not classified). The 45 substances that could not be classified according to the EU classification system due to the lack of adequate animal data are so noted in **Appendix III-A**.

Based on the data provided in the eight studies, and when results across multiply tested substances were combined to generate a single consensus call per test substance, the BCOP test method has an accuracy of 68% to 92%, a sensitivity of 52% to 100%, a specificity of 64% to 100%, a false positive rate of 0% to 36%, and a false negative rate of 0% to 48% (**Table III-4**).

In terms of an overall accuracy analysis, combining the data from Gautheron et al. (1994), Balls et al. (1995), Swanson et al. (1995), Gettings et al. (1996), Southee (1998), Swanson and Harbell (2000), and Bailey et al. (2004), the BCOP test method has an accuracy of 80% (114/143), a sensitivity of 82% (33/40), a specificity of 79% (81/103), a false positive rate of 21% (22/103), and a false negative rate of 18% (7/40). The performance characteristics for the pooled studies are provided in **Table III-4**. Data from Casterton et al. (1996) were not included in the overall accuracy analysis since the protocol used to generate BCOP data differed considerably from the other studies (e.g., a spectrophotometer was used to measure opacity instead of an opacitometer; solids were applied neat instead of as a 20% solution or suspension).

2.4 Accuracy of the BCOP Test Method for the GHS Ocular Hazard Classification System, by Chemical Class and Property of Interest-Reanalysis

In order to further evaluate discordant responses of the BCOP test method relative to the *in vivo* hazard classification, several accuracy sub-analyses were performed. These included specific classes of chemicals with sufficiently robust numbers of substances ($n \geq 5$), as well as certain properties of interest considered relevant to ocular toxicity testing (e.g., pesticides, surfactants, pH, physical form). Because the international community will soon adopt the GHS classification system for hazard labeling (UN [2003]), and considering that there were only modest differences in overall BCOP test method accuracy among the three regulatory classification systems (i.e., EPA, EU, GHS), these sub-analyses were focused only on the GHS system.

As indicated in **Table III-5**, there were some notable trends in the performance of the BCOP test method among these subgroups of substances. The chemical class of substances that was most consistently overpredicted according the GHS classification system (i.e., were false positives[6]) by the BCOP test method is alcohols. Nine out the 19 overpredicted substances were alcohols. The remaining chemical classes represented among the overpredicted substances were carboxylic acids (3), ketones (3), heterocyclic compounds (2), esters (1), and hydrocarbons (1). Among the 35 substances labeled as surfactants only 5% (1/21) were overpredicted by the BCOP test method. The only overpredicted surfactant was a surfactant-containing formulation.

[6] False positive in this context refers to a substance that was classified as a severe ocular irritant by the BCOP test method, but as a nonsevere (mild or moderate) irritant or nonirritant based on *in vivo* data.

Table III-4. Evaluation of the Performance of the BCOP Test Method In Predicting Ocular Corrosives and Severe Irritants Compared to the *In Vivo* Rabbit Eye Test Method, as Defined by the EU[1] Classification System, by Study and Overall

Data Source	Anal.[2]	N[3]	Accuracy		Sensitivity		Specificity		Positive Predictivity		Negative Predictivity		False Positive Rate		False Negative Rate	
			%	No.[4]	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Gautheron et al. 1994 (new)[5,6]	IVIS	48/52	73[7]	35/48	71	5/7	73	30/41	31	5/16	94	30/32	27	11/41	29	2/7
Gautheron et al. 1994 (old)[5]	IVIS	51/52	75[7]	38/51	75	6/8	74	32/43	39	7/18	94	31/33	26	11/43	25	2/8
Balls et al. 1995 (new)	IVIS	50/59	68[7]	34/50	74	14/19	64	20/31	56	14/25	80	20/25	36	11/31	26	5/19
Balls et al. 1995 (old)	IVIS	59/59	71	42/59	76	16/21	68	26/38	55	16/29	83	25/30	34	13/38	24	5/21
Swanson et al. 1995 (new)	IVIS	9/20	89	8/9	100	6/6	67	2/3	86	6/7	100	2/2	33	1/3	0	0/6
Swanson et al. 1995 (old)	IVIS	9/20	78	7/9	100	5/5	50	2/4	71	5/7	100	2/2	50	2/4	0	0/5
Gettings et al. 1996 (new)	Perm	23/25	87	20/23	75	6/8	93	14/15	86	6/7	88	14/16	7	1/15	25	2/8
Gettings et al. 1996 (old)	Perm	25/25	80	20/25	67	4/6	84	16/19	57	4/7	89	16/18	16	3/19	33	2/6
Casterton et al. 1996 (new)	O/P	54/97	70	38/54	52	13/25	86	25/29	76	13/17	68	25/37	14	4/29	48	12/25
Casterton et al. 1996 (old)	O/P	60/97	73	44/60	54	13/24	86	31/36	72	13/18	74	31/42	14	5/36	46	11/24
Southee 1998 (new)	IVIS	14/16	79[7]	11/14	67	4/6	88	7/8	80	4/5	78	7/9	12	1/8	33	2/6
Southee 1998 (old)	IVIS	15/16	73[7]	11/15	60	3/5	80	8/10	60	3/5	80	8/10	20	2/10	40	2/5
Swanson & Harbell 2000 (new)	IVIS	9/13	78	7/9	100	1/1	75	6/8	33	1/3	100	6/6	25	2/8	0	0/1
Swanson & Harbell 2000 (old)	IVIS	9/13	78	7/9	100	1/1	75	6/8	33	1/3	100	6/6	25	2/8	0	0/1

2062

Data Source	Anal.[2]	N[3]	Accuracy		Sensitivity		Specificity		Positive Predictivity		Negative Predictivity		False Positive Rate		False Negative Rate	
			%	No.[4]	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Bailey et al. 2004 (new)	IVIS	13/16	92	12/13	67	2/3	100	10/10	100	2/2	91	10/11	0	0/10	33	1/3
Bailey et al. 2004 (old)	IVIS	16/16	94	15/16	67	2/3	100	13/13	100	2/2	93	13/14	0	0/13	33	1/3
Entire Data Set (new)[8]		143/203	80	114/143	82	33/40	79	81/103	60	33/55	92	81/88	21	22/103	18	7/40
Entire Data Set (old)		157/200	77	121/157	78	31/40	77	90/117	55	33/60	91	88/97	23	27/117	23	9/40

2063 [1]EU = European Union (EU [2001]).
2064 [2]Anal. = Analytical method used to transform the sample data into BCOP classification. IVIS = *In Vitro* Irritancy Score developed by Gautheron et al.
2065 (1994). Perm = Permeability value only used to classify *in vitro* ocular irritancy in the BCOP assay; an OD_{490} value >0.600 was considered a severe irritant.
2066 O/P = irritation class based on the endpoint (opacity or permeability) with the highest score for its respective range (Casterton et al. [1996]).
2067 [3]N = Number of substances included in this analysis/the total number of substances in the study.
2068 [4]Data used to calculate percentage.
2069 [5]Accuracy analysis based on EEC (1984) classifications in Gautheron et al. (1994).
2070 [6]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on the previous analysis included in the Draft BCOP BRD.
2071 [7]Performance calculated using the overall *in vitro* classification based on the majority and/or most severe classification among the multiple testing
2072 laboratories and tests (for substances tested multiple times in a laboratory).
2073 [8]Data from Gautheron et al. (1994), Balls et al. (1995), Swanson et al. (1995), Gettings et al. (1996), Southee (1998), Swanson and Harbell (2000), and
2074 Bailey et al (2004) were pooled together and an overall *in vitro* classification was assigned for each test substance based on the majority and/or most severe
2075 classification obtained across tests and testing laboratories. Data from Casterton et al. (1996) were not included in this analysis since the protocol used to
2076 generate BCOP data differed considerably from the other studies (e.g., a spectrophotometer was used to measure opacity instead of an opacitometer, and
2077 solids were applied neat instead of as a 20% solution or suspension).

Table III-5. False Negative and False Positive Rates of the BCOP Test Method, by Chemical Class and Properties of Interest, for the GHS[1] Classification System

Category	N[2]	False Positive Rate[3]		False Negative Rate[4]	
		%	No.[5]	%	No.
Overall	147	20	21/104	16	7/43
Chemical Class[6]					
Alcohol	21	50	9/18	67	2/3
Amine/Amidine	8	0	0/4	0	0/4
Carboxylic acid	16	33	3/9	14	1/7
Ester	12	12	1/8	0	0/4
Ether/Polyether	6	0	0/5	0	0/1
Heterocycle	12	33	2/6	17	1/6
Hydrocarbon	11	9	1/11	-	0/0
Inorganic salt	5	0	0/3	0	0/2
Ketone	9	33	3/9	-	0/0
Onium compound	11	0	0/3	0	0/8
Properties of Interest					
Liquids	93	26	18/69	4	1/24
Solids	34	10	2/20	43	6/14
Pesticide	8	33	1/3	40	2/5
Surfactant – Total[7]	35	5	1/21	7	1/14
-nonionic	5	0	0/4	0	0/1
-anionic	3	0	0/2	100	1/1
-cationic	6	0	0/1	0	0/7
pH – Total[8]	24	-	-	21	5/24
- acidic (pH < 7.0)	11	-	-	18	2/11
- basic (pH > 7.0)	13	-	-	23	3/13
Category 1 Subgroup[9] - Total	38	-	-	18	7/38
- 4 (CO=4 at any time)	20	-	-	15	3/20
- 3 (severity/persistence)	1	-	-	0	0/1
- 2 (severity)	4	-	-	25	1/4
- 2-4 combined[10]	25	-	-	17	4/24
- 1 (persistence)	13	-	-	23	3/13

[1]GHS = Globally Harmonized System (UN [2003]).

[2]N = number of substances.

[3]False Positive Rate = the proportion of all negative substances that are falsely identified as positive *in vitro*.

[4]False Negative Rate = the proportion of all positive substances that are falsely identified as negative *in vitro*.

[5]Data used to calculate the percentage.

[6]Chemical classes included in this table are represented by at least five substances tested in the BCOP test method and assignments are based on the MeSH categories (www.nlm.nih.gov/mesh) as defined in **Appendix B**.

[7]Combines single chemicals labeled as surfactants along with surfactant-containing formulations.

[8]Total number of GHS Category 1 substances for which pH information was obtained.

[9]NICEATM-defined subgroups assigned based on the lesions that drove classification of a GHS Category 1 substance. 1: based on lesions that are persistent; 2: based on lesions that are severe (not including Corneal Opacity [CO]=4); 3: based on lesions that are severe (not including CO=4) and persistent; 4: CO = 4 at any time.

[10]Subcategories 2 to 4 combined to allow for a direct comparison of GHS Category 1 substances classified *in vivo* based on some lesion severity component and those classified based on persistent lesions alone.

With regard to physical form of the substances overpredicted by the BCOP test method, 18 were liquids and two were solids. Considering the proportion of the total available database, liquids (93/127; 73%) appear more likely than solids (34/127; 27%) to be overpredicted by the BCOP test method

Although there were a relatively small number (4) of substances (i.e., were false negatives[7]), alcohols (2) were most often underpredicted by the BCOP test method according to the GHS classification system (see **Appendix III-A**). The other chemical classes represented were carboxylic acids (1) and heterocyclic compounds (1). As can be seen in **Table III-5**, the 35 substances labeled as surfactants were rarely underpredicted by the BCOP test method (7% [1/14] false negative rate). The only underpredicted surfactant was an anionic form. With regard to physical form of the substances underpredicted by the BCOP test method, 6 were solids and one was a liquid. Despite the proportion of the total available database, solids (34/127; 27%) appear more likely than liquids (93/127; 73%) to be underpredicted by the BCOP test method. There was no definitive difference among the underpredicted substances for which pH information was available, as two were acidic (pH < 7.0) and three were basic (pH > 7.0), and considering the comparable proportion of acidic and basic underpredicted substances (2/11; 18% vs. 3/13; 23%). Finally, the 38 underpredicted substances were more likely to be substances classified *in vivo* based on persistent lesions, rather than on severe lesions, as evidenced by an analysis of NICEATM-defined GHS Category 1 sub-groupings (**Table III-5**).

2.5 Accuracy of the BCOP Test Method for Identifying Ocular Corrosives and Severe Irritants – Summary of Reanalysis

As detailed in **Section III-1.0**, additional or new data relevant to the BCOP test method were received after the Expert Panel meeting on January 11 and 12, 2005 that increased the size of the comparative BCOP:*in vivo* rabbit eye test database from 120 to 147 substances for the GHS classification system (UN [2003]), 117-143 for the EPA classification system (EPA [1996]). Conversely, the size of the comparative BCOP:*in vivo* rabbit eye test database was decreased from 157 to 143 substances for the EU classification system (EU [2001]). As can be seen in **Tables III-2** through **III-4**, the overall accuracy stayed the same (draft BCOP BRD: 77-80%, depending on the classification system used; reanalysis: 80% for all classification systems). The false positive rate was reduced from 23% (draft BCOP BRD analysis) to 21% (reanalysis) for the EU classification system, but was increased from 17-19% (draft BRD BCOP analysis) to 19-20% (reanalysis) for the EPA and GHS classification systems, respectively, while the false negative rate was reduced for all three classification systems (from 23-27% [draft BCOP BRD analysis] to 16-25% [reanalysis]).

Similar to the original analysis, the revised analysis indicated that alcohols are often overpredicted (50% [9/18] false positive rate) in the BCOP test method. Carboxylic acids (3/9) and heterocyclic compounds (2/6) had a false negative rate of 33%.

[7] False negative in this context refers to a substance that was classified as a nonsevere (mild or moderate) irritant or nonirritant by the BCOP test method, but as a severe irritant based on *in vivo* data.

As noted in **Section III-2.4**, 18 of the 20 overpredicted substances were liquids while two were solids. Considering the proportion of the total available database, liquids (93) appear more likely than solids (34) to be overpredicted by the BCOP test method. In comparison to the original analysis, the overprediction of solid substances was reduced (from 44% [4/9] to 10% [2/20] false positive rate), while the false positive rate for liquids was increased from 21% (14/66) to 26% (18/69).

With regard to physical form of the substances underpredicted by the BCOP test method, six were solids and one was a liquid. Given the proportion of the total available database, solids (34/127; 27%) appear more likely than liquids (93/127; 73%) to be underpredicted by the BCOP test method. In comparison to the original analysis, the underprediction of solid substances was increased (from 31% [4/13] to 43% [6/14] false negative rate), while the false negative rate for liquids was reduced in the revised analysis from 18% (5/28) to 4% (1/24).

Using the expanded database, an analysis was conducted of the ability of the BCOP test method to identify ocular corrosives and severe irritants, depending on the nature of the *in vivo* ocular lesions (i.e., severity and/or persistence) responsible for classification of a substance as an ocular corrosive/severe irritant. As indicated in **Table III-5**, the 38 underpredicted substances were more likely to be substances classified *in vivo* based on persistent lesions (false negative rate = 23% [3/13]), rather than on severe lesions (false negative rate = 17% [4/24]).

A new analysis not included originally was an evaluation of accuracy related to acidic or basic pH. Among the five underpredicted substances for which pH information was available, 2 were acidic (pH < 7.0) and three were basic (pH > 7.0). Basic substances (13) occupy a comparable proportion of the total database to acidic substances (11), and therefore these differences do not appear to be significant. However, it is noted that pH information was obtained for only 28 of the 43 total Category 1 substances.

Table III-6 provides a summary of the revised analysis of the overall performance of the BCOP test method defined by the GHS classification system (UN [2003]). As noted from this analysis, the false positive substances were scattered among the three "nonsevere irritant" classifications (i.e., GHS Category 2A, 2B, or nonirritant). This includes nine (9/75) nonirritating substances that were classified as severe irritants by the BCOP. However, the mild irritants (Category 2B; n = 1/7) were less likely to be overpredicted as severe irritants/ocular corrosives than the moderate irritants (Category 2A, n = 11/22). The small number of false negative substances (7) was most often confined to those classified, based on BCOP test results, as moderate irritants (n=5) although two false negative substances were classified as mild irritants.

In the reanalysis, compared to the overall false positive rate for the BCOP test method (20%; 21/104) the false positive rate for alcohols is 50% (9/18). However, the revised analysis indicates that the false positive rate for ketones is smaller than originally determined (False positive rate: draft BCOP BRD analysis: 2/3, 67%; reanalysis: 3/9, 33%; Solid false positive). Likewise, the false positive rate for solids is smaller than

Table III-6. Overall Performance of the BCOP Test Method in the Predicting the Irritancy of a Substance as Defined by the GHS[1] Classification System

		***In Vitro* Classification (BCOP)**			
		Severe	**Moderate[2]**	**Mild**	***Total***
***In Vivo* Classification (GHS)**	**Category 1**	36	5	2	**43**
	Category 2A	11	7	4	**22**
	Category 2B	1	4	2	**7**
	Nonirritant	9	22	44	**75**
	Total	**57**	**38**	**52**	**147[3]**

[1]GHS = Globally Harmonized System (UN [2003]).
[2]*In vitro* classification of moderate also includes those substances classified as "nonsevere" in some BCOP studies.
[3]Thirty substances included in **Appendix III-A** had insufficient data with which to assign a precise GHS classification and therefore were not included in this table.

previously calculated (False positive rate: draft BCOP BRD analysis: 4/9, 44%; reanalysis: 2/20, 10%). Furthermore, the reanalysis indicated that the false negative rate of liquids was smaller than previously determined (draft BCOP BRD analysis: 5/28, 18%; reanalysis: 1/24, 4%). Based on the reanalysis, the false positive and false negative rates for identification of ocular corrosives/severe irritants among surfactants and surfactant containing formulations were 5% (1/21) and 7% (1/14), respectively.

3.0 RELIABILITY OF THE BCOP TEST METHOD - REANALYSIS

An assessment of test method reliability (intralaboratory repeatability and intra- and inter-laboratory reproducibility) is an essential element of any evaluation of the performance of an alternative test method (ICCVAM [2003]). Repeatability refers to the closeness of agreement between test results obtained within a single laboratory when the procedure is performed on the same substance under identical conditions within a given time period (ICCVAM [1997, 2003]). Intralaboratory reproducibility refers to the determination of the extent to which qualified personnel within the same laboratory can replicate results using a specific test protocol at different times. Interlaboratory reproducibility refers to the determination of the extent to which different laboratories can replicate results using the same protocol and test chemicals, and indicates the extent to which a test method can be transferred successfully among laboratories. A reliability assessment includes reviewing the rationale for selecting the substances used to evaluate test method reliability, a discussion of the extent to which the substances tested represent the range of possible test outcomes and the properties of the various substances for which the test method is proposed for use, and a quantitative and/or qualitative analysis of repeatability and intra- and inter-laboratory reproducibility. In addition, measures of central tendency and variation are summarized for historical control data (negative, vehicle, positive), where applicable.

As noted in the draft BCOP BRD, quantitative BCOP test method data were available for replicate corneas within individual experiments or for replicate experiments within an individual laboratory for three studies (Gettings et al. [1996]; Southee [1998]; data submission from Dr. Joseph Sina). Therefore, an evaluation of the repeatability and intralaboratory reproducibility of the BCOP test method could be conducted. Additionally, comparable BCOP data were available for multiple laboratories within each of three comparative validation studies (Gautheron et al. [1994]; Balls et al. [1995]; Southee [1998]), which allowed for an evaluation of the interlaboratory reproducibility of the BCOP test method.

3.1 Substances Used to Re-evaluate the Reliability of the BCOP Test Method

Intralaboratory reliability analyses were conducted on the data from Gettings et al. (1996), Southee (1998) and a data submission from Dr. Joseph Sina. For the Gettings et al. (1996) study, mean permeability data from three different experiments on the 25 surfactant-based formulations evaluated the CTFA Phase III study were obtained, as well as the mean permeability value for the three experiments, the standard deviation and the corresponding %CV values. Dr. Joseph Sina submitted a study of 43 substances, which included detailed BCOP data for replicate corneas. In the Southee (1998) study, 16 substances were evaluated in three laboratories multiple times (2 to 5 experiments) for a total of 122 tests.

Interlaboratory reliability analyses were conducted on the data from Gautheron et al. (1994), Balls et al. (1995), and Southee (1998). Gautheron et al. (1994) included 52 substances, including 22 liquids, 22 solids, and eight surfactants (both solids and liquids). Balls et al. (1995) included 60 substances (i.e., there were 52 different substances with four substances tested at two different concentrations and two substances tested at three concentrations, for a total of 60 possible ocular irritation outcomes). One substance (thiourea) was tested *in vitro* in the BCOP test method but, due to its excessive toxicity *in vivo*, was excluded from the comparison of *in vitro* and *in vivo* test results. As noted above, the Southee (1998) study included 16 substances evaluated in three laboratories multiple times.

3.2 Reanalysis of BCOP Test Method Intralaboratory Repeatability

Generally, analyses of intralaboratory repeatability have included approaches such as:

- a CV analysis, which is a statistical measure of the deviation of a variable from its mean (e.g., Holzhütter et al. [1996])
- ANOVA methods (e.g., Holzhütter et al. [1996]; ASTM [1999])

Two studies discussed in **Section 2.0** included intralaboratory repeatability data. For the Southee (1998) study, quantitative BCOP test method data were available for replicate corneas within individual experiments repeated two to five times for each test substance in three different laboratories. CV analyses were performed on within-experiment BCOP data, using the *In Vitro* Irritancy Score obtained for each test substance within each of the three testing laboratories. In addition, Dr. Joseph Sina submitted a study of 43 substances, which included detailed BCOP data for replicate corneas. A CV analysis was conducted

on the subset of substances provided by Dr. Sina that were tested using an incubation temperature of 32˚C, the recommended temperature for incubations in the proposed standardized protocol described in Appendix A of the draft BCOP BRD; substances incubated at room temperature were not included in this analysis. The updated information received subsequent to the release of the draft BCOP BRD did not affect these analyses and therefore these are not discussed again here (see the draft BCOP BRD, published November 1, 2004).

3.3 Reanalysis of BCOP Test Method Intralaboratory Reproducibility

Generally, analyses of intralaboratory reproducibility have included approaches such as:

- a CV analysis, which is a statistical measure of the deviation of a variable from its mean (e.g., Holzhütter et al. [1996])
- ANOVA methods (e.g., Holzhütter et al. [1996]; ASTM [1999])

Two of the studies discussed in **Section 2.0** included intralaboratory reproducibility data (Gettings et al. [1996]; Southee [1998]). For the Southee (1998) study, quantitative BCOP test method data were available for replicate corneas within individual experiments repeated two to five times for each test substance in three different laboratories. CV analyses were performed on between-experiment BCOP data, using the *In Vitro* Irritancy Score obtained for each test substance within each of the three testing laboratories. For the Gettings et al. (1996) study, Dr. John Harbell provided the mean permeability data obtained from three different experiments on the 25 surfactant-based formulations evaluated the Cosmetic, Toiletry, and Fragrance Association (CTFA) Phase III study, as well as the mean permeability value for the three experiments, the standard deviation and the corresponding %CV values. The updated information received subsequent to the release of the draft BCOP BRD did not affect these analyses and therefore these are not discussed again here (see the draft BCOP BRD, November 1, 2004).

3.4 Reanalysis of BCOP Test Method Interlaboratory Reproducibility

Generally, analyses of interlaboratory variability have included approaches such as:

- the extent of concordance among laboratories in assigning the same regulatory classification for a particular substance (e.g., Holzhütter et al. [1996])
- bivariant scatter diagrams/correlation analyses for pairs of laboratories to assess the extent possibility of divergence (e.g., Holzhütter et al. [1996])
- a CV analysis (e.g., Holzhütter et al. [1996])
- ANOVA methods (e.g., Holzhütter et al. [1996]; ASTM [1999])

Several of the studies discussed in **Section 2.0** included interlaboratory data for at least a subset of the substances evaluated. The ability of the BCOP test method to reproducibly identify ocular corrosives/severe irritants versus nonsevere irritants/nonirritants was evaluated using two approaches. While the draft BRD contained the same analysis as detailed below, new information regarding *in vivo* classification of substances according to the three regulatory classification schemes was provided, which resulted in changes to

the classification of some substances. Therefore, a revised analysis was conducted to reflect the updated classifications. However, while the tables include the comparative results from the original and revised analyses, the results discussed in the text pertain to the revised analysis only.

In the first approach, a qualitative assessment of reproducibility was conducted. In this evaluation, the individual laboratory *in vitro* ocular irritation classification for each substance was used to evaluate the extent of agreement among the participating laboratories in their ability to identify ocular corrosives/severe irritants versus nonsevere irritants/nonirritants. The reliability of BCOP was assessed separately for each study (i.e., publication). Substances classified, based on BCOP data, as corrosive/severe irritants or nonsevere irritants/nonirritants were further classified by their *in vivo* rabbit eye test results, as determined within the GHS, EPA, and EU classification schemes. Because the focus of this reliability assessment is on the interlaboratory reproducibility of BCOP in identifying corrosives/severe irritants versus nonsevere irritants/nonirritants, considerable variability could exist among laboratories in their classification of substances as nonsevere irritants or nonirritants (e.g., three laboratories could classify a chemical as a nonirritant and one laboratory could classify the same chemical as an moderate irritant; for this analysis this would be considered 100% agreement between laboratories) that would not be apparent from this analysis.

3.4.1 Qualitative Reanalysis of Interlaboratory Reproducibility

3.4.1.1 *GHS Ocular Hazard Classification System*

Reliability analyses for the BCOP test method were evaluated for the following three studies: Balls et al. (1995), Gautheron et al. (1994), and Southee (1998). The agreement of classification calls among participating laboratories and the relationship to the *in vivo* classification (UN [2003]) for the substances tested in each validation in each study is provided in **Table III-7**.

For the study by Balls et al. (1995), the five participating laboratories were in 100% agreement in regard to the ocular irritancy classification for 41 (68%) of the 60 substances tested. The extent of agreement between testing laboratories was the same for substances identified from *in vivo* rabbit eye data as corrosives/severe irritants or as nonsevere irritants/nonirritants (76% of the accurately identified severe and nonsevere substances were shown to have 100% classification agreement among testing laboratories). Comparatively, greater disparity between individual substance classifications was observed for substances that were identified as false positives (i.e., positive *in vitro* but negative *in vivo*). For instance, 63% of the false positives exhibited less than 100% agreement in the irritancy classifications among laboratories.

For the study by Gautheron et al. (1994), there was 100% agreement in regard to the ocular irritancy classification for 35 (67%) of the 52 substances, which were tested in either 11 or 12 laboratories. Discordance in the classification results was present for

Table III-7. Evaluation of the Reliability of the BCOP Test Method in Predicting Ocular Corrosives and Severe Irritants as Defined by the GHS[1] Classification System, by Study

Report	Classification (*In Vivo/In Vitro*)[2]	No. of Testing Labs	N[3]	Substances with 100% Agreement among Labs[4]	Substances with 91-92% Agreement among Labs	Substances with 82-83% Agreement among Labs	Substances with 80% Agreement among Labs	Substances with 73% Agreement among Labs	Substances with 64-67% Agreement among Labs	Substances with 58-60% Agreement among Labs	Substances with ≤ 55% Agreement among Labs
Balls et al. (1995)	+/+ (new)[5]	5	17	13 (76%)			3 (18%)			1 (6%)	
	+/+ (old)[5]	5	17	14 (82%			2 (12%)			1 (6%)	
	+/- (new)	5	5	3 (60%)			1 (20%)			1 (20%)	
	+/- (old)	5	5	3 (60%)			1 (20%)			1 (20%)	
	-/+ (new)	5	11	4 (36%)			4 (36%)			3 (27%)	
	-/+ (old)	5	12	4 (33%)			5 (42%)			3 (25%)	
	-/- (new)	5	21	16 (76%)			2 (10%)			3 (14%)	
	-/- (old)	5	23	17 (74%)			2 (9%)			4 (17%)	
	?/- (new)	5	4	3 (75%)						1 (25%)	
	?/- (old)	5	2	2 (100%)						0 (0%)	
	?/+ (new)	5	2	2 (100%)							
	?/+ (old)	5	1	1 (100%)							
	Total (new)		60	41 (68%)			10 (17%)			9 (15%)	
	Total (old)		60	41 (68%)			10 (17%)			9 (15%)	
Gautheron et al. (1994)	+/+ (new)	11	5	3 (60%)		1 (10%)					1 (10%)
		12	1	1(100%)							
	+/+ (old)	11	4	2 (50%)		1 (25%)					1 (25%)
		12	1	1 (100%)							
	+/- (new)	11	1			1(100%)					
		12	1	1(100%)							
	+/- (old)	11	1			1 (100%)					
		12	1	1 (100%)							
	-/+ (new)	11	4	2 (50%)		1 (25%)		1 (25%)			
		12	5	2 (40%)	1 (20%)						2 (40%)
	-/+ (old)	11	1						1 (100%)		
	-/- (new)	11	2			1 (50%)			1 (50%)		
		12	28	23 (81%)	1 (4%)	3 (11%)			1 (4%)		
	-/- (old)	11	4	3 (75%)			1 (25%)				
		12	1			1 (100%)					
	?/- (new)	11	1					1 (100%)			
		12	1	1 (100%)							
	?/- (old)	11	11	8 (73%)		2 (18%)		1 (9%)			

Report	Classification (*In Vivo/In Vitro*)[2]	No. of Testing Labs	N[3]	Substances with 100% Agreement among Labs[4]	Substances with 91-92% Agreement among Labs	Substances with 82-83% Agreement among Labs	Substances with 80% Agreement among Labs	Substances with 73% Agreement among Labs	Substances with 64-67% Agreement among Labs	Substances with 58-60% Agreement among Labs	Substances with ≤ 55% Agreement among Labs
		12	16	15 (94%)	1 (6%)						
	?/+ (new)	11	3	1 (33%)	1 (33%)				1 (33%)		
	?/+ (old)	11	7	4 (57%)	1 (14%)	1 (14%)		1 (14%)			
		12	4	2 (50%)	1 (25%)					1 (25%)	
	Total (new)		52	34 (65%)	3 (6%)	7 (13%)		2 (4%)	3 (6%)		3 (6%)
	Total (old)		51	36 (71%)	3 (6%)	6 (12%)	1 (2%)	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Southee (1998)	+/+ (new)	3	4	4 (100%)							
	+/+ (old)	3	3	3 (100%)							
	+/- (new)	3	3	3 (100%)							
	+/- (old)	3	3	3 (100%)							
	-/+ (new)	3	1	1 (100%)							
	-/+ (old)	3	2	2 (100%)							
	-/- (new)	3	7	6 (86%)					1 (14%)		
	-/- (old)	3	6	5 (83%)					1 (17%)		
	?/- (new)	3	1	1 (100%)							
	?/- (old)	3	2	2 (100%							
	?/+ (new)	-	0								
	?/+ (old)	-	0								
	Total (new)		16	15 (94%)					1 (6%)		
	Total (old)		16	15 (94%)					1 (6%)		

[1]GHS = Globally Harmonized System (UN [2003]).

[2]A "+" indicates that the substance was assigned an overall classification of corrosive or a severe irritant (Category 1); a "-" indicates that the substance was assigned an overall classification of nonsevere irritant (Category 2A, 2B) or nonirritant; a "?" indicates that, due to the lack of appropriate *in vivo* data (e.g., studies were terminated too early to assess reversibility of effects; insufficient dose volume), a GHS classification could not be made. See **Section 2.0** for a description of the rules followed to classify the ocular irritancy of test substances tested multiple times *in vitro*.

[3]N = number of substances.

[4]Number in parentheses indicates percentage of tested chemicals.

[5]New = accuracy statistics based on revised analysis; Old = accuracy statistics based on the previous analysis included in the draft BCOP BRD.

substances that were correctly identified as corrosives/severe irritants and as nonsevere irritants/nonirritants. For the study by Southee (1998), there was 100% agreement in regard to the ocular irritancy classification for 15 (94%) of the 16 substances. Discordance in the classification results was present for only one substance that was correctly identified as a nonsevere irritant/nonirritant.

3.4.1.2 *EPA Ocular Hazard Classification System*

Reliability analyses for the BCOP test method were evaluated for the following three studies: Balls et al. (1995), Gautheron et al. (1994), and Southee (1998). The agreement of classification calls among participating laboratories and its relationship to the *in vivo* classification (EPA [1996]) for the substances tested in each validation in each study is provided in **Table III-8**.

The participating laboratories of Balls et al. (1995) were in 100% agreement in regard to the ocular irritancy classification for 40 (67%) of the 60 substances tested. The agreement among laboratories was greatest for accurately identified corrosives/severe irritants when compared to any other combination of *in vivo* and *in vitro* results (77% of the accurately identified corrosives/severe irritants exhibited 100% classification agreement among laboratories). Comparatively, greater disparity between individual substance classifications was observed for substances that were identified as false positives. For instance, 61% of the false positives exhibited less than 100% agreement among laboratories in the irritancy classifications.

The participating laboratories of Gautheron et al. (1994) were in 100% agreement in regard to the ocular irritancy classification (corrosive/severe irritant or nonsevere irritant/nonirritant) for 36 (71%) of the 51 tested substances. Discordant results were observed for substances that were correctly identified as corrosive/severe irritant or nonsevere/irritant/nonirritant, as well as for false negatives and false positives.

For the report by Southee (1998), there was 100% agreement in regard to the ocular irritancy classification (corrosive/severe irritant or nonsevere irritant/nonirritant) for 15 (94%) of the 16 substances. Discordance in the classification results was present for only one substance that was correctly identified as a nonsevere irritant/nonirritant.

3.4.1.3 *EU Ocular Hazard Classification System*

Reliability analyses for the BCOP test method were evaluated for the following three studies: Balls et al. (1995), Gautheron et al. (1994), and Southee (1998). The agreement of classification calls among participating laboratories and its relationship to the *in vivo* classification (EU [2001]) for the substances tested in each validation in each study is provided in **Table III-9**.

The participating laboratories were in 100% agreement in regard to the ocular irritancy classification for 40 (67%) of the 60 substances tested by Balls et al. (1995). The extent of agreement among laboratories was greatest for accurately identified corrosives/severe irritants when compared to any other combination of *in vivo* and *in vitro* results (86% of the accurately identified corrosives/severe irritants exhibited 100% classification agreement

Table III-8. Evaluation of the Reliability of the BCOP Test Method In Predicting Ocular Corrosives and Severe Irritants as Defined by the EPA[1] Classification System, by Study

Report	Classification (*In Vivo/In Vitro*)[2]	No. of Testing Labs	N[3]	Substances with 100% Agreement among Labs[4]	Substances with 91-92% Agreement among Labs	Substances with 82-83% Agreement among Labs	Substances with 80% Agreement among Labs	Substances with 73% Agreement among Labs	Substances with 64-67% Agreement among Labs	Substances with 58-60% Agreement among Labs	Substances with ≤ 55% Agreement among Labs
Balls et al. (1995)	+/+ (new)[5]	5	13	10 (77%)			2 (15%)			1 (8%)	
	+/+ (old)[5]	5	17	14 (82%)			2 (12%)			1 (6%)	
	+/- (new)	5	5	3 (60%)			1 (20%)			1 (20%)	
	+/- (old)	5	5	3 (60%)			1 (20%)			1 (20%)	
	-/+ (new)	5	13	5 (38%)			5 (38%)			3 (23%)	
	-/+ (old)	5	12	4 (33%)			5 (42%)			3 (25%)	
	-/- (new)	5	22	15 (68%)			4 (33%)			3 (25%)	
	-/- (old)	5	23	17 (74%)			2 (9%)			4 (17%)	
	?/- (new)	5	3	3 (100%)							
	?/- (old)	5	2	2 (100%)							
	?/+ (new)	5	4	4 (100%)							
	?/+ (old)	5	1	1 (100%)							
	Total (new)		60	40 (67%)			12 (20%)			8 (13%)	
	Total (old)		60	41 (68%)			10 (17%)			9 (15%)	
Gautheron et al. (1994)	+/+ (new)	11	4	2 (50%)		1 (25%)					1 (25%)
		12	1	1 (100%)							
	+/+ (old)	11	2			1 (33%)					1 (33%)
		12	1	1 (100%)							
	+/- (new)	11	1			1 (100%)					
		12	1	1 (100%)							
	+/- (old)	11	1			1 (100%)					
		12	1	1 (100%)							
	-/+ (new)	11	5	3 (60%)				1 (20%)	1 (20%		
		12	5	2 (40%)	1 (20%)					1 (20%)	1 (20%)
	-/+ (old)	11	1						1 (100%)		
	-/- (new)	11	11	8 (73%)		2 (18%)			1 (9%)		
		12	19	17 (90%)	1 (5%)	1 (5%)					
	-/- (old)	11	4	3 (75%)			1 (25%)				
		12	1			1 (100%)					
	?/- (new)	11	1					1 (100%)			
		12	1	1 (100%)							
	?/- (old)	11	11	8 (73%)		2 (18%)		1 (9%)			
		12	16	15 (94%)	1 (6%)						

Report	Classification (*In Vivo/In Vitro*)[2]	No. of Testing Labs	N[3]	Substances with 100% Agreement among Labs[4]	Substances with 91-92% Agreement among Labs	Substances with 82-83% Agreement among Labs	Substances with 80% Agreement among Labs	Substances with 73% Agreement among Labs	Substances with 64-67% Agreement among Labs	Substances with 58-60% Agreement among Labs	Substances with ≤ 55% Agreement among Labs
	?/+ (new)	11	2	1 (50%)	1 (50%)						
	?/+ (old)	11	9	6 (57%)	1 (14%)	1 (14%)		1 (14%)			
		12	4	2 (50%)	1 (25%)					1 (25%)	
	Total (new)		51	36 (71%)	3 (6%)	5 (10%)		2 (4%)	2 (4%)	1 (2%)	2 (4%)
	Total (old)		51	36 (71%)	3 (6%)	6 (12%)	1 (2%)	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Southee (1998)	+/+ (new)	3	2	2 (100%)							
	+/+ (old)	3	3	3 (100%)							
	+/- (new)	3	3	3 (100%)							
	+/- (old)	3	3	3 (100%)							
	-/+ (new)	3	2	2 (100%)							
	-/+ (old)	3	2	2 (100%)							
	-/- (new)	3	7	6 (86%)					1 (14%)		
	-/- (old)	3	6	5 (83%)					1 (17%)		
	?/- (new)	3	1	1 (100%)							
	?/- (old)	3	2	2 (100%)							
	?/+ (new)	3	1	1 (100%)							
	?/+ (old)	-	0								
	Total (new)		16	15 (94%)					1 (6%)		
	Total (old)		16	15 (94%)					1 (6%)		

[1]EPA = U.S. Environmental Protection Agency (EPA [1996]).

[2]A "+" indicates that the substance was assigned an overall classification of corrosive or a severe irritant (Category I); a "-" indicates that the substance was assigned an overall classification of nonsevere irritant (Category II, III) or nonirritant (category IV); a "?" indicates that, due to the lack of appropriate *in vivo* data (e.g., studies were terminated too early to assess reversibility of effects; insufficient dose volume), an EPA classification could not be made. See **Section 2.0** for a description of the rules followed to classify the ocular irritancy of test substances tested multiple times *in vitro*.

[3]N = number of substances.

[4]Number in parentheses indicates percentage of tested chemicals.

[5]New = accuracy statistics based on revised analysis; Old = accuracy statistics based on the previous analysis included in the draft BCOP BRD.

among laboratories). Comparatively, greater disparity between individual substance classifications was observed for substances that were identified as false positives, false negatives, and those substances accurately classified as nonsevere irritants/nonirritants. For instance, 63% of the false positives exhibited less than 100% agreement among laboratories in irritancy classifications.

The participating laboratories in Gautheron et al. (1994) were in 100% agreement in regard to the ocular irritancy classification for 36 (69%) of the 52 tested substances. Discordant results were observed for substances that were correctly identified as corrosive/severe irritant or nonsevere/irritant/nonirritant, as well as for false negatives and false positives.

For the report by Southee (1998), there was 100% agreement in regard to the ocular irritancy classification (corrosive/severe irritant or nonsevere irritant/nonirritant) for 15 (94%) of the 16 substances.

3.4.2 Quantitative Reanalysis of Interlaboratory Reproducibility

As detailed in the draft BCOP BRD, to provide a quantitative assessment of interlaboratory variability, individual laboratory BCOP test results were used to calculate a mean and CV for the *In Vitro* Irritancy Score for each substance tested in Gautheron et al. (1994), Balls et al. (1995) and Southee (1998). Although a wide range of CV values were noted, mean and median CV values for the Balls et al. (1995) and the Southee (1998) study were less than 35%. These values were higher for the Gautheron et al. (1994) study (168% and 47%, respectively), although lower values were noted for substances predicted as severe irritants/corrosives in the BCOP test method (36% and 17% for mean and median CV values). The additional information received subsequent to the release of the draft BCOP BRD (November 1, 2004) did not affect these analyses, and therefore a reanalysis was not necessary.

3.4.3 Additional Reanalyses of Interlaboratory Reproducibility

As described in the draft BCOP BRD, Gautheron et al. (1994) found that 82.7% of the substances tested were classified the same by all laboratories when using a three-category system (i.e., mild irritant (BCOP score [0-25], moderate irritant [25.1-55] and severe irritant [≥55.1]). Also described in the draft BCOP BRD is the analysis of Balls et al. (1995), in which the interlaboratory correlation of BCOP results (permeability value, opacity value, and *In Vitro* Irritancy Score) generated from the five laboratories that participated this study was determined. This analysis yielded a wide range of correlation coefficients for the subsets of test substances.

The additional information received subsequent to the release of the draft BCOP BRD (November 1, 2004) did not affect these analyses, and therefore a reanalysis was not necessary.

2469 **Table III-9. Evaluation of the Reliability of the BCOP Test Method In Predicting Ocular Corrosives and Severe Irritants as**
2470 **Defined by the EU[1] Classification System, by Study**
2471

Report	Classification (*In Vivo/In Vitro*)[2]	No. of Testing Labs	N[3]	Substances with 100% Agreement among Labs[4]	Substances with 91-92% Agreement among Labs	Substances with 82-83% Agreement among Labs	Substances with 80% Agreement among Labs	Substances with 73% Agreement among Labs	Substances with 64-67% Agreement among Labs	Substances with 58-60% Agreement among Labs	Substances with ≤ 55% Agreement among Labs
Balls et al. (1995)	+/+ (new)[5]	5	14	12 (86%)			2 (14%)				
	+/+ (old)[5]	5	16	14 (88%)			2 (12%)				
	+/- (new)	5	5	2 (40%)			1 (20%)			2 (40%)	
	+/- (old)	5	5	3 (60%)			1 (20%)			1 (20%)	
	-/+ (new)	5	11	4 (36%)			4 (36%)			3 (27%)	
	-/+ (old)	5	13	4 (31%)			5 (38%)			4 (31%)	
	-/- (new)	5	20	15 (75%)			2 (10%)			3 (15%)	
	-/- (old)	5	25	19 (76%)			2 (8%)			4 (16%)	
	?/- (new)	5	5	5 (100%)							
	?/- (old)	-	0								
	?/+ (new)	5	5	3 (60%)			1 (20%)			1 (20%)	
	?/+ (old)	5	1	1 (100%)							
	Total (new)		60	40 (67%)			10 (17%)			9 (15%)	
	Total (old)		60	41 (68%)			10 (17%)			9 (15%)	
Gautheron et al. (1994)	+/+ (new)	11	5	3 (60%)		1 (20%)					1 (20%)
		12	1	1 (100%)							
	+/+ (old)	11	5	3 (60%)		1 (20%)					1 (20%)
		12	1	1 (100%)							
	+/- (new)	11	1			1 (100%)					
		12	1	1 (100%)							
	+/- (old)	11	1			1 (100%)					
		12	1	1 (100%)							
	-/+ (new)	11	5	2 (40%		1 (20%)		1 (20%)	1 (20%)		
		12	5	2 (40%)	1 (20%)					1 (20%)	1 (20%)
	-/+ (old)	11	4	1 (25%)	1 (25%)	1 (25%)		1 (25%)			
		12	5	2 (40%)	1 (20%)				1 (20%)	1 (20%)	
	-/- (new)	11	15	12 (80%)		2 (13%)			1 (7%)		
		12	15	13 (87%)	1 (7%)	1 (7%)					
	-/- (old)	11	15	11 (73%)		2 (13%)		1 (7%)	1 (7%)		
		12	17	15 (88%)	1 (6%)	1 (6%)					
	?/- (new)	11	1					1 (100%)			
		12	1	1 (100%)							
	?/- (old)	11	1	1 (100%)							

Report	Classification (*In Vivo/In Vitro*)[2]	No. of Testing Labs	N[3]	Substances with 100% Agreement among Labs[4]	Substances with 91-92% Agreement among Labs	Substances with 82-83% Agreement among Labs	Substances with 80% Agreement among Labs	Substances with 73% Agreement among Labs	Substances with 64-67% Agreement among Labs	Substances with 58-60% Agreement among Labs	Substances with ≤ 55% Agreement among Labs
	?/+ (new)	11	2	1 (50%)	1 (50%)						
	?/+ (old)	-	0								
	Total (new)		52	36 (69%)	3 (6%)	6 (12%)		2 (4%)	2 (4%)	1 (2%)	2 (4%)
	Total (old)		50	35 (70%)	3 (6%)	6 (12%)	1 (2%)	2 (4%)	2 (2%)	1 (2%)	1 (2%)
Southee (1998)	+/+ (new)	3	4	4 (100%)							
	+/+ (old)	3	3	3 (100%)							
	+/- (new)	3	2	2 (100%)							
	+/- (old)	3	2	2 (100%)							
	-/+ (new)	3	1	1 (100%)							
	-/+ (old)	3	2	2 (100%)							
	-/- (new)	3	7	6 (86%)					1 (14%)		
	-/- (old)	3	8	7 (88%)					1 (12%)		
	?/- (new)	3	2	2 (100%)							
	?/- (old)	3	1	1 (100%)							
	?/+ (new)	-	0								
	?/+ (old)	-	0								
	Total (new)		16	15 (94%)					1 (6%)		
	Total (old)		16	15 (94%)					1 (6%)		

[1]EU = European Union (EU [2001]).

[2]A "+" indicates that the substance was assigned an overall classification of corrosive or a severe irritant (Category I); a "-" indicates that the substance was assigned an overall classification of nonsevere irritant (Category II, III) or nonirritant (category IV); a "?" indicates that, due to the lack of appropriate *in vivo* data (e.g., studies were terminated too early to assess reversibility of effects; insufficient dose volume), an EPA classification could not be made. See **Section 2.0** for a description of the rules followed to classify the ocular irritancy of test substances tested multiple times *in vitro*.

[3]N indicates number of substances.

[4]Number in parentheses indicates percentage of tested chemicals.

[5]New = accuracy statistics based on revised analysis; Old = accuracy statistics based on the previous analysis included in the draft BCOP BRD.

3.5 BCOP Test Method Historical Positive and Negative Control Data - Reanalysis

An example of historical data for positive controls was provided by IIVS (current as of July 22, 2004), and is provided in the draft BCOP BRD.

3.6 Reliability of the BCOP Test Method for Identifying Ocular Corrosives and Severe Irritants – Summary of Reanalysis

As described in the draft BCOP BRD, a quantitative assessment of intralaboratory data (*In Vitro* Irritancy Scores) from two studies (Southee [1998]; Sina submission) was conducted for substances predicted as severe eye irritants. For the 16 substances evaluated in the Southee (1998) study, the median %CV for *In Vitro* Irritancy Scores for replicate corneas ranged from 11.8 to 14.2 for the three laboratories. For the 29 substances evaluated by Dr. Sina, the within experiment mean and median %CV values for *In Vitro* Irritancy Scores were 71 and 35, respectively. The dataset provided by Dr. Sina included 10 substances with low *In Vitro* Irritancy Scores, contributing to the increased variability of this dataset. However, the range of %CV values for the five substances predicted as severe irritants (*In Vitro* Scores >55.1) in this study is 1.1 to 13.

Also described in the draft BCOP BRD is a quantitative assessment of intralaboratory data (*In Vitro* Irritancy Scores) from two studies (Gettings et al. [1996]; Southee [1998]). For the Gettings et al. (1996) study, the between experiment (n=3) mean and median %CV values for permeability values were 33.4 and 29.0, respectively, for 25 surfactant-based personal care cleaning formulations. For the Southee (1998) study, the between experiment %CV values of *In Vitro* Irritancy Scores for the 16 substances tested two or more times in Laboratory 1, Laboratory 2, and Laboratory 3 was less than 35%. The mean %CV values for this study ranged from 12.6 to 14.8 for the three laboratories, while the median %CV values ranged from 6.7 to 12.4.

These analyses of intralaboratory reliability were not affected by the information received subsequent to the release of the draft BCOP BRD (November 1, 2004). However, the previous analysis also included an evaluation of interlaboratory reproducibility using both qualitative and quantitative approaches. While the quantitative analysis was unaffected by the new information that was received, the qualitative analysis (correct classification as an ocular corrosive/severe irritant or as a non-corrosive/nonsevere irritant) of the data provided for multiple laboratories in three studies (Gautheron et al. [1994]; Balls et al. [1995]; Southee [1998]) mandated that this analysis be repeated. The results for this analysis are presented in **Tables III-7** to **III-9**. The five participating laboratories for the Balls et al. (1995) study were in 100% agreement in regard to the ocular irritancy classification for 40 (67%) of the 60 substances tested *in vitro* in the study. In general, the extent of agreement between testing laboratories was greatest for substances identified from *in vivo* rabbit eye data as corrosives or severe irritants when compared to any other combination of *in vivo* and *in vitro* results (76% to 86%, depending on the classification system used, of the accurately identified severe substances were shown to have 100% classification agreement among testing laboratories). For the study by Gautheron et al. (1994), there was 100% agreement in regard to the ocular

irritancy classification for 35 to 36 (67% to 69%) of the 52 substances, which were tested in either 11 or 12 laboratories. Finally, for the study by Southee (1998), there was 100% agreement in regard to the ocular irritancy classification for 15 (94%) of the 16 substances.

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APPENDIX III-A

SUBSTANCES USED IN THE BCOP TEST METHOD REANALYSIS

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Substances Used in BCOP Test Method Reanalysis

Substance	CASRN[1]	Chemical Class	Product Class	Form Tested	Solubility	Concentration Tested	Purity (%)	Lab No.	In VitroTest Call[2]	In Vitro Consensus Call[2]	In Vivo GHS[4,5]	GHS Category 1 SubClass[6]	In Vivo EPA[7,8]	In Vivo EU[9,10]	Reference
Acetone	67-64-1	Ketone	Solvent; Antiseptic; Chemical intermediate; Raw material	liquid	water soluble	100%	99	1	Very severe	Very Severe	Category 2A		Category II	R36	Balls et al. (1995)
Acetone	67-64-1	Ketone	Solvent; Antiseptic; Chemical intermediate; Raw material	liquid	water soluble	100%	99	2	Very severe	Very Severe	Category 2A		Category II	R36	Balls et al. (1995)
Acetone	67-64-1	Ketone	Solvent; Antiseptic; Chemical intermediate; Raw material	liquid	water soluble	100%	99	3	Very severe	Very Severe	Category 2A		Category II	R36	Balls et al. (1995)
Acetone	67-64-1	Ketone	Solvent; Antiseptic; Chemical intermediate; Raw material	liquid	water soluble	100%	99	4	Very severe	Very Severe	Category 2A		Category II	R36	Balls et al. (1995)
Acetone	67-64-1	Ketone	Solvent; Antiseptic; Chemical intermediate; Raw material	liquid	water soluble	100%	99	5	Very severe	Very Severe	Category 2A		Category II	R36	Balls et al. (1995)
Ammonium nitrate	6484-52-2	Inorganic salt; Onium compound	Fertilizer; Chemical intermediate; Industrial explosive	solid	water soluble	20%	>99.9	1	Mild	Mild	Category 2B		Category III	R36	Balls et al. (1995)
Ammonium nitrate	6484-52-2	Inorganic salt; Onium compound	Fertilizer; Chemical intermediate; Industrial explosive	solid	water soluble	20%	>99.9	2	Mild	Mild	Category 2B		Category III	R36	Balls et al. (1995)
Ammonium nitrate	6484-52-2	Inorganic salt; Onium compound	Fertilizer; Chemical intermediate; Industrial explosive	solid	water soluble	20%	>99.9	3	Mild	Mild	Category 2B		Category III	R36	Balls et al. (1995)
Ammonium nitrate	6484-52-2	Inorganic salt; Onium compound	Fertilizer; Chemical intermediate; Industrial explosive	solid	water soluble	20%	>99.9	4	Mild	Mild	Category 2B		Category III	R36	Balls et al. (1995)
Ammonium nitrate	6484-52-2	Inorganic salt; Onium compound	Fertilizer; Chemical intermediate; Industrial explosive	solid	water soluble	20%	>99.9	5	Mild	Mild	Category 2B		Category III	R36	Balls et al. (1995)
L-Aspartic acid	70-47-3	Amino acid	Organic intermediate; Fungicides; Germicides	solid	water soluble	20%	100	1	Mild	Mild	SCNM[11]		SCNM	SCNM	Balls et al. (1995)
L-Aspartic acid	70-47-3	Amino acid	Organic intermediate; Fungicides; Germicides	solid	water soluble	20%	100	2	Mild	Mild	SCNM		SCNM	SCNM	Balls et al. (1995)
L-Aspartic acid	70-47-3	Amino acid	Organic intermediate; Fungicides; Germicides	solid	water soluble	20%	100	3	Mild	Mild	SCNM		SCNM	SCNM	Balls et al. (1995)
L-Aspartic acid	70-47-3	Amino acid	Organic intermediate; Fungicides; Germicides	solid	water soluble	20%	100	4	Mild	Mild	SCNM		SCNM	SCNM	Balls et al. (1995)
L-Aspartic acid	70-47-3	Amino acid	Organic intermediate; Fungicides; Germicides	solid	water soluble	20%	100	5	Mild	Mild	SCNM		SCNM	SCNM	Balls et al. (1995)
Benzalkonium chloride (10%)	8001-54-5	Inorganic salt; Onium compound	Surfactant (cationic); Bactericide; Fungicide; Preservative	liquid	surfactant	10%	98	1	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Benzalkonium chloride (10%)	8001-54-5	Inorganic salt; Onium compound	Surfactant (cationic); Bactericide; Fungicide; Preservative	liquid	surfactant	10%	98	2	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Benzalkonium chloride (10%)	8001-54-5	Inorganic salt; Onium compound	Surfactant (cationic); Bactericide; Fungicide; Preservative	liquid	surfactant	10%	98	3	Very severe	Very Severe	Category 1	4	Category I	R41	Balls et al. (1995)
Benzalkonium chloride (10%)	8001-54-5	Inorganic salt; Onium compound	Surfactant (cationic); Bactericide; Fungicide; Preservative	liquid	surfactant	10%	98	4	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Benzalkonium chloride (10%)	8001-54-5	Inorganic salt; Onium compound	Surfactant (cationic); Bactericide; Fungicide; Preservative	liquid	surfactant	10%	98	5	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Benzalkonium chloride (5%)	8001-54-5	Inorganic salt; Onium compound	Surfactant (cationic); Bactericide; Fungicide; Preservative	liquid	surfactant	5%	98	1	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Benzalkonium chloride (5%)	8001-54-5	Inorganic salt; Onium compound	Surfactant (cationic); Bactericide; Fungicide; Preservative	liquid	surfactant	5%	98	2	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Benzalkonium chloride (5%)	8001-54-5	Inorganic salt; Onium compound	Surfactant (cationic); Bactericide; Fungicide; Preservative	liquid	surfactant	5%	98	3	Very severe	Very Severe	Category 1	2	Category I	R41	Balls et al. (1995)
Benzalkonium chloride (5%)	8001-54-5	Inorganic salt; Onium compound	Surfactant (cationic); Bactericide; Fungicide; Preservative	liquid	surfactant	5%	98	4	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Benzalkonium chloride (5%)	8001-54-5	Inorganic salt; Onium compound	Surfactant (cationic); Bactericide; Fungicide; Preservative	liquid	surfactant	5%	98	5	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Benzalkonium chloride (1 %)	8001-54-5	Inorganic salt; Onium compound	Surfactant (cationic); Bactericide; Fungicide; Preservative	liquid	surfactant	1%	98	1	Very severe	Very Severe	Category 1		Category II	R41	Balls et al. (1995)
Benzalkonium chloride (1 %)	8001-54-5	Inorganic salt; Onium compound	Surfactant (cationic); Bactericide; Fungicide; Preservative	liquid	surfactant	1%	98	2	Very severe	Very Severe	Category 1		Category II	R41	Balls et al. (1995)
Benzalkonium chloride (1 %)	8001-54-5	Inorganic salt; Onium compound	Surfactant (cationic); Bactericide; Fungicide; Preservative	liquid	surfactant	1%	98	3	Very severe	Very Severe	Category 1	1	Category II	R41	Balls et al. (1995)
Benzalkonium chloride (1 %)	8001-54-5	Inorganic salt; Onium compound	Surfactant (cationic); Bactericide; Fungicide; Preservative	liquid	surfactant	1%	98	4	Severe	Very Severe	Category 1		Category II	R41	Balls et al. (1995)
Benzalkonium chloride (1 %)	8001-54-5	Inorganic salt; Onium compound	Surfactant (cationic); Bactericide; Fungicide; Preservative	liquid	surfactant	1%	98	5	Severe	Very Severe	Category 1		Category II	R41	Balls et al. (1995)
Benzoyl-L-tartaric acid	2743-38-6	Carboxylic acid; Ester	Optical resolution agent	solid	water insoluble	20%	-	1	Very severe	Very Severe	Category 1		SCNM	R41	Balls et al. (1995)
Benzoyl-L-tartaric acid	2743-38-6	Carboxylic acid; Ester	Optical resolution agent	solid	water insoluble	20%	-	2	Very severe	Very Severe	Category 1		SCNM	R41	Balls et al. (1995)
Benzoyl-L-tartaric acid	2743-38-6	Carboxylic acid; Ester	Optical resolution agent	solid	water insoluble	20%	-	3	Very severe	Very Severe	Category 1	2	SCNM	R41	Balls et al. (1995)
Benzoyl-L-tartaric acid	2743-38-6	Carboxylic acid; Ester	Optical resolution agent	solid	water insoluble	20%	-	4	Very severe	Very Severe	Category 1		SCNM	R41	Balls et al. (1995)
Benzoyl-L-tartaric acid	2743-38-6	Carboxylic acid; Ester	Optical resolution agent	solid	water insoluble	20%	-	5	Very severe	Very Severe	Category 1		SCNM	R41	Balls et al. (1995)
Butyl acetate	123-86-4	Ester	Sovent; Synthetic flavor ingredient	liquid	water insoluble*	100%	99	1	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Butyl acetate	123-86-4	Ester	Sovent; Synthetic flavor ingredient	liquid	water insoluble*	100%	99	2	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Butyl acetate	123-86-4	Ester	Sovent; Synthetic flavor ingredient	liquid	water insoluble*	100%	99	3	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Butyl acetate	123-86-4	Ester	Sovent; Synthetic flavor ingredient	liquid	water insoluble*	100%	99	4	Mild	Moderate	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Butyl acetate	123-86-4	Ester	Sovent; Synthetic flavor ingredient	liquid	water insoluble*	100%	99	5	Mild	Moderate	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
gamma-Butyrolactone	96-48-0	Heterocyclic, Lactone	Synthetic intermmediate; Solvent	liquid	water soluble	100%	>99	1	Very severe	Severe	Category 2A		Category II	R36	Balls et al. (1995)
gamma-Butyrolactone	96-48-0	Heterocyclic, Lactone	Synthetic intermmediate; Solvent	liquid	water soluble	100%	>99	2	Moderate	Severe	Category 2A		Category II	R36	Balls et al. (1995)
gamma-Butyrolactone	96-48-0	Heterocyclic, Lactone	Synthetic intermmediate; Solvent	liquid	water soluble	100%	>99	3	Moderate	Severe	Category 2A		Category II	R36	Balls et al. (1995)
gamma-Butyrolactone	96-48-0	Heterocyclic, Lactone	Synthetic intermmediate; Solvent	liquid	water soluble	100%	>99	4	Very severe	Severe	Category 2A		Category II	R36	Balls et al. (1995)

Substance	CASRN[1]	Chemical Class	Product Class	Form Tested	Solubility	Concentration Tested	Purity (%)	Lab No.	In VitroTest Call[2]	In Vitro Consensus Call[3]	In Vivo GHS[4,5]	GHS Category 1 SubClass[6]	In Vivo EPA[7,8]	In Vivo EU[9,10]	Reference
gamma-Butyrolactone	96-48-0	Heterocyclic, Lactone	Synthetic intermediate; Solvent	liquid	water soluble	100%	>99	5	Severe	Severe	Category 2A		Category II	R36	Balls et al. (1995)
Captan 90 concentrate	133-06-2	Imide, Organic sulfur compound	Pesticide	solid	water soluble	20%	90	1	Moderate	Moderate	Category 1		Category I	R41	Balls et al. (1995)
Captan 90 concentrate	133-06-2	Imide, Organic sulfur compound	Pesticide	solid	water soluble	20%	90	2	Moderate	Moderate	Category 1		Category I	R41	Balls et al. (1995)
Captan 90 concentrate	133-06-2	Imide, Organic sulfur compound	Pesticide	solid	water soluble	20%	90	3	Moderate	Moderate	Category 1	4	Category I	R41	Balls et al. (1995)
Captan 90 concentrate	133-06-2	Imide, Organic sulfur compound	Pesticide	solid	water soluble	20%	90	4	Very severe	Moderate	Category 1		Category I	R41	Balls et al. (1995)
Captan 90 concentrate	133-06-2	Imide, Organic sulfur compound	Pesticide	solid	water soluble	20%	90	5	Moderate	Moderate	Category 1		Category I	R41	Balls et al. (1995)
4-Carboxybenzaldehyde	619-66-9	Carboxylic acid, Aldehyde	Not classified	solid	water insoluble*	20%	95	1	Very severe	Severe	Category 2A		Category II	R36	Balls et al. (1995)
4-Carboxybenzaldehyde	619-66-9	Carboxylic acid, Aldehyde	Not classified	solid	water insoluble*	20%	95	2	Very severe	Severe	Category 2A		Category II	R36	Balls et al. (1995)
4-Carboxybenzaldehyde	619-66-9	Carboxylic acid, Aldehyde	Not classified	solid	water insoluble*	20%	95	3	Severe	Severe	Category 2A		Category II	R36	Balls et al. (1995)
4-Carboxybenzaldehyde	619-66-9	Carboxylic acid, Aldehyde	Not classified	solid	water insoluble*	20%	95	4	Severe	Severe	Category 2A		Category II	R36	Balls et al. (1995)
4-Carboxybenzaldehyde	619-66-9	Carboxylic acid, Aldehyde	Not classified	solid	water insoluble*	20%	95	5	Severe	Severe	Category 2A		Category II	R36	Balls et al. (1995)
Cetylpyridinium bromide (6%)	140-72-7	Heterocyclic, Onium compound	Surfactant (cationic), Germicide, Laboratory reagent	liquid	surfactant	6%	98	1	Severe	Severe	Category 1		SCNM	R41	Balls et al. (1995)
Cetylpyridinium bromide (6%)	140-72-7	Heterocyclic, Onium compound	Surfactant (cationic), Germicide, Laboratory reagent	liquid	surfactant	6%	98	2	Very severe	Severe	Category 1		SCNM	R41	Balls et al. (1995)
Cetylpyridinium bromide (6%)	140-72-7	Heterocyclic, Onium compound	Surfactant (cationic), Germicide, Laboratory reagent	liquid	surfactant	6%	98	3	Severe	Severe	Category 1	2	SCNM	R41	Balls et al. (1995)
Cetylpyridinium bromide (6%)	140-72-7	Heterocyclic, Onium compound	Surfactant (cationic), Germicide, Laboratory reagent	liquid	surfactant	6%	98	4	Severe	Severe	Category 1		SCNM	R41	Balls et al. (1995)
Cetylpyridinium bromide (6%)	140-72-7	Heterocyclic, Onium compound	Surfactant (cationic), Germicide, Laboratory reagent	liquid	surfactant	6%	98	5	Severe	Severe	Category 1		SCNM	R41	Balls et al. (1995)
Cetylpyridinium bromide (10%)	140-72-7	Heterocyclic, Onium compound	Surfactant (cationic), Germicide, Laboratory reagent	liquid	surfactant	10%	98	1	Moderate	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Cetylpyridinium bromide (10%)	140-72-7	Heterocyclic, Onium compound	Surfactant (cationic), Germicide, Laboratory reagent	liquid	surfactant	10%	98	2	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Cetylpyridinium bromide (10%)	140-72-7	Heterocyclic, Onium compound	Surfactant (cationic), Germicide, Laboratory reagent	liquid	surfactant	10%	98	3	Very severe	Very Severe	Category 1	4	Category I	R41	Balls et al. (1995)
Cetylpyridinium bromide (10%)	140-72-7	Heterocyclic, Onium compound	Surfactant (cationic), Germicide, Laboratory reagent	liquid	surfactant	10%	98	4	Severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Cetylpyridinium bromide (10%)	140-72-7	Heterocyclic, Onium compound	Surfactant (cationic), Germicide, Laboratory reagent	liquid	surfactant	10%	98	5	Severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Cetylpyridinium bromide (0.1%)	140-72-7	Heterocyclic, Onium compound	Surfactant (cationic), Germicide, Laboratory reagent	liquid	surfactant	0.10%	98	1	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Cetylpyridinium bromide (0.1%)	140-72-7	Heterocyclic, Onium compound	Surfactant (cationic), Germicide, Laboratory reagent	liquid	surfactant	0.10%	98	2	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Cetylpyridinium bromide (0.1%)	140-72-7	Heterocyclic, Onium compound	Surfactant (cationic), Germicide, Laboratory reagent	liquid	surfactant	0.10%	98	3	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Cetylpyridinium bromide (0.1%)	140-72-7	Heterocyclic, Onium compound	Surfactant (cationic), Germicide, Laboratory reagent	liquid	surfactant	0.10%	98	4	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Cetylpyridinium bromide (0.1%)	140-72-7	Heterocyclic, Onium compound	Surfactant (cationic), Germicide, Laboratory reagent	liquid	surfactant	0.10%	98	5	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Chlorhexidine	55-56-1	Amine/Amidine	Disinfectant; Mouthwash; Anti-infective agent	solid	water insoluble*	20%	n.p.[12]	1	Very severe	Very Severe	Category 1		SCNM	SCNM	Balls et al. (1995)
Chlorhexidine	55-56-1	Amine/Amidine	Disinfectant; Mouthwash; Anti-infective agent	solid	water insoluble*	20%	n.p.	2	Very severe	Very Severe	Category 1		SCNM	SCNM	Balls et al. (1995)
Chlorhexidine	55-56-1	Amine/Amidine	Disinfectant; Mouthwash; Anti-infective agent	solid	water insoluble*	20%	n.p.	3	Very severe	Very Severe	Category 1	4	SCNM	SCNM	Balls et al. (1995)
Chlorhexidine	55-56-1	Amine/Amidine	Disinfectant; Mouthwash; Anti-infective agent	solid	water insoluble*	20%	n.p.	4	Very severe	Very Severe	Category 1		SCNM	SCNM	Balls et al. (1995)
Chlorhexidine	55-56-1	Amine/Amidine	Disinfectant; Mouthwash; Anti-infective agent	solid	water insoluble*	20%	n.p.	5	Very severe	Very Severe	Category 1		SCNM	SCNM	Balls et al. (1995)
Cyclohexanol	108-93-0	Alcohol	Sovent; Chemical intermediate	liquid	water soluble	100%	97	1	Very severe	Moderate	Category 1		Category I	R41	Balls et al. (1995)
Cyclohexanol	108-93-0	Alcohol	Sovent; Chemical intermediate	liquid	water soluble	100%	97	2	Moderate	Moderate	Category 1		Category I	R41	Balls et al. (1995)
Cyclohexanol	108-93-0	Alcohol	Sovent; Chemical intermediate	liquid	water soluble	100%	97	3	Severe	Moderate	Category 1	2	Category I	R41	Balls et al. (1995)
Cyclohexanol	108-93-0	Alcohol	Sovent; Chemical intermediate	liquid	water soluble	100%	97	4	Moderate	Moderate	Category 1		Category I	R41	Balls et al. (1995)
Cyclohexanol	108-93-0	Alcohol	Sovent; Chemical intermediate	liquid	water soluble	100%	97	5	Moderate	Moderate	Category 1		Category I	R41	Balls et al. (1995)
Dibenzyl phosphate	1623-08-1	Ester, Organophosphorus compound	Not classified	solid	water insoluble*	20%	99	1	Very severe	Very Severe	Category 2A		Category II	R36	Balls et al. (1995)
Dibenzyl phosphate	1623-08-1	Ester, Organophosphorus compound	Not classified	solid	water insoluble*	20%	99	2	Very severe	Very Severe	Category 2A		Category II	R36	Balls et al. (1995)
Dibenzyl phosphate	1623-08-1	Ester, Organophosphorus compound	Not classified	solid	water insoluble*	20%	99	3	Very severe	Very Severe	Category 2A		Category II	R36	Balls et al. (1995)
Dibenzyl phosphate	1623-08-1	Ester, Organophosphorus compound	Not classified	solid	water insoluble*	20%	99	4	Very severe	Very Severe	Category 2A		Category II	R36	Balls et al. (1995)
Dibenzyl phosphate	1623-08-1	Ester, Organophosphorus compound	Not classified	solid	water insoluble*	20%	99	5	Very severe	Very Severe	Category 2A		Category II	R36	Balls et al. (1995)
2,6-Dichlorobenzoyl chloride	4659-45-4	Acyl halide	Anti-infective; Anti-fungal; Preservative	liquid	water insoluble*	100%	99	1	Mild	Mild	Category 2A		Category II	SCNM	Balls et al. (1995)
2,6-Dichlorobenzoyl chloride	4659-45-4	Acyl halide	Anti-infective; Anti-fungal; Preservative	liquid	water insoluble*	100%	99	2	Mild	Mild	Category 2A		Category II	SCNM	Balls et al. (1995)
2,6-Dichlorobenzoyl chloride	4659-45-4	Acyl halide	Anti-infective; Anti-fungal; Preservative	liquid	water insoluble*	100%	99	3	Mild	Mild	Category 2A		Category II	SCNM	Balls et al. (1995)
2,6-Dichlorobenzoyl chloride	4659-45-4	Acyl halide	Anti-infective; Anti-fungal; Preservative	liquid	water insoluble*	100%	99	4	Mild	Mild	Category 2A		Category II	SCNM	Balls et al. (1995)
2,6-Dichlorobenzoyl chloride	4659-45-4	Acyl halide	Anti-infective; Anti-fungal; Preservative	liquid	water insoluble*	100%	99	5	Mild	Mild	Category 2A		Category II	SCNM	Balls et al. (1995)
2,2-Dimethylbutanoic acid	595-37-9	Carboxylic acid	Pharmaceutical metabolite	liquid	water insoluble	100%	96	1	Very severe	Very Severe	SCNM		Category I	SCNM	Balls et al. (1995)
2,2-Dimethylbutanoic acid	595-37-9	Carboxylic acid	Pharmaceutical metabolite	liquid	water insoluble	100%	96	2	Very severe	Very Severe	SCNM		Category I	SCNM	Balls et al. (1995)
2,2-Dimethylbutanoic acid	595-37-9	Carboxylic acid	Pharmaceutical metabolite	liquid	water insoluble	100%	96	3	Very severe	Very Severe	SCNM		Category I	SCNM	Balls et al. (1995)
2,2-Dimethylbutanoic acid	595-37-9	Carboxylic acid	Pharmaceutical metabolite	liquid	water insoluble	100%	96	4	Very severe	Very Severe	SCNM		Category I	SCNM	Balls et al. (1995)
2,2-Dimethylbutanoic acid	595-37-9	Carboxylic acid	Pharmaceutical metabolite	liquid	water insoluble	100%	96	5	Severe	Very Severe	SCNM		Category I	SCNM	Balls et al. (1995)
2,5-Dimethylhexanediol	110-03-2	Alcohol	Intermediate for pharmaceticals, pesticides, perfumes	solid	water insoluble	20%	99.5	1	Mild	Mild	Category 1		Category I	R41	Balls et al. (1995)

Substance	CASRN[1]	Chemical Class	Product Class	Form Tested	Solubility	Concentration Tested	Purity (%)	Lab No.	In VitroTest Call[2]	In Vitro Consensus Call[2]	In Vivo GHS[4,5]	GHS Category 1 SubClass[6]	In Vivo EPA[7,8]	In Vivo EU[9,10]	Reference
2,5-Dimethylhexanediol	110-03-2	Alcohol	Intermediate for pharmaceuticals, pesticides, perfumes	solid	water insoluble	20%	99.5	2	Moderate	Mild	Category 1		Category I	R41	Balls et al. (1995)
2,5-Dimethylhexanediol	110-03-2	Alcohol	Intermediate for pharmaceuticals, pesticides, perfumes	solid	water insoluble	20%	99.5	3	Mild	Mild	Category 1	1	Category I	R41	Balls et al. (1995)
2,5-Dimethylhexanediol	110-03-2	Alcohol	Intermediate for pharmaceuticals, pesticides, perfumes	solid	water insoluble	20%	99.5	4	Moderate	Mild	Category 1		Category I	R41	Balls et al. (1995)
2,5-Dimethylhexanediol	110-03-2	Alcohol	Intermediate for pharmaceuticals, pesticides, perfumes	solid	water insoluble	20%	99.5	5	Mild	Mild	Category 1		Category I	R41	Balls et al. (1995)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	1	Severe	Severe	Category 2A		Category III	Nonirritant	Balls et al. (1995)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	2	Moderate	Severe	Category 2A		Category III	Nonirritant	Balls et al. (1995)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	3	Severe	Severe	Category 2A		Category III	Nonirritant	Balls et al. (1995)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	4	Very severe	Severe	Category 2A		Category III	Nonirritant	Balls et al. (1995)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	5	Severe	Severe	Category 2A		Category III	Nonirritant	Balls et al. (1995)
Ethyl acetate	141-78-6	Ester	Solvent; Synthetic flavoring	liquid	water soluble	100%	99	1	Mild	Moderate	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Ethyl acetate	141-78-6	Ester	Solvent; Synthetic flavoring	liquid	water soluble	100%	99	2	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Ethyl acetate	141-78-6	Ester	Solvent; Synthetic flavoring	liquid	water soluble	100%	99	3	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Ethyl acetate	141-78-6	Ester	Solvent; Synthetic flavoring	liquid	water soluble	100%	99	4	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Ethyl acetate	141-78-6	Ester	Solvent; Synthetic flavoring	liquid	water soluble	100%	99	5	Mild	Moderate	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
2-Ethyl-1-hexanol	104-76-7	Alcohol	Solvent; Plasticizer	liquid	water soluble	100%	99	1	Severe	Nonsevere	Category 2A		Category II	R36	Balls et al. (1995)
2-Ethyl-1-hexanol	104-76-7	Alcohol	Solvent; Plasticizer	liquid	water soluble	100%	99	2	Moderate	Nonsevere	Category 2A		Category II	R36	Balls et al. (1995)
2-Ethyl-1-hexanol	104-76-7	Alcohol	Solvent; Plasticizer	liquid	water soluble	100%	99	3	Moderate	Nonsevere	Category 2A		Category II	R36	Balls et al. (1995)
2-Ethyl-1-hexanol	104-76-7	Alcohol	Solvent; Plasticizer	liquid	water soluble	100%	99	4	Severe	Nonsevere	Category 2A		Category II	R36	Balls et al. (1995)
2-Ethyl-1-hexanol	104-76-7	Alcohol	Solvent; Plasticizer	liquid	water soluble	100%	99	5	Mild	Nonsevere	Category 2A		Category II	R36	Balls et al. (1995)
Ethyl-2-methylacetoacetate	609-14-3	Ketone, Ester	Not classified	liquid	water soluble*	100%	97	1	Moderate	Mild	Category 2B		Category III	Nonirritant	Balls et al. (1995)
Ethyl-2-methylacetoacetate	609-14-3	Ketone, Ester	Not classified	liquid	water soluble*	100%	97	2	Mild	Mild	Category 2B		Category III	Nonirritant	Balls et al. (1995)
Ethyl-2-methylacetoacetate	609-14-3	Ketone, Ester	Not classified	liquid	water soluble*	100%	97	3	Mild	Mild	Category 2B		Category III	Nonirritant	Balls et al. (1995)
Ethyl-2-methylacetoacetate	609-14-3	Ketone, Ester	Not classified	liquid	water soluble*	100%	97	4	Mild	Mild	Category 2B		Category III	Nonirritant	Balls et al. (1995)
Ethyl-2-methylacetoacetate	609-14-3	Ketone, Ester	Not classified	liquid	water soluble*	100%	97	5	Mild	Mild	Category 2B		Category III	Nonirritant	Balls et al. (1995)
Ethyl trimethyl acetate	3938-95-2	Ester	Solvent	liquid	water insoluble*	100%	99	1	Moderate	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Ethyl trimethyl acetate	3938-95-2	Ester	Solvent	liquid	water insoluble*	100%	99	2	Moderate	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Ethyl trimethyl acetate	3938-95-2	Ester	Solvent	liquid	water insoluble*	100%	99	3	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Ethyl trimethyl acetate	3938-95-2	Ester	Solvent	liquid	water insoluble*	100%	99	4	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Ethyl trimethyl acetate	3938-95-2	Ester	Solvent	liquid	water insoluble*	100%	99	5	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Fomesafen	72128-02-0	Imide, Ether, Nitro compound	Pesticide	solid	water soluble	20%	97.5	1	Moderate	Nonsevere	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Fomesafen	72128-02-0	Imide, Ether, Nitro compound	Pesticide	solid	water soluble	20%	97.5	2	Very severe	Nonsevere	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Fomesafen	72128-02-0	Imide, Ether, Nitro compound	Pesticide	solid	water soluble	20%	97.5	3	Severe	Nonsevere	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Fomesafen	72128-02-0	Imide, Ether, Nitro compound	Pesticide	solid	water soluble	20%	97.5	4	Mild	Nonsevere	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Fomesafen	72128-02-0	Imide, Ether, Nitro compound	Pesticide	solid	water soluble	20%	97.5	5	Mild	Nonsevere	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Glycerol	56-81-5	Alcohol	Solvent; Plasticizer; Lubricant; Emollient; Drug vehicle	liquid	water soluble	100%	>99.5	1	Mild	Mild	Nonirritant		Category IV	Nonirritant	Balls et al. (1995)
Glycerol	56-81-5	Alcohol	Solvent; Plasticizer; Lubricant; Emollient; Drug vehicle	liquid	water soluble	100%	>99.5	2	Mild	Mild	Nonirritant		Category IV	Nonirritant	Balls et al. (1995)
Glycerol	56-81-5	Alcohol	Solvent; Plasticizer; Lubricant; Emollient; Drug vehicle	liquid	water soluble	100%	>99.5	3	Mild	Mild	Nonirritant		Category IV	Nonirritant	Balls et al. (1995)
Glycerol	56-81-5	Alcohol	Solvent; Plasticizer; Lubricant; Emollient; Drug vehicle	liquid	water soluble	100%	>99.5	4	Mild	Mild	Nonirritant		Category IV	Nonirritant	Balls et al. (1995)
Glycerol	56-81-5	Alcohol	Solvent; Plasticizer; Lubricant; Emollient; Drug vehicle	liquid	water soluble	100%	>99.5	5	Mild	Mild	Nonirritant		Category IV	Nonirritant	Balls et al. (1995)
n-Hexanol	111-27-3	Alcohol	Solvent; Chemical intermediate; Synthetic flavor ingredient	liquid	water insoluble*	100%	98	1	Severe	Severe/Very Severe	Category 2A		Category II	R36	Balls et al. (1995)
n-Hexanol	111-27-3	Alcohol	Solvent; Chemical intermediate; Synthetic flavor ingredient	liquid	water insoluble*	100%	98	2	Very severe	Severe/Very Severe	Category 2A		Category II	R36	Balls et al. (1995)
n-Hexanol	111-27-3	Alcohol	Solvent; Chemical intermediate; Synthetic flavor ingredient	liquid	water insoluble*	100%	98	3	Severe	Severe/Very Severe	Category 2A		Category II	R36	Balls et al. (1995)
n-Hexanol	111-27-3	Alcohol	Solvent; Chemical intermediate; Synthetic flavor ingredient	liquid	water insoluble*	100%	98	4	Moderate	Severe/Very Severe	Category 2A		Category II	R36	Balls et al. (1995)
n-Hexanol	111-27-3	Alcohol	Solvent; Chemical intermediate; Synthetic flavor ingredient	liquid	water insoluble*	100%	98	5	Moderate	Severe/Very Severe	Category 2A		Category II	R36	Balls et al. (1995)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	99	1	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	99	2	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	99	3	Very severe	Very Severe	Category 1	4	Category I	R41	Balls et al. (1995)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	99	4	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	99	5	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Isobutanol	78-83-1	Alcohol	Solvent; Chemical intermediate; Flavor ingredient	liquid	water insoluble*	100%	99.9	1	Moderate	Moderate	Category 2A		Category II	R36	Balls et al. (1995)
Isobutanol	78-83-1	Alcohol	Solvent; Chemical intermediate; Flavor ingredient	liquid	water insoluble*	100%	99.9	2	Severe	Moderate	Category 2A		Category II	R36	Balls et al. (1995)
Isobutanol	78-83-1	Alcohol	Solvent; Chemical intermediate; Flavor ingredient	liquid	water insoluble*	100%	99.9	3	Severe	Moderate	Category 2A		Category II	R36	Balls et al. (1995)
Isobutanol	78-83-1	Alcohol	Solvent; Chemical intermediate; Flavor ingredient	liquid	water insoluble*	100%	99.9	4	Moderate	Moderate	Category 2A		Category II	R36	Balls et al. (1995)
Isobutanol	78-83-1	Alcohol	Solvent; Chemical intermediate; Flavor ingredient	liquid	water insoluble*	100%	99.9	5	Moderate	Moderate	Category 2A		Category II	R36	Balls et al. (1995)

Substance	CASRN[1]	Chemical Class	Product Class	Form Tested	Solubility	Concentration Tested	Purity (%)	Lab No.	In VitroTest Call[2]	In Vitro Consensus Call[2]	In Vivo GHS[4,5]	GHS Category 1 SubClass[6]	In Vivo EPA[7,8]	In Vivo EU[9,10]	Reference
Isopropanol	67-63-0	Alcohol	Solvent; Aerosol formulations (ingredient)	liquid	water soluble	100%	99.9	1	Moderate	Severe	Category 2A		Category III	SCNM	Balls et al. (1995)
Isopropanol	67-63-0	Alcohol	Solvent; Aerosol formulations (ingredient)	liquid	water soluble	100%	99.9	2	Severe	Severe	Category 2A		Category III	SCNM	Balls et al. (1995)
Isopropanol	67-63-0	Alcohol	Solvent; Aerosol formulations (ingredient)	liquid	water soluble	100%	99.9	3	Severe	Severe	Category 2A		Category III	SCNM	Balls et al. (1995)
Isopropanol	67-63-0	Alcohol	Solvent; Aerosol formulations (ingredient)	liquid	water soluble	100%	99.9	4	Severe	Severe	Category 2A		Category III	SCNM	Balls et al. (1995)
Isopropanol	67-63-0	Alcohol	Solvent; Aerosol formulations (ingredient)	liquid	water soluble	100%	99.9	5	Moderate	Severe	Category 2A		Category III	SCNM	Balls et al. (1995)
Maneb	12427-38-2	Amine/Amidine, Organic salt, Urea compound	Pesticide	solid	water soluble	20%	90	1	Severe	Nonsevere	SCNM		Category III	SCNM	Balls et al. (1995)
Maneb	12427-38-2	Amine/Amidine, Organic salt, Urea compound	Pesticide	solid	water soluble	20%	90	2	Mild	Nonsevere	SCNM		Category III	SCNM	Balls et al. (1995)
Maneb	12427-38-2	Amine/Amidine, Organic salt, Urea compound	Pesticide	solid	water soluble	20%	90	3	Mild	Nonsevere	SCNM		Category III	SCNM	Balls et al. (1995)
Maneb	12427-38-2	Amine/Amidine, Organic salt, Urea compound	Pesticide	solid	water soluble	20%	90	4	Severe	Nonsevere	SCNM		Category III	SCNM	Balls et al. (1995)
Maneb	12427-38-2	Amine/Amidine, Organic salt, Urea compound	Pesticide	solid	water soluble	20%	90	5	Moderate	Nonsevere	SCNM		Category III	SCNM	Balls et al. (1995)
Methyl acetate	79-20-9	Ester	Solvent; Chemical intermediate; Synthetic flavor ingredient	liquid	water soluble	100%	98	1	Severe	Moderate	Category 2A		Category II	R36	Balls et al. (1995)
Methyl acetate	79-20-9	Ester	Solvent; Chemical intermediate; Synthetic flavor ingredient	liquid	water soluble	100%	98	2	Moderate	Moderate	Category 2A		Category II	R36	Balls et al. (1995)
Methyl acetate	79-20-9	Ester	Solvent; Chemical intermediate; Synthetic flavor ingredient	liquid	water soluble	100%	98	3	Moderate	Moderate	Category 2A		Category II	R36	Balls et al. (1995)
Methyl acetate	79-20-9	Ester	Solvent; Chemical intermediate; Synthetic flavor ingredient	liquid	water soluble	100%	98	4	Moderate	Moderate	Category 2A		Category II	R36	Balls et al. (1995)
Methyl acetate	79-20-9	Ester	Solvent; Chemical intermediate; Synthetic flavor ingredient	liquid	water soluble	100%	98	5	Moderate	Moderate	Category 2A		Category II	R36	Balls et al. (1995)
Methyl cyanoacetate	105-34-0	Ester, Nitrile compound	Adhesive; Pharmaceutical intermediate	liquid	water soluble*	100%	99	1	Mild	Mild	Category 2A		Category II	R36	Balls et al. (1995)
Methyl cyanoacetate	105-34-0	Ester, Nitrile compound	Adhesive; Pharmaceutical intermediate	liquid	water soluble*	100%	99	2	Mild	Mild	Category 2A		Category II	R36	Balls et al. (1995)
Methyl cyanoacetate	105-34-0	Ester, Nitrile compound	Adhesive; Pharmaceutical intermediate	liquid	water soluble*	100%	99	3	Mild	Mild	Category 2A		Category II	R36	Balls et al. (1995)
Methyl cyanoacetate	105-34-0	Ester, Nitrile compound	Adhesive; Pharmaceutical intermediate	liquid	water soluble*	100%	99	4	Mild	Mild	Category 2A		Category II	R36	Balls et al. (1995)
Methyl cyanoacetate	105-34-0	Ester, Nitrile compound	Adhesive; Pharmaceutical intermediate	liquid	water soluble*	100%	99	5	Mild	Mild	Category 2A		Category II	R36	Balls et al. (1995)
Methylcyclopentane	96-37-7	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	liquid	water insoluble*	100%	>99	1	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Methylcyclopentane	96-37-7	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	liquid	water insoluble*	100%	>99	2	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Methylcyclopentane	96-37-7	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	liquid	water insoluble*	100%	>99	3	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Methylcyclopentane	96-37-7	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	liquid	water insoluble*	100%	>99	4	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Methylcyclopentane	96-37-7	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	liquid	water insoluble*	100%	>99	5	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Methyl ethyl ketone	78-93-3	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	liquid	water soluble	100%	99	1	Very severe	Severe	Category 2A		Category III	R36	Balls et al. (1995)
Methyl ethyl ketone	78-93-3	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	liquid	water soluble	100%	99	2	Severe	Severe	Category 2A		Category III	R36	Balls et al. (1995)
Methyl ethyl ketone	78-93-3	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	liquid	water soluble	100%	99	3	Moderate	Severe	Category 2A		Category III	R36	Balls et al. (1995)
Methyl ethyl ketone	78-93-3	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	liquid	water soluble	100%	99	4	Severe	Severe	Category 2A		Category III	R36	Balls et al. (1995)
Methyl ethyl ketone	78-93-3	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	liquid	water soluble	100%	99	5	Severe	Severe	Category 2A		Category III	R36	Balls et al. (1995)
Methyl isobutyl ketone	108-10-1	Ketone	Solvent; Synthetic flavor; Drycleaning	liquid	water insoluble*	100%	98	1	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Methyl isobutyl ketone	108-10-1	Ketone	Solvent; Synthetic flavor; Drycleaning	liquid	water insoluble*	100%	98	2	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Methyl isobutyl ketone	108-10-1	Ketone	Solvent; Synthetic flavor; Drycleaning	liquid	water insoluble*	100%	98	3	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Methyl isobutyl ketone	108-10-1	Ketone	Solvent; Synthetic flavor; Drycleaning	liquid	water insoluble*	100%	98	4	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Methyl isobutyl ketone	108-10-1	Ketone	Solvent; Synthetic flavor; Drycleaning	liquid	water insoluble*	100%	98	5	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
1-Naphthalene acetic acid	86-87-3	Carboxylic acid, Polycyclic compound	Pesticide	solid	water insoluble*	20%	96	1	Very severe	Very Severe	Category 1		Category I	SCNM	Balls et al. (1995)
1-Naphthalene acetic acid	86-87-3	Carboxylic acid, Polycyclic compound	Pesticide	solid	water insoluble*	20%	96	2	Severe	Very Severe	Category 1		Category I	SCNM	Balls et al. (1995)
1-Naphthalene acetic acid	86-87-3	Carboxylic acid, Polycyclic compound	Pesticide	solid	water insoluble*	20%	96	3	Moderate	Very Severe	Category 1	NC	Category I	SCNM	Balls et al. (1995)
1-Naphthalene acetic acid	86-87-3	Carboxylic acid, Polycyclic compound	Pesticide	solid	water insoluble*	20%	96	4	Very severe	Very Severe	Category 1		Category I	SCNM	Balls et al. (1995)
1-Naphthalene acetic acid	86-87-3	Carboxylic acid, Polycyclic compound	Pesticide	solid	water insoluble*	20%	96	5	Severe	Very Severe	Category 1		Category I	SCNM	Balls et al. (1995)
1-Naphthalene acetic acid, Na salt	61-31-4	Carboxylic acid (salt), Polycyclic compound	Pesticide	solid	water soluble*	20%	95	1	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
1-Naphthalene acetic acid, Na salt	61-31-4	Carboxylic acid (salt), Polycyclic compound	Pesticide	solid	water soluble*	20%	95	2	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
1-Naphthalene acetic acid, Na salt	61-31-4	Carboxylic acid (salt), Polycyclic compound	Pesticide	solid	water soluble*	20%	95	3	Very severe	Very Severe	Category 1	1	Category I	R41	Balls et al. (1995)
1-Naphthalene acetic acid, Na salt	61-31-4	Carboxylic acid (salt), Polycyclic compound	Pesticide	solid	water soluble*	20%	95	4	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)

Substance	CASRN[1]	Chemical Class	Product Class	Form Tested	Solubility	Concentration Tested	Purity (%)	Lab No.	In VitroTest Call[2]	In Vitro Consensus Call[2]	In Vivo GHS[4,5]	GHS Category 1 SubClass[6]	In Vivo EPA[7,8]	In Vivo EU[5,10]	Reference
1-Naphthalene acetic acid, Na salt	61-31-4	Carboxylic acid (salt), Polycyclic compound	Pesticide	solid	water soluble*	20%	95	5	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
n-Octanol	111-87-5	Alcohol	Solvent; Fragrance	liquid	water insoluble*	100%	>99	1	Moderate	Moderate	Category 2B		Category II	R36	Balls et al. (1995)
n-Octanol	111-87-5	Alcohol	Solvent; Fragrance	liquid	water insoluble*	100%	>99	2	Severe	Moderate	Category 2B		Category II	R36	Balls et al. (1995)
n-Octanol	111-87-5	Alcohol	Solvent; Fragrance	liquid	water insoluble*	100%	>99	3	Moderate	Moderate	Category 2B		Category II	R36	Balls et al. (1995)
n-Octanol	111-87-5	Alcohol	Solvent; Fragrance	liquid	water insoluble*	100%	>99	4	Mild	Moderate	Category 2B		Category II	R36	Balls et al. (1995)
n-Octanol	111-87-5	Alcohol	Solvent; Fragrance	liquid	water insoluble*	100%	>99	5	Moderate	Moderate	Category 2B		Category II	R36	Balls et al. (1995)
Parafluoraniline	371-40-4	Amine/Amidine	Intermediate for herbicides, Dyes	liquid	water insoluble	100%	99	1	Moderate	Moderate	SCNM		SCNM	SCNM	Balls et al. (1995)
Parafluoraniline	371-40-4	Amine/Amidine	Intermediate for herbicides, Dyes	liquid	water insoluble	100%	99	2	Moderate	Moderate	SCNM		SCNM	SCNM	Balls et al. (1995)
Parafluoraniline	371-40-4	Amine/Amidine	Intermediate for herbicides, Dyes	liquid	water insoluble	100%	99	3	Moderate	Moderate	SCNM		SCNM	SCNM	Balls et al. (1995)
Parafluoraniline	371-40-4	Amine/Amidine	Intermediate for herbicides, Dyes	liquid	water insoluble	100%	99	4	Moderate	Moderate	SCNM		SCNM	SCNM	Balls et al. (1995)
Parafluoraniline	371-40-4	Amine/Amidine	Intermediate for herbicides, Dyes	liquid	water insoluble	100%	99	5	Moderate	Moderate	SCNM		SCNM	SCNM	Balls et al. (1995)
Polyethylene glycol 400	25322-68-3	Alcohol, Polyether	Surfactant (nonionic), Lubricant, Plasticizer, Solvent	liquid	surfactant	100%	n.p.	1	Mild	Mild	Nonirritant		Category IV	Nonirritant	Balls et al. (1995)
Polyethylene glycol 400	25322-68-3	Alcohol, Polyether	Surfactant (nonionic), Lubricant, Plasticizer, Solvent	liquid	surfactant	100%	n.p.	2	Mild	Mild	Nonirritant		Category IV	Nonirritant	Balls et al. (1995)
Polyethylene glycol 400	25322-68-3	Alcohol, Polyether	Surfactant (nonionic), Lubricant, Plasticizer, Solvent	liquid	surfactant	100%	n.p.	3	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Balls et al. (1995)
Polyethylene glycol 400	25322-68-3	Alcohol, Polyether	Surfactant (nonionic), Lubricant, Plasticizer, Solvent	liquid	surfactant	100%	n.p.	4	Mild	Mild	Nonirritant		Category IV	Nonirritant	Balls et al. (1995)
Polyethylene glycol 400	25322-68-3	Alcohol, Polyether	Surfactant (nonionic), Lubricant, Plasticizer, Solvent	liquid	surfactant	100%	n.p.	5	Mild	Mild	Nonirritant		Category IV	Nonirritant	Balls et al. (1995)
Potassium cyanate	590-28-3	Inorganic salt	Herbicide; Pharmaceutical intermediate	solid	water soluble	20%	97	1	Mild	Mild	SCNM		SCNM	SCNM	Balls et al. (1995)
Potassium cyanate	590-28-3	Inorganic salt	Herbicide; Pharmaceutical intermediate	solid	water soluble	20%	97	2	Mild	Mild	SCNM		SCNM	SCNM	Balls et al. (1995)
Potassium cyanate	590-28-3	Inorganic salt	Herbicide; Pharmaceutical intermediate	solid	water soluble	20%	97	3	Mild	Mild	SCNM		SCNM	SCNM	Balls et al. (1995)
Potassium cyanate	590-28-3	Inorganic salt	Herbicide; Pharmaceutical intermediate	solid	water soluble	20%	97	4	Mild	Mild	SCNM		SCNM	SCNM	Balls et al. (1995)
Potassium cyanate	590-28-3	Inorganic salt	Herbicide; Pharmaceutical intermediate	solid	water soluble	20%	97	5	Mild	Mild	SCNM		SCNM	SCNM	Balls et al. (1995)
Promethazine hydrochloride	58-33-3	Amine/Amidine, Heterocyclic, Organic sulfur compound	Antihistamine; Anti-nausea drug	solid	water soluble*	20%	98	1	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Promethazine hydrochloride	58-33-3	Amine/Amidine, Heterocyclic, Organic sulfur compound	Antihistamine; Anti-nausea drug	solid	water soluble*	20%	98	2	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Promethazine hydrochloride	58-33-3	Amine/Amidine, Heterocyclic, Organic sulfur compound	Antihistamine; Anti-nausea drug	solid	water soluble*	20%	98	3	Very severe	Very Severe	Category 1	3	Category I	R41	Balls et al. (1995)
Promethazine hydrochloride	58-33-3	Amine/Amidine, Heterocyclic, Organic sulfur compound	Antihistamine; Anti-nausea drug	solid	water soluble*	20%	98	4	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Promethazine hydrochloride	58-33-3	Amine/Amidine, Heterocyclic, Organic sulfur compound	Antihistamine; Anti-nausea drug	solid	water soluble*	20%	98	5	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Pyridine	110-86-1	Heterocyclic	Solvent; Intermediate for pharmaceuticals, dyes, pesticides	liquid	water soluble	100%	>99.9	1	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Pyridine	110-86-1	Heterocyclic	Solvent; Intermediate for pharmaceuticals, dyes, pesticides	liquid	water soluble	100%	>99.9	2	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Pyridine	110-86-1	Heterocyclic	Solvent; Intermediate for pharmaceuticals, dyes, pesticides	liquid	water soluble	100%	>99.9	3	Very severe	Very Severe	Category 1	4	Category I	R41	Balls et al. (1995)
Pyridine	110-86-1	Heterocyclic	Solvent; Intermediate for pharmaceuticals, dyes, pesticides	liquid	water soluble	100%	>99.9	4	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Pyridine	110-86-1	Heterocyclic	Solvent; Intermediate for pharmaceuticals, dyes, pesticides	liquid	water soluble	100%	>99.9	5	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Quinacrine	69-05-6	Heterocyclic	Drug/Therapeutic agent	solid	water soluble*	20%	n.p.	1	Mild	Mild	Category 1		Category I	R41	Balls et al. (1995)
Quinacrine	69-05-6	Heterocyclic	Drug/Therapeutic agent	solid	water soluble*	20%	n.p.	2	Mild	Mild	Category 1		Category I	R41	Balls et al. (1995)
Quinacrine	69-05-6	Heterocyclic	Drug/Therapeutic agent	solid	water soluble*	20%	n.p.	3	Mild	Mild	Category 1	1	Category I	R41	Balls et al. (1995)
Quinacrine	69-05-6	Heterocyclic	Drug/Therapeutic agent	solid	water soluble*	20%	n.p.	4	Mild	Mild	Category 1		Category I	R41	Balls et al. (1995)
Quinacrine	69-05-6	Heterocyclic	Drug/Therapeutic agent	solid	water soluble*	20%	n.p.	5	Mild	Mild	Category 1		Category I	R41	Balls et al. (1995)
Sodium hydroxide (10%)	1310-73-2	Alkali	Caustic agent	liquid	water soluble	10%	reagent grade	1	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Sodium hydroxide (10%)	1310-73-2	Alkali	Caustic agent	liquid	water soluble	10%	reagent grade	2	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Sodium hydroxide (10%)	1310-73-2	Alkali	Caustic agent	liquid	water soluble	10%	reagent grade	3	Very severe	Very Severe	Category 1	4	Category I	R41	Balls et al. (1995)
Sodium hydroxide (10%)	1310-73-2	Alkali	Caustic agent	liquid	water soluble	10%	reagent grade	4	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Sodium hydroxide (10%)	1310-73-2	Alkali	Caustic agent	liquid	water soluble	10%	reagent grade	5	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Sodium hydroxide (1%)	1310-73-2	Alkali	Caustic agent	liquid	water soluble	1%	reagent grade	1	Very severe	Very Severe	Category 2B		Category III	R36	Balls et al. (1995)
Sodium hydroxide (1%)	1310-73-2	Alkali	Caustic agent	liquid	water soluble	1%	reagent grade	2	Very severe	Very Severe	Category 2B		Category III	R36	Balls et al. (1995)
Sodium hydroxide (1%)	1310-73-2	Alkali	Caustic agent	liquid	water soluble	1%	reagent grade	3	Very severe	Very Severe	Category 2B		Category III	R36	Balls et al. (1995)
Sodium hydroxide (1%)	1310-73-2	Alkali	Caustic agent	liquid	water soluble	1%	reagent grade	4	Very severe	Very Severe	Category 2B		Category III	R36	Balls et al. (1995)
Sodium hydroxide (1%)	1310-73-2	Alkali	Caustic agent	liquid	water soluble	1%	reagent grade	5	Very severe	Very Severe	Category 2B		Category III	R36	Balls et al. (1995)
Sodium lauryl sulfate (3 %)	151-21-3	Carboxylic acid (salt)	Surfactant (anionic), Detergent	liquid	surfactant	3%	98	1	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Sodium lauryl sulfate (3 %)	151-21-3	Carboxylic acid (salt)	Surfactant (anionic), Detergent	liquid	surfactant	3%	98	2	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Sodium lauryl sulfate (3 %)	151-21-3	Carboxylic acid (salt)	Surfactant (anionic), Detergent	liquid	surfactant	3%	98	3	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Sodium lauryl sulfate (3 %)	151-21-3	Carboxylic acid (salt)	Surfactant (anionic), Detergent	liquid	surfactant	3%	98	4	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Sodium lauryl sulfate (3 %)	151-21-3	Carboxylic acid (salt)	Surfactant (anionic), Detergent	liquid	surfactant	3%	98	5	Mild	Moderate	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Sodium lauryl sulfate (15 %)	151-21-3	Carboxylic acid (salt)	Surfactant (anionic), Detergent	liquid	surfactant	15%	98	1	Moderate	Severe	Category 1		Category I	R36	Balls et al. (1995)
Sodium lauryl sulfate (15 %)	151-21-3	Carboxylic acid (salt)	Surfactant (anionic), Detergent	liquid	surfactant	15%	98	2	Very severe	Severe	Category 1		Category I	R36	Balls et al. (1995)
Sodium lauryl sulfate (15 %)	151-21-3	Carboxylic acid (salt)	Surfactant (anionic), Detergent	liquid	surfactant	15%	98	3	Severe	Severe	Category 1	NC	Category I	R36	Balls et al. (1995)
Sodium lauryl sulfate (15 %)	151-21-3	Carboxylic acid (salt)	Surfactant (anionic), Detergent	liquid	surfactant	15%	98	4	Severe	Severe	Category 1		Category I	R36	Balls et al. (1995)
Sodium lauryl sulfate (15 %)	151-21-3	Carboxylic acid (salt)	Surfactant (anionic), Detergent	liquid	surfactant	15%	98	5	Moderate	Severe	Category 1		Category I	R36	Balls et al. (1995)
Sodium oxalate	62-76-0	Carboxylic acid (salt)	Textile finishing; Pyrotechnic, Industrial byproduct	solid	water soluble	20%	>99	1	Mild	Mild	Category 1		Category I	R41	Balls et al. (1995)

Substance	CASRN[1]	Chemical Class	Product Class	Form Tested	Solubility	Concentration Tested	Purity (%)	Lab No.	In VitroTest Call[2]	In Vitro Consensus Call[2]	In Vivo GHS[4,5]	GHS Category 1 SubClass[6]	In Vivo EPA[7,8]	In Vivo EU[9,10]	Reference
Sodium oxalate	62-76-0	Carboxylic acid (salt)	Textile finishing; Pyrotechnic, Industrial byproduct	solid	water soluble	20%	>99	2	Mild	Mild	Category 1		Category I	R41	Balls et al. (1995)
Sodium oxalate	62-76-0	Carboxylic acid (salt)	Textile finishing; Pyrotechnic, Industrial byproduct	solid	water soluble	20%	>99	3	Mild	Mild	Category 1	4	Category I	R41	Balls et al. (1995)
Sodium oxalate	62-76-0	Carboxylic acid (salt)	Textile finishing; Pyrotechnic, Industrial byproduct	solid	water soluble	20%	>99	4	Moderate	Mild	Category 1		Category I	R41	Balls et al. (1995)
Sodium oxalate	62-76-0	Carboxylic acid (salt)	Textile finishing; Pyrotechnic, Industrial byproduct	solid	water soluble	20%	>99	5	Mild	Mild	Category 1		Category I	R41	Balls et al. (1995)
Sodium perborate	10486-00-7	Inorganic salt, Boron compound	Household cleaner; Detergent	solid	water soluble	20%	98.6	1	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Sodium perborate	10486-00-7	Inorganic salt, Boron compound	Household cleaner; Detergent	solid	water soluble	20%	98.6	2	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Sodium perborate	10486-00-7	Inorganic salt, Boron compound	Household cleaner; Detergent	solid	water soluble	20%	98.6	3	Very severe	Very Severe	Category 1	4	Category I	R41	Balls et al. (1995)
Sodium perborate	10486-00-7	Inorganic salt, Boron compound	Household cleaner; Detergent	solid	water soluble	20%	98.6	4	Severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Sodium perborate	10486-00-7	Inorganic salt, Boron compound	Household cleaner; Detergent	solid	water soluble	20%	98.6	5	Severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Tetraaminopyrimidine sulfate	5392-28-9	Amine, Heterocycle, Inorganic salt	Not classified	solid	water insoluble*	20%	97	1	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Tetraaminopyrimidine sulfate	5392-28-9	Amine, Heterocycle, Inorganic salt	Not classified	solid	water insoluble*	20%	97	2	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Tetraaminopyrimidine sulfate	5392-28-9	Amine, Heterocycle, Inorganic salt	Not classified	solid	water insoluble*	20%	97	3	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Tetraaminopyrimidine sulfate	5392-28-9	Amine, Heterocycle, Inorganic salt	Not classified	solid	water insoluble*	20%	97	4	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Tetraaminopyrimidine sulfate	5392-28-9	Amine, Heterocycle, Inorganic salt	Not classified	solid	water insoluble*	20%	97	5	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Thiourea	62-56-6	Organic sulfur compound	Photographic agent; Flame-retardant; Chelation reagent and catalyst; Chemical intermediate; Pesticide; Drug/Therapeutic agent	solid	water soluble	20%	>99	1	Very severe	Very Severe	Animal died		Animal died	Animal died	Balls et al. (1995)
Thiourea	62-56-6	Organic sulfur compound	Photographic agent; Flame-retardant; Chelation reagent and catalyst; Chemical intermediate; Pesticide; Drug/Therapeutic agent	solid	water soluble	20%	>99	2	Very severe	Very Severe	Animal died		Animal died	Animal died	Balls et al. (1995)
Thiourea	62-56-6	Organic sulfur compound	Photographic agent; Flame-retardant; Chelation reagent and catalyst; Chemical intermediate; Pesticide; Drug/Therapeutic agent	solid	water soluble	20%	>99	3	Very severe	Very Severe	Animal died		Animal died	Animal died	Balls et al. (1995)
Thiourea	62-56-6	Organic sulfur compound	Photographic agent; Flame-retardant; Chelation reagent and catalyst; Chemical intermediate; Pesticide; Drug/Therapeutic agent	solid	water soluble	20%	>99	4	Very severe	Very Severe	Animal died		Animal died	Animal died	Balls et al. (1995)
Thiourea	62-56-6	Organic sulfur compound	Photographic agent; Flame-retardant; Chelation reagent and catalyst; Chemical intermediate; Pesticide; Drug/Therapeutic agent	solid	water soluble	20%	>99	5	Very severe	Very Severe	Animal died		Animal died	Animal died	Balls et al. (1995)
Toluene	108-88-3	Hydrocarbon (cyclic)	Solvent	liquid	water insoluble*	100%	99	1	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Toluene	108-88-3	Hydrocarbon (cyclic)	Solvent	liquid	water insoluble*	100%	99	2	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Toluene	108-88-3	Hydrocarbon (cyclic)	Solvent	liquid	water insoluble*	100%	99	3	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Toluene	108-88-3	Hydrocarbon (cyclic)	Solvent	liquid	water insoluble*	100%	99	4	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Toluene	108-88-3	Hydrocarbon (cyclic)	Solvent	liquid	water insoluble*	100%	99	5	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Trichloroacetic acid (30%)	76-03-9	Carboxylic acid	Caustic agent; Fixative; Herbicide	liquid	water soluble	30%	reagent grade	1	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Trichloroacetic acid (30%)	76-03-9	Carboxylic acid	Caustic agent; Fixative; Herbicide	liquid	water soluble	30%	reagent grade	2	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Trichloroacetic acid (30%)	76-03-9	Carboxylic acid	Caustic agent; Fixative; Herbicide	liquid	water soluble	30%	reagent grade	3	Very severe	Very Severe	Category 1	4	Category I	R41	Balls et al. (1995)
Trichloroacetic acid (30%)	76-03-9	Carboxylic acid	Caustic agent; Fixative; Herbicide	liquid	water soluble	30%	reagent grade	4	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Trichloroacetic acid (30%)	76-03-9	Carboxylic acid	Caustic agent; Fixative; Herbicide	liquid	water soluble	30%	reagent grade	5	Very severe	Very Severe	Category 1		Category I	R41	Balls et al. (1995)
Trichloroacetic acid (3%)	76-03-9	Carboxylic acid	Caustic agent; Fixative; Herbicide	liquid	water soluble	3%	reagent grade	1	Very severe	Severe/Very Severe	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Trichloroacetic acid (3%)	76-03-9	Carboxylic acid	Caustic agent; Fixative; Herbicide	liquid	water soluble	3%	reagent grade	2	Moderate	Severe/Very Severe	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Trichloroacetic acid (3%)	76-03-9	Carboxylic acid	Caustic agent; Fixative; Herbicide	liquid	water soluble	3%	reagent grade	3	Severe	Severe/Very Severe	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Trichloroacetic acid (3%)	76-03-9	Carboxylic acid	Caustic agent; Fixative; Herbicide	liquid	water soluble	3%	reagent grade	4	Very severe	Severe/Very Severe	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Trichloroacetic acid (3%)	76-03-9	Carboxylic acid	Caustic agent; Fixative; Herbicide	liquid	water soluble	3%	reagent grade	5	Severe	Severe/Very Severe	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Triton X-100 (5 %)	9002-93-1	Ether	Surfactant (nonionic), Detergent, Emulsifier	liquid	surfactant	5%	98	1	Severe	Very Severe	Category 2A		Category III	Nonirritant	Balls et al. (1995)
Triton X-100 (5 %)	9002-93-1	Ether	Surfactant (nonionic), Detergent, Emulsifier	liquid	surfactant	5%	98	2	Very severe	Very Severe	Category 2A		Category III	Nonirritant	Balls et al. (1995)
Triton X-100 (5 %)	9002-93-1	Ether	Surfactant (nonionic), Detergent, Emulsifier	liquid	surfactant	5%	98	3	Very severe	Very Severe	Category 2A		Category III	Nonirritant	Balls et al. (1995)
Triton X-100 (5 %)	9002-93-1	Ether	Surfactant (nonionic), Detergent, Emulsifier	liquid	surfactant	5%	98	4	Very severe	Very Severe	Category 2A		Category III	Nonirritant	Balls et al. (1995)
Triton X-100 (5 %)	9002-93-1	Ether	Surfactant (nonionic), Detergent, Emulsifier	liquid	surfactant	5%	98	5	Moderate	Very Severe	Category 2A		Category III	Nonirritant	Balls et al. (1995)
Triton X-100 (10%)	9002-93-1	Ether	Surfactant (nonionic), Detergent, Emulsifier	liquid	surfactant	10%	98	1	Very severe	Severe/Very Severe	Category 1		Category II	R41	Balls et al. (1995)
Triton X-100 (10%)	9002-93-1	Ether	Surfactant (nonionic), Detergent, Emulsifier	liquid	surfactant	10%	98	2	Severe	Severe/Very Severe	Category 1		Category II	R41	Balls et al. (1995)
Triton X-100 (10%)	9002-93-1	Ether	Surfactant (nonionic), Detergent, Emulsifier	liquid	surfactant	10%	98	3	Very severe	Severe/Very Severe	Category 1	NC	Category II	R41	Balls et al. (1995)
Triton X-100 (10%)	9002-93-1	Ether	Surfactant (nonionic), Detergent, Emulsifier	liquid	surfactant	10%	98	4	Severe	Severe/Very Severe	Category 1		Category II	R41	Balls et al. (1995)
Triton X-100 (10%)	9002-93-1	Ether	Surfactant (nonionic), Detergent, Emulsifier	liquid	surfactant	10%	98	5	Moderate	Severe/Very Severe	Category 1		Category II	R41	Balls et al. (1995)
Tween 20	9005-64-5	Ester, Polyether	Surfactant (nonionic), Detergent	liquid	surfactant	n.p.	98	1	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Tween 20	9005-64-5	Ester, Polyether	Surfactant (nonionic), Detergent	liquid	surfactant	n.p.	98	2	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Tween 20	9005-64-5	Ester, Polyether	Surfactant (nonionic), Detergent	liquid	surfactant	n.p.	98	3	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)

Substance	CASRN[1]	Chemical Class	Product Class	Form Tested	Solubility	Concentration Tested	Purity (%)	Lab No.	In VitroTest Call[2]	In Vitro Consensus Call[3]	In Vivo GHS[4,5]	GHS Category 1 SubClass[6]	In Vivo EPA[7,8]	In Vivo EU[5,10]	Reference
Tween 20	9005-64-5	Ester, Polyether	Surfactant (nonionic), Detergent	liquid	surfactant	n.p.	98	4	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Tween 20	9005-64-5	Ester, Polyether	Surfactant (nonionic), Detergent	liquid	surfactant	n.p.	98	5	Mild	Mild	Nonirritant		Category III	Nonirritant	Balls et al. (1995)
Allyl alcohol	107-18-6	Alcohol	Pesticide	liquid	n.p.	100%	n.p.	1	Severe	Severe	Category 2A		Category III	R36	Gautheron et al. (1994)
Allyl alcohol	107-18-6	Alcohol	Pesticide	liquid	n.p.	100%	n.p.	2	Severe	Severe	Category 2A		Category III	R36	Gautheron et al. (1994)
Allyl alcohol	107-18-6	Alcohol	Pesticide	liquid	n.p.	100%	n.p.	3	Severe	Severe	Category 2A		Category III	R36	Gautheron et al. (1994)
Allyl alcohol	107-18-6	Alcohol	Pesticide	liquid	n.p.	100%	n.p.	4	Severe	Severe	Category 2A		Category III	R36	Gautheron et al. (1994)
Allyl alcohol	107-18-6	Alcohol	Pesticide	liquid	n.p.	100%	n.p.	5	Severe	Severe	Category 2A		Category III	R36	Gautheron et al. (1994)
Allyl alcohol	107-18-6	Alcohol	Pesticide	liquid	n.p.	100%	n.p.	6	Severe	Severe	Category 2A		Category III	R36	Gautheron et al. (1994)
Allyl alcohol	107-18-6	Alcohol	Pesticide	liquid	n.p.	100%	n.p.	7	Severe	Severe	Category 2A		Category III	R36	Gautheron et al. (1994)
Allyl alcohol	107-18-6	Alcohol	Pesticide	liquid	n.p.	100%	n.p.	8	Severe	Severe	Category 2A		Category III	R36	Gautheron et al. (1994)
Allyl alcohol	107-18-6	Alcohol	Pesticide	liquid	n.p.	100%	n.p.	9	Severe	Severe	Category 2A		Category III	R36	Gautheron et al. (1994)
Allyl alcohol	107-18-6	Alcohol	Pesticide	liquid	n.p.	100%	n.p.	10	Severe	Severe	Category 2A		Category III	R36	Gautheron et al. (1994)
Allyl alcohol	107-18-6	Alcohol	Pesticide	liquid	n.p.	100%	n.p.	11	Severe	Severe	Category 2A		Category III	R36	Gautheron et al. (1994)
Allyl alcohol	107-18-6	Alcohol	Pesticide	liquid	n.p.	100%	n.p.	12	Severe	Severe	Category 2A		Category III	R36	Gautheron et al. (1994)
Aluminum hydroxide	21645-51-2	Alkali, Aluminum compound	Chemical intermediate, Dessicant	solid	n.p.	20%	n.p.	1	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Aluminum hydroxide	21645-51-2	Alkali, Aluminum compound	Chemical intermediate, Dessicant	solid	n.p.	20%	n.p.	2	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Aluminum hydroxide	21645-51-2	Alkali, Aluminum compound	Chemical intermediate, Dessicant	solid	n.p.	20%	n.p.	3	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Aluminum hydroxide	21645-51-2	Alkali, Aluminum compound	Chemical intermediate, Dessicant	solid	n.p.	20%	n.p.	4	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Aluminum hydroxide	21645-51-2	Alkali, Aluminum compound	Chemical intermediate, Dessicant	solid	n.p.	20%	n.p.	5	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Aluminum hydroxide	21645-51-2	Alkali, Aluminum compound	Chemical intermediate, Dessicant	solid	n.p.	20%	n.p.	6	Moderate	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Aluminum hydroxide	21645-51-2	Alkali, Aluminum compound	Chemical intermediate, Dessicant	solid	n.p.	20%	n.p.	7	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Aluminum hydroxide	21645-51-2	Alkali, Aluminum compound	Chemical intermediate, Dessicant	solid	n.p.	20%	n.p.	8	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Aluminum hydroxide	21645-51-2	Alkali, Aluminum compound	Chemical intermediate, Dessicant	solid	n.p.	20%	n.p.	9	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Aluminum hydroxide	21645-51-2	Alkali, Aluminum compound	Chemical intermediate, Dessicant	solid	n.p.	20%	n.p.	10	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Aluminum hydroxide	21645-51-2	Alkali, Aluminum compound	Chemical intermediate, Dessicant	solid	n.p.	20%	n.p.	11	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Aluminum hydroxide	21645-51-2	Alkali, Aluminum compound	Chemical intermediate, Dessicant	solid	n.p.	20%	n.p.	12	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2-Aminophenol	95-55-6	-	Chemical intermediate	solid	n.p.	20%	n.p.	1	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
2-Aminophenol	95-55-6	-	Chemical intermediate	solid	n.p.	20%	n.p.	2	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
2-Aminophenol	95-55-6	-	Chemical intermediate	solid	n.p.	20%	n.p.	3	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
2-Aminophenol	95-55-6	-	Chemical intermediate	solid	n.p.	20%	n.p.	4	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
2-Aminophenol	95-55-6	-	Chemical intermediate	solid	n.p.	20%	n.p.	5	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
2-Aminophenol	95-55-6	-	Chemical intermediate	solid	n.p.	20%	n.p.	6	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
2-Aminophenol	95-55-6	-	Chemical intermediate	solid	n.p.	20%	n.p.	7	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
2-Aminophenol	95-55-6	-	Chemical intermediate	solid	n.p.	20%	n.p.	8	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
2-Aminophenol	95-55-6	-	Chemical intermediate	solid	n.p.	20%	n.p.	9	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
2-Aminophenol	95-55-6	-	Chemical intermediate	solid	n.p.	20%	n.p.	10	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
2-Aminophenol	95-55-6	-	Chemical intermediate	solid	n.p.	20%	n.p.	11	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
2-Aminophenol	95-55-6	-	Chemical intermediate	solid	n.p.	20%	n.p.	12	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Anthracene	120-12-7	Polycyclic	Dye manufacturing agent	solid	n.p.	20%	n.p.	1	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Anthracene	120-12-7	Polycyclic	Dye manufacturing agent	solid	n.p.	20%	n.p.	2	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Anthracene	120-12-7	Polycyclic	Dye manufacturing agent	solid	n.p.	20%	n.p.	3	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Anthracene	120-12-7	Polycyclic	Dye manufacturing agent	solid	n.p.	20%	n.p.	4	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Anthracene	120-12-7	Polycyclic	Dye manufacturing agent	solid	n.p.	20%	n.p.	5	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Anthracene	120-12-7	Polycyclic	Dye manufacturing agent	solid	n.p.	20%	n.p.	6	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Anthracene	120-12-7	Polycyclic	Dye manufacturing agent	solid	n.p.	20%	n.p.	7	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Anthracene	120-12-7	Polycyclic	Dye manufacturing agent	solid	n.p.	20%	n.p.	8	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Anthracene	120-12-7	Polycyclic	Dye manufacturing agent	solid	n.p.	20%	n.p.	9	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Anthracene	120-12-7	Polycyclic	Dye manufacturing agent	solid	n.p.	20%	n.p.	10	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Anthracene	120-12-7	Polycyclic	Dye manufacturing agent	solid	n.p.	20%	n.p.	11	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Anthracene	120-12-7	Polycyclic	Dye manufacturing agent	solid	n.p.	20%	n.p.	12	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Benzethonium chloride	121-54-0	Amine, Onium compound	Bactericide	surfactant	n.p.	10%	n.p.	1	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Benzethonium chloride	121-54-0	Amine, Onium compound	Bactericide	surfactant	n.p.	10%	n.p.	2	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Benzethonium chloride	121-54-0	Amine, Onium compound	Bactericide	surfactant	n.p.	10%	n.p.	3	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Benzethonium chloride	121-54-0	Amine, Onium compound	Bactericide	surfactant	n.p.	10%	n.p.	4	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Benzethonium chloride	121-54-0	Amine, Onium compound	Bactericide	surfactant	n.p.	10%	n.p.	5	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Benzethonium chloride	121-54-0	Amine, Onium compound	Bactericide	surfactant	n.p.	10%	n.p.	6	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Benzethonium chloride	121-54-0	Amine, Onium compound	Bactericide	surfactant	n.p.	10%	n.p.	7	Severe	Severe	Category 1	4	Category I	R41	Gautheron et al. (1994)
Benzethonium chloride	121-54-0	Amine, Onium compound	Bactericide	surfactant	n.p.	10%	n.p.	8	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Benzethonium chloride	121-54-0	Amine, Onium compound	Bactericide	surfactant	n.p.	10%	n.p.	9	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Benzethonium chloride	121-54-0	Amine, Onium compound	Bactericide	surfactant	n.p.	10%	n.p.	10	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Benzethonium chloride	121-54-0	Amine, Onium compound	Bactericide	surfactant	n.p.	10%	n.p.	11	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Benzethonium chloride	121-54-0	Amine, Onium compound	Bactericide	surfactant	n.p.	10%	n.p.	12	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Betaine monohydrate	590-47-6	Amino acid, Onium compound	Not classified	solid	n.p.	20%	n.p.	1	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Betaine monohydrate	590-47-6	Amino acid, Onium compound	Not classified	solid	n.p.	20%	n.p.	2	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Betaine monohydrate	590-47-6	Amino acid, Onium compound	Not classified	solid	n.p.	20%	n.p.	3	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Betaine monohydrate	590-47-6	Amino acid, Onium compound	Not classified	solid	n.p.	20%	n.p.	4	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Betaine monohydrate	590-47-6	Amino acid, Onium compound	Not classified	solid	n.p.	20%	n.p.	5	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Betaine monohydrate	590-47-6	Amino acid, Onium compound	Not classified	solid	n.p.	20%	n.p.	6	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Betaine monohydrate	590-47-6	Amino acid, Onium compound	Not classified	solid	n.p.	20%	n.p.	7	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Betaine monohydrate	590-47-6	Amino acid, Onium compound	Not classified	solid	n.p.	20%	n.p.	8	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Betaine monohydrate	590-47-6	Amino acid, Onium compound	Not classified	solid	n.p.	20%	n.p.	9	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Betaine monohydrate	590-47-6	Amino acid, Onium compound	Not classified	solid	n.p.	20%	n.p.	10	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Betaine monohydrate	590-47-6	Amino acid, Onium compound	Not classified	solid	n.p.	20%	n.p.	11	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Betaine monohydrate	590-47-6	Amino acid, Onium compound	Not classified	solid	n.p.	20%	n.p.	12	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
BRIJ-35	9002-92-0	Alcohol	Emulsifier	surfactant	n.p.	10%	n.p.	1	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
BRIJ-35	9002-92-0	Alcohol	Emulsifier	surfactant	n.p.	10%	n.p.	2	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
BRIJ-35	9002-92-0	Alcohol	Emulsifier	surfactant	n.p.	10%	n.p.	3	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
BRIJ-35	9002-92-0	Alcohol	Emulsifier	surfactant	n.p.	10%	n.p.	4	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
BRIJ-35	9002-92-0	Alcohol	Emulsifier	surfactant	n.p.	10%	n.p.	5	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
BRIJ-35	9002-92-0	Alcohol	Emulsifier	surfactant	n.p.	10%	n.p.	6	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
BRIJ-35	9002-92-0	Alcohol	Emulsifier	surfactant	n.p.	10%	n.p.	7	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
BRIJ-35	9002-92-0	Alcohol	Emulsifier	surfactant	n.p.	10%	n.p.	8	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
BRIJ-35	9002-92-0	Alcohol	Emulsifier	surfactant	n.p.	10%	n.p.	9	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
BRIJ-35	9002-92-0	Alcohol	Emulsifier	surfactant	n.p.	10%	n.p.	10	n.a.	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)

Substance	CASRN[1]	Chemical Class	Product Class	Form Tested	Solubility	Concentration Tested	Purity (%)	Lab No.	In VitroTest Call[2]	In Vitro Consensus Call[3]	In Vivo GHS[4,5]	GHS Category 1 SubClass[6]	In Vivo EPA[7,8]	In Vivo EU[9,10]	Reference
BRIJ-35	9002-92-0	Alcohol	Emulsifier	surfactant	n.p.	10%	n.p.	11	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
BRIJ-35	9002-92-0	Alcohol	Emulsifier	surfactant	n.p.	10%	n.p.	12	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Butyrolactone	96-48-0	Lactone, Heterocycle	Synthetic intermediate; Solvent	liquid	water soluble	100%	n.p.	1	Moderate	Moderate	Category 2A		Category II	R36	Gautheron et al. (1994)
Butyrolactone	96-48-0	Lactone, Heterocycle	Synthetic intermediate; Solvent	liquid	water soluble	100%	n.p.	2	Moderate	Moderate	Category 2A		Category II	R36	Gautheron et al. (1994)
Butyrolactone	96-48-0	Lactone, Heterocycle	Synthetic intermediate; Solvent	liquid	water soluble	100%	n.p.	3	Severe	Moderate	Category 2A		Category II	R36	Gautheron et al. (1994)
Butyrolactone	96-48-0	Lactone, Heterocycle	Synthetic intermediate; Solvent	liquid	water soluble	100%	n.p.	4	Moderate	Moderate	Category 2A		Category II	R36	Gautheron et al. (1994)
Butyrolactone	96-48-0	Lactone, Heterocycle	Synthetic intermediate; Solvent	liquid	water soluble	100%	n.p.	5	Moderate	Moderate	Category 2A		Category II	R36	Gautheron et al. (1994)
Butyrolactone	96-48-0	Lactone, Heterocycle	Synthetic intermediate; Solvent	liquid	water soluble	100%	n.p.	6	Moderate	Moderate	Category 2A		Category II	R36	Gautheron et al. (1994)
Butyrolactone	96-48-0	Lactone, Heterocycle	Synthetic intermediate; Solvent	liquid	water soluble	100%	n.p.	7	Severe	Moderate	Category 2A		Category II	R36	Gautheron et al. (1994)
Butyrolactone	96-48-0	Lactone, Heterocycle	Synthetic intermediate; Solvent	liquid	water soluble	100%	n.p.	8	Moderate	Moderate	Category 2A		Category II	R36	Gautheron et al. (1994)
Butyrolactone	96-48-0	Lactone, Heterocycle	Synthetic intermediate; Solvent	liquid	water soluble	100%	n.p.	9	Moderate	Moderate	Category 2A		Category II	R36	Gautheron et al. (1994)
Butyrolactone	96-48-0	Lactone, Heterocycle	Synthetic intermediate; Solvent	liquid	water soluble	100%	n.p.	10	Moderate	Moderate	Category 2A		Category II	R36	Gautheron et al. (1994)
Butyrolactone	96-48-0	Lactone, Heterocycle	Synthetic intermediate; Solvent	liquid	water soluble	100%	n.p.	11	Moderate	Moderate	Category 2A		Category II	R36	Gautheron et al. (1994)
Butyrolactone	96-48-0	Lactone, Heterocycle	Synthetic intermediate; Solvent	liquid	water soluble	100%	n.p.	12	Moderate	Moderate	Category 2A		Category II	R36	Gautheron et al. (1994)
Cyclohexanone	108-94-1	Ketone, Hydrocarbon (cyclic)	Solvent, Chemical intermediate	liquid	n.p.	100%	n.p.	1	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Cyclohexanone	108-94-1	Ketone, Hydrocarbon (cyclic)	Solvent, Chemical intermediate	liquid	n.p.	100%	n.p.	2	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Cyclohexanone	108-94-1	Ketone, Hydrocarbon (cyclic)	Solvent, Chemical intermediate	liquid	n.p.	100%	n.p.	3	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Cyclohexanone	108-94-1	Ketone, Hydrocarbon (cyclic)	Solvent, Chemical intermediate	liquid	n.p.	100%	n.p.	4	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Cyclohexanone	108-94-1	Ketone, Hydrocarbon (cyclic)	Solvent, Chemical intermediate	liquid	n.p.	100%	n.p.	5	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Cyclohexanone	108-94-1	Ketone, Hydrocarbon (cyclic)	Solvent, Chemical intermediate	liquid	n.p.	100%	n.p.	6	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Cyclohexanone	108-94-1	Ketone, Hydrocarbon (cyclic)	Solvent, Chemical intermediate	liquid	n.p.	100%	n.p.	7	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Cyclohexanone	108-94-1	Ketone, Hydrocarbon (cyclic)	Solvent, Chemical intermediate	liquid	n.p.	100%	n.p.	8	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Cyclohexanone	108-94-1	Ketone, Hydrocarbon (cyclic)	Solvent, Chemical intermediate	liquid	n.p.	100%	n.p.	9	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Cyclohexanone	108-94-1	Ketone, Hydrocarbon (cyclic)	Solvent, Chemical intermediate	liquid	n.p.	100%	n.p.	10	n.a.	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Cyclohexanone	108-94-1	Ketone, Hydrocarbon (cyclic)	Solvent, Chemical intermediate	liquid	n.p.	100%	n.p.	11	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Cyclohexanone	108-94-1	Ketone, Hydrocarbon (cyclic)	Solvent, Chemical intermediate	liquid	n.p.	100%	n.p.	12	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Deoxycholic acid, sodium salt	302-95-4	Alcohol, Carboxylic acid (salt)	Detergent, Chemical intermediate	surfactant	n.p.	10%	n.p.	1	Severe	Severe	Category 2A		Category II	R36	Gautheron et al. (1994)
Deoxycholic acid, sodium salt	302-95-4	Alcohol, Carboxylic acid (salt)	Detergent, Chemical intermediate	surfactant	n.p.	10%	n.p.	2	Severe	Severe	Category 2A		Category II	R36	Gautheron et al. (1994)
Deoxycholic acid, sodium salt	302-95-4	Alcohol, Carboxylic acid (salt)	Detergent, Chemical intermediate	surfactant	n.p.	10%	n.p.	3	Severe	Severe	Category 2A		Category II	R36	Gautheron et al. (1994)
Deoxycholic acid, sodium salt	302-95-4	Alcohol, Carboxylic acid (salt)	Detergent, Chemical intermediate	surfactant	n.p.	10%	n.p.	4	Severe	Severe	Category 2A		Category II	R36	Gautheron et al. (1994)
Deoxycholic acid, sodium salt	302-95-4	Alcohol, Carboxylic acid (salt)	Detergent, Chemical intermediate	surfactant	n.p.	10%	n.p.	5	Severe	Severe	Category 2A		Category II	R36	Gautheron et al. (1994)
Deoxycholic acid, sodium salt	302-95-4	Alcohol, Carboxylic acid (salt)	Detergent, Chemical intermediate	surfactant	n.p.	10%	n.p.	6	Severe	Severe	Category 2A		Category II	R36	Gautheron et al. (1994)
Deoxycholic acid, sodium salt	302-95-4	Alcohol, Carboxylic acid (salt)	Detergent, Chemical intermediate	surfactant	n.p.	10%	n.p.	7	Severe	Severe	Category 2A		Category II	R36	Gautheron et al. (1994)
Deoxycholic acid, sodium salt	302-95-4	Alcohol, Carboxylic acid (salt)	Detergent, Chemical intermediate	surfactant	n.p.	10%	n.p.	8	Moderate	Severe	Category 2A		Category II	R36	Gautheron et al. (1994)
Deoxycholic acid, sodium salt	302-95-4	Alcohol, Carboxylic acid (salt)	Detergent, Chemical intermediate	surfactant	n.p.	10%	n.p.	9	Severe	Severe	Category 2A		Category II	R36	Gautheron et al. (1994)
Deoxycholic acid, sodium salt	302-95-4	Alcohol, Carboxylic acid (salt)	Detergent, Chemical intermediate	surfactant	n.p.	10%	n.p.	10	Severe	Severe	Category 2A		Category II	R36	Gautheron et al. (1994)
Deoxycholic acid, sodium salt	302-95-4	Alcohol, Carboxylic acid (salt)	Detergent, Chemical intermediate	surfactant	n.p.	10%	n.p.	11	Severe	Severe	Category 2A		Category II	R36	Gautheron et al. (1994)
Deoxycholic acid, sodium salt	302-95-4	Alcohol, Carboxylic acid (salt)	Detergent, Chemical intermediate	surfactant	n.p.	10%	n.p.	12	Severe	Severe	Category 2A		Category II	R36	Gautheron et al. (1994)
Diacetone alcohol	123-42-2	Ketone, Alcohol	Solvent	liquid	n.p.	100%	n.p.	1	Moderate	Moderate	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Diacetone alcohol	123-42-2	Ketone, Alcohol	Solvent	liquid	n.p.	100%	n.p.	2	Moderate	Moderate	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Diacetone alcohol	123-42-2	Ketone, Alcohol	Solvent	liquid	n.p.	100%	n.p.	3	Severe	Moderate	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Diacetone alcohol	123-42-2	Ketone, Alcohol	Solvent	liquid	n.p.	100%	n.p.	4	Moderate	Moderate	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Diacetone alcohol	123-42-2	Ketone, Alcohol	Solvent	liquid	n.p.	100%	n.p.	5	Moderate	Moderate	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Diacetone alcohol	123-42-2	Ketone, Alcohol	Solvent	liquid	n.p.	100%	n.p.	6	Moderate	Moderate	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Diacetone alcohol	123-42-2	Ketone, Alcohol	Solvent	liquid	n.p.	100%	n.p.	7	Moderate	Moderate	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Diacetone alcohol	123-42-2	Ketone, Alcohol	Solvent	liquid	n.p.	100%	n.p.	8	Moderate	Moderate	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Diacetone alcohol	123-42-2	Ketone, Alcohol	Solvent	liquid	n.p.	100%	n.p.	9	Severe	Moderate	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Diacetone alcohol	123-42-2	Ketone, Alcohol	Solvent	liquid	n.p.	100%	n.p.	10	n.a.	Moderate	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Diacetone alcohol	123-42-2	Ketone, Alcohol	Solvent	liquid	n.p.	100%	n.p.	11	Moderate	Moderate	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Diacetone alcohol	123-42-2	Ketone, Alcohol	Solvent	liquid	n.p.	100%	n.p.	12	Severe	Moderate	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Dibenzoyl-L-tartaric acid	2743-38-6	Carboxylic acid; Ester	Optical resolution agent	solid	n.p.	20%	n.p.	1	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Dibenzoyl-L-tartaric acid	2743-38-6	Carboxylic acid; Ester	Optical resolution agent	solid	n.p.	20%	n.p.	2	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Dibenzoyl-L-tartaric acid	2743-38-6	Carboxylic acid; Ester	Optical resolution agent	solid	n.p.	20%	n.p.	3	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Dibenzoyl-L-tartaric acid	2743-38-6	Carboxylic acid; Ester	Optical resolution agent	solid	n.p.	20%	n.p.	4	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Dibenzoyl-L-tartaric acid	2743-38-6	Carboxylic acid; Ester	Optical resolution agent	solid	n.p.	20%	n.p.	5	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Dibenzoyl-L-tartaric acid	2743-38-6	Carboxylic acid; Ester	Optical resolution agent	solid	n.p.	20%	n.p.	6	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Dibenzoyl-L-tartaric acid	2743-38-6	Carboxylic acid; Ester	Optical resolution agent	solid	n.p.	20%	n.p.	7	Severe	Severe	Category 1	2	Category I	R41	Gautheron et al. (1994)
Dibenzoyl-L-tartaric acid	2743-38-6	Carboxylic acid; Ester	Optical resolution agent	solid	n.p.	20%	n.p.	8	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Dibenzoyl-L-tartaric acid	2743-38-6	Carboxylic acid; Ester	Optical resolution agent	solid	n.p.	20%	n.p.	9	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Dibenzoyl-L-tartaric acid	2743-38-6	Carboxylic acid; Ester	Optical resolution agent	solid	n.p.	20%	n.p.	10	n.a.	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Dibenzoyl-L-tartaric acid	2743-38-6	Carboxylic acid; Ester	Optical resolution agent	solid	n.p.	20%	n.p.	11	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Dibenzoyl-L-tartaric acid	2743-38-6	Carboxylic acid; Ester	Optical resolution agent	solid	n.p.	20%	n.p.	12	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
2,4-Dichloro-5-sulfamoylbenzoic acid	2736-23-4	Alcohol	Intermediate for pharmaceuticals, pesticides, perfumes	solid	n.p.	20%	n.p.	1	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2,4-Dichloro-5-sulfamoylbenzoic acid	2736-23-4	Alcohol	Intermediate for pharmaceuticals, pesticides, perfumes	solid	n.p.	20%	n.p.	2	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2,4-Dichloro-5-sulfamoylbenzoic acid	2736-23-4	Alcohol	Intermediate for pharmaceuticals, pesticides, perfumes	solid	n.p.	20%	n.p.	3	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2,4-Dichloro-5-sulfamoylbenzoic acid	2736-23-4	Alcohol	Intermediate for pharmaceuticals, pesticides, perfumes	solid	n.p.	20%	n.p.	4	Moderate	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)

Substance	CASRN[1]	Chemical Class	Product Class	Form Tested	Solubility	Concentration Tested	Purity (%)	Lab No.	In VitroTest Call[2]	In Vitro Consensus Call[3]	In Vivo GHS[4,5]	GHS Category 1 SubClass[6]	In Vivo EPA[7,8]	In Vivo EU[9,10]	Reference
2,4-Dichloro-5-sulfamoylbenzoic acid	2736-23-4	Alcohol	Intermediate for pharmaceuticals, pesticides, perfumes	solid	n.p.	20%	n.p.	5	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2,4-Dichloro-5-sulfamoylbenzoic acid	2736-23-4	Alcohol	Intermediate for pharmaceuticals, pesticides, perfumes	solid	n.p.	20%	n.p.	6	Moderate	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2,4-Dichloro-5-sulfamoylbenzoic acid	2736-23-4	Alcohol	Intermediate for pharmaceuticals, pesticides, perfumes	solid	n.p.	20%	n.p.	7	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2,4-Dichloro-5-sulfamoylbenzoic acid	2736-23-4	Alcohol	Intermediate for pharmaceuticals, pesticides, perfumes	solid	n.p.	20%	n.p.	8	Severe	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2,4-Dichloro-5-sulfamoylbenzoic acid	2736-23-4	Alcohol	Intermediate for pharmaceuticals, pesticides, perfumes	solid	n.p.	20%	n.p.	9	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2,4-Dichloro-5-sulfamoylbenzoic acid	2736-23-4	Alcohol	Intermediate for pharmaceuticals, pesticides, perfumes	solid	n.p.	20%	n.p.	10	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2,4-Dichloro-5-sulfamoylbenzoic acid	2736-23-4	Alcohol	Intermediate for pharmaceuticals, pesticides, perfumes	solid	n.p.	20%	n.p.	11	Moderate	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2,4-Dichloro-5-sulfamoylbenzoic acid	2736-23-4	Alcohol	Intermediate for pharmaceuticals, pesticides, perfumes	solid	n.p.	20%	n.p.	12	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Dimethylbiguanide	657-24-9	Amidine	Pharmaceutical	solid	n.p.	20%	n.p.	1	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Dimethylbiguanide	657-24-9	Amidine	Pharmaceutical	solid	n.p.	20%	n.p.	2	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Dimethylbiguanide	657-24-9	Amidine	Pharmaceutical	solid	n.p.	20%	n.p.	3	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Dimethylbiguanide	657-24-9	Amidine	Pharmaceutical	solid	n.p.	20%	n.p.	4	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Dimethylbiguanide	657-24-9	Amidine	Pharmaceutical	solid	n.p.	20%	n.p.	5	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Dimethylbiguanide	657-24-9	Amidine	Pharmaceutical	solid	n.p.	20%	n.p.	6	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Dimethylbiguanide	657-24-9	Amidine	Pharmaceutical	solid	n.p.	20%	n.p.	7	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Dimethylbiguanide	657-24-9	Amidine	Pharmaceutical	solid	n.p.	20%	n.p.	8	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Dimethylbiguanide	657-24-9	Amidine	Pharmaceutical	solid	n.p.	20%	n.p.	9	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Dimethylbiguanide	657-24-9	Amidine	Pharmaceutical	solid	n.p.	20%	n.p.	10	n.a.	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Dimethylbiguanide	657-24-9	Amidine	Pharmaceutical	solid	n.p.	20%	n.p.	11	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Dimethylbiguanide	657-24-9	Amidine	Pharmaceutical	solid	n.p.	20%	n.p.	12	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Dimethyl sulfoxide	67-68-5	Organic sulfur compound	Solvent	liquid	n.p.	100%	n.p.	1	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Dimethyl sulfoxide	67-68-5	Organic sulfur compound	Solvent	liquid	n.p.	100%	n.p.	2	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Dimethyl sulfoxide	67-68-5	Organic sulfur compound	Solvent	liquid	n.p.	100%	n.p.	3	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Dimethyl sulfoxide	67-68-5	Organic sulfur compound	Solvent	liquid	n.p.	100%	n.p.	4	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Dimethyl sulfoxide	67-68-5	Organic sulfur compound	Solvent	liquid	n.p.	100%	n.p.	5	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Dimethyl sulfoxide	67-68-5	Organic sulfur compound	Solvent	liquid	n.p.	100%	n.p.	6	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Dimethyl sulfoxide	67-68-5	Organic sulfur compound	Solvent	liquid	n.p.	100%	n.p.	7	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Dimethyl sulfoxide	67-68-5	Organic sulfur compound	Solvent	liquid	n.p.	100%	n.p.	8	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Dimethyl sulfoxide	67-68-5	Organic sulfur compound	Solvent	liquid	n.p.	100%	n.p.	9	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Dimethyl sulfoxide	67-68-5	Organic sulfur compound	Solvent	liquid	n.p.	100%	n.p.	10	n.a.	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Dimethyl sulfoxide	67-68-5	Organic sulfur compound	Solvent	liquid	n.p.	100%	n.p.	11	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Dimethyl sulfoxide	67-68-5	Organic sulfur compound	Solvent	liquid	n.p.	100%	n.p.	12	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
EDTA, di-potassium salt	25102-12-9	Amine, Carboxylic acid (salt)	Chelator	solid	n.p.	20%	n.p.	1	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
EDTA, di-potassium salt	25102-12-9	Amine, Carboxylic acid (salt)	Chelator	solid	n.p.	20%	n.p.	2	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
EDTA, di-potassium salt	25102-12-9	Amine, Carboxylic acid (salt)	Chelator	solid	n.p.	20%	n.p.	3	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
EDTA, di-potassium salt	25102-12-9	Amine, Carboxylic acid (salt)	Chelator	solid	n.p.	20%	n.p.	4	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
EDTA, di-potassium salt	25102-12-9	Amine, Carboxylic acid (salt)	Chelator	solid	n.p.	20%	n.p.	5	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
EDTA, di-potassium salt	25102-12-9	Amine, Carboxylic acid (salt)	Chelator	solid	n.p.	20%	n.p.	6	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
EDTA, di-potassium salt	25102-12-9	Amine, Carboxylic acid (salt)	Chelator	solid	n.p.	20%	n.p.	7	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
EDTA, di-potassium salt	25102-12-9	Amine, Carboxylic acid (salt)	Chelator	solid	n.p.	20%	n.p.	8	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
EDTA, di-potassium salt	25102-12-9	Amine, Carboxylic acid (salt)	Chelator	solid	n.p.	20%	n.p.	9	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
EDTA, di-potassium salt	25102-12-9	Amine, Carboxylic acid (salt)	Chelator	solid	n.p.	20%	n.p.	10	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
EDTA, di-potassium salt	25102-12-9	Amine, Carboxylic acid (salt)	Chelator	solid	n.p.	20%	n.p.	11	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
EDTA, di-potassium salt	25102-12-9	Amine, Carboxylic acid (salt)	Chelator	solid	n.p.	20%	n.p.	12	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	1	Severe	Severe	SCNM		Category II	Nonirritant	Gautheron et al. (1994)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	2	Severe	Severe	SCNM		Category II	Nonirritant	Gautheron et al. (1994)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	3	Severe	Severe	SCNM		Category II	Nonirritant	Gautheron et al. (1994)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	4	Moderate	Severe	SCNM		Category II	Nonirritant	Gautheron et al. (1994)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	5	Severe	Severe	SCNM		Category II	Nonirritant	Gautheron et al. (1994)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	6	Severe	Severe	SCNM		Category II	Nonirritant	Gautheron et al. (1994)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	7	Severe	Severe	SCNM		Category II	Nonirritant	Gautheron et al. (1994)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	8	Moderate	Severe	SCNM		Category II	Nonirritant	Gautheron et al. (1994)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	9	Moderate	Severe	SCNM		Category II	Nonirritant	Gautheron et al. (1994)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	10	n.a.	Severe	SCNM		Category II	Nonirritant	Gautheron et al. (1994)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	11	Severe	Severe	SCNM		Category II	Nonirritant	Gautheron et al. (1994)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	12	Moderate	Severe	SCNM		Category II	Nonirritant	Gautheron et al. (1994)
2-Ethoxyethanol	110-80-5	Alcohol	Solvent	liquid	n.p.	100%	n.p.	1	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2-Ethoxyethanol	110-80-5	Alcohol	Solvent	liquid	n.p.	100%	n.p.	2	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2-Ethoxyethanol	110-80-5	Alcohol	Solvent	liquid	n.p.	100%	n.p.	3	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2-Ethoxyethanol	110-80-5	Alcohol	Solvent	liquid	n.p.	100%	n.p.	4	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2-Ethoxyethanol	110-80-5	Alcohol	Solvent	liquid	n.p.	100%	n.p.	5	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2-Ethoxyethanol	110-80-5	Alcohol	Solvent	liquid	n.p.	100%	n.p.	6	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2-Ethoxyethanol	110-80-5	Alcohol	Solvent	liquid	n.p.	100%	n.p.	7	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2-Ethoxyethanol	110-80-5	Alcohol	Solvent	liquid	n.p.	100%	n.p.	8	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2-Ethoxyethanol	110-80-5	Alcohol	Solvent	liquid	n.p.	100%	n.p.	9	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2-Ethoxyethanol	110-80-5	Alcohol	Solvent	liquid	n.p.	100%	n.p.	10	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2-Ethoxyethanol	110-80-5	Alcohol	Solvent	liquid	n.p.	100%	n.p.	11	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2-Ethoxyethanol	110-80-5	Alcohol	Solvent	liquid	n.p.	100%	n.p.	12	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Ethyl acetoacetate	141-97-9	Carboxylic acid, Ketone	Chemical intermediate, Flavoring agent	liquid	n.p.	100%	n.p.	1	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Ethyl acetoacetate	141-97-9	Carboxylic acid, Ketone	Chemical intermediate, Flavoring agent	liquid	n.p.	100%	n.p.	2	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Ethyl acetoacetate	141-97-9	Carboxylic acid, Ketone	Chemical intermediate, Flavoring agent	liquid	n.p.	100%	n.p.	3	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Ethyl acetoacetate	141-97-9	Carboxylic acid, Ketone	Chemical intermediate, Flavoring agent	liquid	n.p.	100%	n.p.	4	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Ethyl acetoacetate	141-97-9	Carboxylic acid, Ketone	Chemical intermediate, Flavoring agent	liquid	n.p.	100%	n.p.	5	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Ethyl acetoacetate	141-97-9	Carboxylic acid, Ketone	Chemical intermediate, Flavoring agent	liquid	n.p.	100%	n.p.	6	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Ethyl acetoacetate	141-97-9	Carboxylic acid, Ketone	Chemical intermediate, Flavoring agent	liquid	n.p.	100%	n.p.	7	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)

Substance	CASRN[1]	Chemical Class	Product Class	Form Tested	Solubility	Concentration Tested	Purity (%)	Lab No.	In VitroTest Call[2]	In Vitro Consensus Call[3]	In Vivo GHS[4,5]	GHS Category 1 SubClass[6]	In Vivo EPA[7,8]	In Vivo EU[9,10]	Reference
Ethyl acetoacetate	141-97-9	Carboxylic acid, Ketone	Chemical intermediate, Flavoring agent	liquid	n.p.	100%	n.p.	8	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Ethyl acetoacetate	141-97-9	Carboxylic acid, Ketone	Chemical intermediate, Flavoring agent	liquid	n.p.	100%	n.p.	9	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Ethyl acetoacetate	141-97-9	Carboxylic acid, Ketone	Chemical intermediate, Flavoring agent	liquid	n.p.	100%	n.p.	10	n.a.	Moderate	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Ethyl acetoacetate	141-97-9	Carboxylic acid, Ketone	Chemical intermediate, Flavoring agent	liquid	n.p.	100%	n.p.	11	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Ethyl acetoacetate	141-97-9	Carboxylic acid, Ketone	Chemical intermediate, Flavoring agent	liquid	n.p.	100%	n.p.	12	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Furan	110-00-9	Heterocyclic	Chemical intermediate	liquid	n.p.	100%	n.p.	1	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Furan	110-00-9	Heterocyclic	Chemical intermediate	liquid	n.p.	100%	n.p.	2	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Furan	110-00-9	Heterocyclic	Chemical intermediate	liquid	n.p.	100%	n.p.	3	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Furan	110-00-9	Heterocyclic	Chemical intermediate	liquid	n.p.	100%	n.p.	4	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Furan	110-00-9	Heterocyclic	Chemical intermediate	liquid	n.p.	100%	n.p.	5	Moderate	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Furan	110-00-9	Heterocyclic	Chemical intermediate	liquid	n.p.	100%	n.p.	6	Moderate	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Furan	110-00-9	Heterocyclic	Chemical intermediate	liquid	n.p.	100%	n.p.	7	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Furan	110-00-9	Heterocyclic	Chemical intermediate	liquid	n.p.	100%	n.p.	8	Moderate	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Furan	110-00-9	Heterocyclic	Chemical intermediate	liquid	n.p.	100%	n.p.	9	Moderate	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Furan	110-00-9	Heterocyclic	Chemical intermediate	liquid	n.p.	100%	n.p.	10	Moderate	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Furan	110-00-9	Heterocyclic	Chemical intermediate	liquid	n.p.	100%	n.p.	11	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Furan	110-00-9	Heterocyclic	Chemical intermediate	liquid	n.p.	100%	n.p.	12	Moderate	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Gluconolactone	90-80-2	Carboxylic acid, Lactone, Carbohydrate	Food additive	solid	n.p.	20%	n.p.	1	Severe	Severe	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Gluconolactone	90-80-2	Carboxylic acid, Lactone, Carbohydrate	Food additive	solid	n.p.	20%	n.p.	2	Severe	Severe	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Gluconolactone	90-80-2	Carboxylic acid, Lactone, Carbohydrate	Food additive	solid	n.p.	20%	n.p.	3	Severe	Severe	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Gluconolactone	90-80-2	Carboxylic acid, Lactone, Carbohydrate	Food additive	solid	n.p.	20%	n.p.	4	Severe	Severe	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Gluconolactone	90-80-2	Carboxylic acid, Lactone, Carbohydrate	Food additive	solid	n.p.	20%	n.p.	5	Severe	Severe	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Gluconolactone	90-80-2	Carboxylic acid, Lactone, Carbohydrate	Food additive	solid	n.p.	20%	n.p.	6	Severe	Severe	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Gluconolactone	90-80-2	Carboxylic acid, Lactone, Carbohydrate	Food additive	solid	n.p.	20%	n.p.	7	Severe	Severe	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Gluconolactone	90-80-2	Carboxylic acid, Lactone, Carbohydrate	Food additive	solid	n.p.	20%	n.p.	8	Severe	Severe	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Gluconolactone	90-80-2	Carboxylic acid, Lactone, Carbohydrate	Food additive	solid	n.p.	20%	n.p.	9	Severe	Severe	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Gluconolactone	90-80-2	Carboxylic acid, Lactone, Carbohydrate	Food additive	solid	n.p.	20%	n.p.	10	n.a.	Severe	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Gluconolactone	90-80-2	Carboxylic acid, Lactone, Carbohydrate	Food additive	solid	n.p.	20%	n.p.	11	Severe	Severe	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Gluconolactone	90-80-2	Carboxylic acid, Lactone, Carbohydrate	Food additive	solid	n.p.	20%	n.p.	12	Severe	Severe	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
DL-Glutamic acid	19285-83-7	Amino acid	Not classified	solid	n.p.	20%	n.p.	1	Mild	Mild	SCNM		SCNM	SCNM	Gautheron et al. (1994)
DL-Glutamic acid	19285-83-7	Amino acid	Not classified	solid	n.p.	20%	n.p.	2	Mild	Mild	SCNM		SCNM	SCNM	Gautheron et al. (1994)
DL-Glutamic acid	19285-83-7	Amino acid	Not classified	solid	n.p.	20%	n.p.	3	Mild	Mild	SCNM		SCNM	SCNM	Gautheron et al. (1994)
DL-Glutamic acid	19285-83-7	Amino acid	Not classified	solid	n.p.	20%	n.p.	4	Mild	Mild	SCNM		SCNM	SCNM	Gautheron et al. (1994)
DL-Glutamic acid	19285-83-7	Amino acid	Not classified	solid	n.p.	20%	n.p.	5	Mild	Mild	SCNM		SCNM	SCNM	Gautheron et al. (1994)
DL-Glutamic acid	19285-83-7	Amino acid	Not classified	solid	n.p.	20%	n.p.	6	Nonirritant	Mild	SCNM		SCNM	SCNM	Gautheron et al. (1994)
DL-Glutamic acid	19285-83-7	Amino acid	Not classified	solid	n.p.	20%	n.p.	7	Mild	Mild	SCNM		SCNM	SCNM	Gautheron et al. (1994)
DL-Glutamic acid	19285-83-7	Amino acid	Not classified	solid	n.p.	20%	n.p.	8	Mild	Mild	SCNM		SCNM	SCNM	Gautheron et al. (1994)
DL-Glutamic acid	19285-83-7	Amino acid	Not classified	solid	n.p.	20%	n.p.	9	Mild	Mild	SCNM		SCNM	SCNM	Gautheron et al. (1994)
DL-Glutamic acid	19285-83-7	Amino acid	Not classified	solid	n.p.	20%	n.p.	10	Mild	Mild	SCNM		SCNM	SCNM	Gautheron et al. (1994)
DL-Glutamic acid	19285-83-7	Amino acid	Not classified	solid	n.p.	20%	n.p.	11	Mild	Mild	SCNM		SCNM	SCNM	Gautheron et al. (1994)
DL-Glutamic acid	19285-83-7	Amino acid	Not classified	solid	n.p.	20%	n.p.	12	Nonirritant	Mild	SCNM		SCNM	SCNM	Gautheron et al. (1994)
3-Glycidoxypropyltrimethoxysilane	2530-83-8	Organosilicon compound	Adhesive	liquid	n.p.	100%	n.p.	1	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
3-Glycidoxypropyltrimethoxysilane	2530-83-8	Organosilicon compound	Adhesive	liquid	n.p.	100%	n.p.	2	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
3-Glycidoxypropyltrimethoxysilane	2530-83-8	Organosilicon compound	Adhesive	liquid	n.p.	100%	n.p.	3	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
3-Glycidoxypropyltrimethoxysilane	2530-83-8	Organosilicon compound	Adhesive	liquid	n.p.	100%	n.p.	4	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
3-Glycidoxypropyltrimethoxysilane	2530-83-8	Organosilicon compound	Adhesive	liquid	n.p.	100%	n.p.	5	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
3-Glycidoxypropyltrimethoxysilane	2530-83-8	Organosilicon compound	Adhesive	liquid	n.p.	100%	n.p.	6	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
3-Glycidoxypropyltrimethoxysilane	2530-83-8	Organosilicon compound	Adhesive	liquid	n.p.	100%	n.p.	7	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
3-Glycidoxypropyltrimethoxysilane	2530-83-8	Organosilicon compound	Adhesive	liquid	n.p.	100%	n.p.	8	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
3-Glycidoxypropyltrimethoxysilane	2530-83-8	Organosilicon compound	Adhesive	liquid	n.p.	100%	n.p.	9	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
3-Glycidoxypropyltrimethoxysilane	2530-83-8	Organosilicon compound	Adhesive	liquid	n.p.	100%	n.p.	10	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
3-Glycidoxypropyltrimethoxysilane	2530-83-8	Organosilicon compound	Adhesive	liquid	n.p.	100%	n.p.	11	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
3-Glycidoxypropyltrimethoxysilane	2530-83-8	Organosilicon compound	Adhesive	liquid	n.p.	100%	n.p.	12	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Hexadecyltrimethylammonium bromide	57-09-0	Organic salt, Onium compound	Agricultural chemical; Germicide; Drug/Therapeutic agent	surfactant	n.p.	10%	n.p.	1	Severe	Severe	Category 1	4	Category I	R41	Gautheron et al. (1994)
Hexadecyltrimethylammonium bromide	57-09-0	Organic salt, Onium compound	Agricultural chemical; Germicide; Drug/Therapeutic agent	surfactant	n.p.	10%	n.p.	2	Moderate	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Hexadecyltrimethylammonium bromide	57-09-0	Organic salt, Onium compound	Agricultural chemical; Germicide; Drug/Therapeutic agent	surfactant	n.p.	10%	n.p.	3	Moderate	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Hexadecyltrimethylammonium bromide	57-09-0	Organic salt, Onium compound	Agricultural chemical; Germicide; Drug/Therapeutic agent	surfactant	n.p.	10%	n.p.	4	Moderate	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Hexadecyltrimethylammonium bromide	57-09-0	Organic salt, Onium compound	Agricultural chemical; Germicide; Drug/Therapeutic agent	surfactant	n.p.	10%	n.p.	5	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Hexadecyltrimethylammonium bromide	57-09-0	Organic salt, Onium compound	Agricultural chemical; Germicide; Drug/Therapeutic agent	surfactant	n.p.	10%	n.p.	6	Moderate	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Hexadecyltrimethylammonium bromide	57-09-0	Organic salt, Onium compound	Agricultural chemical; Germicide; Drug/Therapeutic agent	surfactant	n.p.	10%	n.p.	7	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Hexadecyltrimethylammonium bromide	57-09-0	Organic salt, Onium compound	Agricultural chemical; Germicide; Drug/Therapeutic agent	surfactant	n.p.	10%	n.p.	8	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Hexadecyltrimethylammonium bromide	57-09-0	Organic salt, Onium compound	Agricultural chemical; Germicide; Drug/Therapeutic agent	surfactant	n.p.	10%	n.p.	9	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Hexadecyltrimethylammonium bromide	57-09-0	Organic salt, Onium compound	Agricultural chemical; Germicide; Drug/Therapeutic agent	surfactant	n.p.	10%	n.p.	10	n.a.	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Hexadecyltrimethylammonium bromide	57-09-0	Organic salt, Onium compound	Agricultural chemical; Germicide; Drug/Therapeutic agent	surfactant	n.p.	10%	n.p.	11	Moderate	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Hexadecyltrimethylammonium bromide	57-09-0	Organic salt, Onium compound	Agricultural chemical; Germicide; Drug/Therapeutic agent	surfactant	n.p.	10%	n.p.	12	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Hexane	110-54-3	Hydrocarbon (acyclic)	Solvent	liquid	n.p.	100%	n.p.	1	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Hexane	110-54-3	Hydrocarbon (acyclic)	Solvent	liquid	n.p.	100%	n.p.	2	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Hexane	110-54-3	Hydrocarbon (acyclic)	Solvent	liquid	n.p.	100%	n.p.	3	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Hexane	110-54-3	Hydrocarbon (acyclic)	Solvent	liquid	n.p.	100%	n.p.	4	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Hexane	110-54-3	Hydrocarbon (acyclic)	Solvent	liquid	n.p.	100%	n.p.	5	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)

Substance	CASRN[1]	Chemical Class	Product Class	Form Tested	Solubility	Concentration Tested	Purity (%)	Lab No.	In VitroTest Call[2]	In Vitro Consensus Call[3]	In Vivo GHS[4,5]	GHS Category 1 SubClass[6]	In Vivo EPA[7,8]	In Vivo EU[5,10]	Reference
Hexane	110-54-3	Hydrocarbon (acyclic)	Solvent	liquid	n.p.	100%	n.p.	6	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Hexane	110-54-3	Hydrocarbon (acyclic)	Solvent	liquid	n.p.	100%	n.p.	7	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Hexane	110-54-3	Hydrocarbon (acyclic)	Solvent	liquid	n.p.	100%	n.p.	8	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Hexane	110-54-3	Hydrocarbon (acyclic)	Solvent	liquid	n.p.	100%	n.p.	9	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Hexane	110-54-3	Hydrocarbon (acyclic)	Solvent	liquid	n.p.	100%	n.p.	10	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Hexane	110-54-3	Hydrocarbon (acyclic)	Solvent	liquid	n.p.	100%	n.p.	11	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Hexane	110-54-3	Hydrocarbon (acyclic)	Solvent	liquid	n.p.	100%	n.p.	12	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	1	Severe	Severe	Category 1	4	Category I	R41	Gautheron et al. (1994)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	2	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	3	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	4	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	5	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	6	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	7	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	8	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	9	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	10	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	11	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	12	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Iminodibenzyl	494-19-9	Heterocyclic	Personal care product	solid	n.p.	20%	n.p.	1	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Iminodibenzyl	494-19-9	Heterocyclic	Personal care product	solid	n.p.	20%	n.p.	2	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Iminodibenzyl	494-19-9	Heterocyclic	Personal care product	solid	n.p.	20%	n.p.	3	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Iminodibenzyl	494-19-9	Heterocyclic	Personal care product	solid	n.p.	20%	n.p.	4	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Iminodibenzyl	494-19-9	Heterocyclic	Personal care product	solid	n.p.	20%	n.p.	5	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Iminodibenzyl	494-19-9	Heterocyclic	Personal care product	solid	n.p.	20%	n.p.	6	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Iminodibenzyl	494-19-9	Heterocyclic	Personal care product	solid	n.p.	20%	n.p.	7	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Iminodibenzyl	494-19-9	Heterocyclic	Personal care product	solid	n.p.	20%	n.p.	8	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Iminodibenzyl	494-19-9	Heterocyclic	Personal care product	solid	n.p.	20%	n.p.	9	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Iminodibenzyl	494-19-9	Heterocyclic	Personal care product	solid	n.p.	20%	n.p.	10	n.a.	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Iminodibenzyl	494-19-9	Heterocyclic	Personal care product	solid	n.p.	20%	n.p.	11	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Iminodibenzyl	494-19-9	Heterocyclic	Personal care product	solid	n.p.	20%	n.p.	12	Nonirritant	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
N-Lauroylsarcosine, sodium salt	7631-98-3	Amide, Amino acid (salt)	Surfactant (anionic)	surfactant	n.p.	10%	n.p.	1	Moderate	Moderate	Category 2B		Category III	Nonirritant	Gautheron et al. (1994)
N-Lauroylsarcosine, sodium salt	7631-98-3	Amide, Amino acid (salt)	Surfactant (anionic)	surfactant	n.p.	10%	n.p.	2	Moderate	Moderate	Category 2B		Category III	Nonirritant	Gautheron et al. (1994)
N-Lauroylsarcosine, sodium salt	7631-98-3	Amide, Amino acid (salt)	Surfactant (anionic)	surfactant	n.p.	10%	n.p.	3	Moderate	Moderate	Category 2B		Category III	Nonirritant	Gautheron et al. (1994)
N-Lauroylsarcosine, sodium salt	7631-98-3	Amide, Amino acid (salt)	Surfactant (anionic)	surfactant	n.p.	10%	n.p.	4	Moderate	Moderate	Category 2B		Category III	Nonirritant	Gautheron et al. (1994)
N-Lauroylsarcosine, sodium salt	7631-98-3	Amide, Amino acid (salt)	Surfactant (anionic)	surfactant	n.p.	10%	n.p.	5	Moderate	Moderate	Category 2B		Category III	Nonirritant	Gautheron et al. (1994)
N-Lauroylsarcosine, sodium salt	7631-98-3	Amide, Amino acid (salt)	Surfactant (anionic)	surfactant	n.p.	10%	n.p.	6	Moderate	Moderate	Category 2B		Category III	Nonirritant	Gautheron et al. (1994)
N-Lauroylsarcosine, sodium salt	7631-98-3	Amide, Amino acid (salt)	Surfactant (anionic)	surfactant	n.p.	10%	n.p.	7	Moderate	Moderate	Category 2B		Category III	Nonirritant	Gautheron et al. (1994)
N-Lauroylsarcosine, sodium salt	7631-98-3	Amide, Amino acid (salt)	Surfactant (anionic)	surfactant	n.p.	10%	n.p.	8	Moderate	Moderate	Category 2B		Category III	Nonirritant	Gautheron et al. (1994)
N-Lauroylsarcosine, sodium salt	7631-98-3	Amide, Amino acid (salt)	Surfactant (anionic)	surfactant	n.p.	10%	n.p.	9	Severe	Moderate	Category 2B		Category III	Nonirritant	Gautheron et al. (1994)
N-Lauroylsarcosine, sodium salt	7631-98-3	Amide, Amino acid (salt)	Surfactant (anionic)	surfactant	n.p.	10%	n.p.	10	n.a.	Moderate	Category 2B		Category III	Nonirritant	Gautheron et al. (1994)
N-Lauroylsarcosine, sodium salt	7631-98-3	Amide, Amino acid (salt)	Surfactant (anionic)	surfactant	n.p.	10%	n.p.	11	Severe	Moderate	Category 2B		Category III	Nonirritant	Gautheron et al. (1994)
N-Lauroylsarcosine, sodium salt	7631-98-3	Amide, Amino acid (salt)	Surfactant (anionic)	surfactant	n.p.	10%	n.p.	12	Moderate	Moderate	Category 2B		Category III	Nonirritant	Gautheron et al. (1994)
Laurylsulfobetaine	14933-08-5	Amine, Onium compound	Detergent, Surfactant (zwitterionic)	surfactant	n.p.	10%	n.p.	1	Severe	Severe	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Laurylsulfobetaine	14933-08-5	Amine, Onium compound	Detergent, Surfactant (zwitterionic)	surfactant	n.p.	10%	n.p.	2	Severe	Severe	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Laurylsulfobetaine	14933-08-5	Amine, Onium compound	Detergent, Surfactant (zwitterionic)	surfactant	n.p.	10%	n.p.	3	Severe	Severe	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Laurylsulfobetaine	14933-08-5	Amine, Onium compound	Detergent, Surfactant (zwitterionic)	surfactant	n.p.	10%	n.p.	4	Severe	Severe	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Laurylsulfobetaine	14933-08-5	Amine, Onium compound	Detergent, Surfactant (zwitterionic)	surfactant	n.p.	10%	n.p.	5	Severe	Severe	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Laurylsulfobetaine	14933-08-5	Amine, Onium compound	Detergent, Surfactant (zwitterionic)	surfactant	n.p.	10%	n.p.	6	Severe	Severe	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Laurylsulfobetaine	14933-08-5	Amine, Onium compound	Detergent, Surfactant (zwitterionic)	surfactant	n.p.	10%	n.p.	7	Severe	Severe	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Laurylsulfobetaine	14933-08-5	Amine, Onium compound	Detergent, Surfactant (zwitterionic)	surfactant	n.p.	10%	n.p.	8	Severe	Severe	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Laurylsulfobetaine	14933-08-5	Amine, Onium compound	Detergent, Surfactant (zwitterionic)	surfactant	n.p.	10%	n.p.	9	Severe	Severe	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Laurylsulfobetaine	14933-08-5	Amine, Onium compound	Detergent, Surfactant (zwitterionic)	surfactant	n.p.	10%	n.p.	10	n.a.	Severe	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Laurylsulfobetaine	14933-08-5	Amine, Onium compound	Detergent, Surfactant (zwitterionic)	surfactant	n.p.	10%	n.p.	11	Severe	Severe	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Laurylsulfobetaine	14933-08-5	Amine, Onium compound	Detergent, Surfactant (zwitterionic)	surfactant	n.p.	10%	n.p.	12	Moderate	Severe	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Magnesium carbonate	56378-72-4	Inorganic salt	Chemical intermediate	solid	n.p.	20%	n.p.	1	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Magnesium carbonate	56378-72-4	Inorganic salt	Chemical intermediate	solid	n.p.	20%	n.p.	2	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Magnesium carbonate	56378-72-4	Inorganic salt	Chemical intermediate	solid	n.p.	20%	n.p.	3	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Magnesium carbonate	56378-72-4	Inorganic salt	Chemical intermediate	solid	n.p.	20%	n.p.	4	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Magnesium carbonate	56378-72-4	Inorganic salt	Chemical intermediate	solid	n.p.	20%	n.p.	5	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Magnesium carbonate	56378-72-4	Inorganic salt	Chemical intermediate	solid	n.p.	20%	n.p.	6	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Magnesium carbonate	56378-72-4	Inorganic salt	Chemical intermediate	solid	n.p.	20%	n.p.	7	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Magnesium carbonate	56378-72-4	Inorganic salt	Chemical intermediate	solid	n.p.	20%	n.p.	8	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Magnesium carbonate	56378-72-4	Inorganic salt	Chemical intermediate	solid	n.p.	20%	n.p.	9	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Magnesium carbonate	56378-72-4	Inorganic salt	Chemical intermediate	solid	n.p.	20%	n.p.	10	n.a.	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Magnesium carbonate	56378-72-4	Inorganic salt	Chemical intermediate	solid	n.p.	20%	n.p.	11	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Magnesium carbonate	56378-72-4	Inorganic salt	Chemical intermediate	solid	n.p.	20%	n.p.	12	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2-Mercaptopyrimidine	1450-85-7	Acyl halide	Anti-infective; Anti-fungal; Preservative	solid	n.p.	20%	n.p.	1	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
2-Mercaptopyrimidine	1450-85-7	Acyl halide	Anti-infective; Anti-fungal; Preservative	solid	n.p.	20%	n.p.	2	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
2-Mercaptopyrimidine	1450-85-7	Acyl halide	Anti-infective; Anti-fungal; Preservative	solid	n.p.	20%	n.p.	3	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
2-Mercaptopyrimidine	1450-85-7	Acyl halide	Anti-infective; Anti-fungal; Preservative	solid	n.p.	20%	n.p.	4	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
2-Mercaptopyrimidine	1450-85-7	Acyl halide	Anti-infective; Anti-fungal; Preservative	solid	n.p.	20%	n.p.	5	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
2-Mercaptopyrimidine	1450-85-7	Acyl halide	Anti-infective; Anti-fungal; Preservative	solid	n.p.	20%	n.p.	6	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
2-Mercaptopyrimidine	1450-85-7	Acyl halide	Anti-infective; Anti-fungal; Preservative	solid	n.p.	20%	n.p.	7	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
2-Mercaptopyrimidine	1450-85-7	Acyl halide	Anti-infective; Anti-fungal; Preservative	solid	n.p.	20%	n.p.	8	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
2-Mercaptopyrimidine	1450-85-7	Acyl halide	Anti-infective; Anti-fungal; Preservative	solid	n.p.	20%	n.p.	9	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
2-Mercaptopyrimidine	1450-85-7	Acyl halide	Anti-infective; Anti-fungal; Preservative	solid	n.p.	20%	n.p.	10	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)

Substance	CASRN[1]	Chemical Class	Product Class	Form Tested	Solubility	Concentration Tested	Purity (%)	Lab No.	In VitroTest Call[2]	In Vitro Consensus Call[2]	In Vivo GHS[4,5]	GHS Category 1 SubClass[6]	In Vivo EPA[7,8]	In Vivo EU[9,10]	Reference
2-Mercaptopyrimidine	1450-85-7	Acyl halide	Anti-infective; Anti-fungal; Preservative	solid	n.p.	20%	n.p.	11	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
2-Mercaptopyrimidine	1450-85-7	Acyl halide	Anti-infective; Anti-fungal; Preservative	solid	n.p.	20%	n.p.	12	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Methanol	67-56-1	Alcohol	Solvent	liquid	n.p.	100%	n.p.	1	Severe	Severe	Nonirritant		Category II	Nonirritant	Gautheron et al. (1994)
Methanol	67-56-1	Alcohol	Solvent	liquid	n.p.	100%	n.p.	2	Severe	Severe	Nonirritant		Category II	Nonirritant	Gautheron et al. (1994)
Methanol	67-56-1	Alcohol	Solvent	liquid	n.p.	100%	n.p.	3	Moderate	Severe	Nonirritant		Category II	Nonirritant	Gautheron et al. (1994)
Methanol	67-56-1	Alcohol	Solvent	liquid	n.p.	100%	n.p.	4	Severe	Severe	Nonirritant		Category II	Nonirritant	Gautheron et al. (1994)
Methanol	67-56-1	Alcohol	Solvent	liquid	n.p.	100%	n.p.	5	Severe	Severe	Nonirritant		Category II	Nonirritant	Gautheron et al. (1994)
Methanol	67-56-1	Alcohol	Solvent	liquid	n.p.	100%	n.p.	6	Severe	Severe	Nonirritant		Category II	Nonirritant	Gautheron et al. (1994)
Methanol	67-56-1	Alcohol	Solvent	liquid	n.p.	100%	n.p.	7	Moderate	Severe	Nonirritant		Category II	Nonirritant	Gautheron et al. (1994)
Methanol	67-56-1	Alcohol	Solvent	liquid	n.p.	100%	n.p.	8	Mild	Severe	Nonirritant		Category II	Nonirritant	Gautheron et al. (1994)
Methanol	67-56-1	Alcohol	Solvent	liquid	n.p.	100%	n.p.	9	Severe	Severe	Nonirritant		Category II	Nonirritant	Gautheron et al. (1994)
Methanol	67-56-1	Alcohol	Solvent	liquid	n.p.	100%	n.p.	10	n.a.	Severe	Nonirritant		Category II	Nonirritant	Gautheron et al. (1994)
Methanol	67-56-1	Alcohol	Solvent	liquid	n.p.	100%	n.p.	11	Severe	Severe	Nonirritant		Category II	Nonirritant	Gautheron et al. (1994)
Methanol	67-56-1	Alcohol	Solvent	liquid	n.p.	100%	n.p.	12	Severe	Severe	Nonirritant		Category II	Nonirritant	Gautheron et al. (1994)
2-Methoxyethanol	109-86-4	Alcohol	Solvent; Plasticizer	liquid	n.p.	100%	n.p.	1	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2-Methoxyethanol	109-86-4	Alcohol	Solvent; Plasticizer	liquid	n.p.	100%	n.p.	2	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2-Methoxyethanol	109-86-4	Alcohol	Solvent; Plasticizer	liquid	n.p.	100%	n.p.	3	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2-Methoxyethanol	109-86-4	Alcohol	Solvent; Plasticizer	liquid	n.p.	100%	n.p.	4	Moderate	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2-Methoxyethanol	109-86-4	Alcohol	Solvent; Plasticizer	liquid	n.p.	100%	n.p.	5	Moderate	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2-Methoxyethanol	109-86-4	Alcohol	Solvent; Plasticizer	liquid	n.p.	100%	n.p.	6	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2-Methoxyethanol	109-86-4	Alcohol	Solvent; Plasticizer	liquid	n.p.	100%	n.p.	7	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2-Methoxyethanol	109-86-4	Alcohol	Solvent; Plasticizer	liquid	n.p.	100%	n.p.	8	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2-Methoxyethanol	109-86-4	Alcohol	Solvent; Plasticizer	liquid	n.p.	100%	n.p.	9	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2-Methoxyethanol	109-86-4	Alcohol	Solvent; Plasticizer	liquid	n.p.	100%	n.p.	10	n.a.	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2-Methoxyethanol	109-86-4	Alcohol	Solvent; Plasticizer	liquid	n.p.	100%	n.p.	11	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2-Methoxyethanol	109-86-4	Alcohol	Solvent; Plasticizer	liquid	n.p.	100%	n.p.	12	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Methylisobutyl ketone	108-10-1	Ketone	Solvent; Synthetic flavor; Drycleaning	liquid	n.p.	100%	n.p.	1	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Methylisobutyl ketone	108-10-1	Ketone	Solvent; Synthetic flavor; Drycleaning	liquid	n.p.	100%	n.p.	2	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Methylisobutyl ketone	108-10-1	Ketone	Solvent; Synthetic flavor; Drycleaning	liquid	n.p.	100%	n.p.	3	Moderate	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Methylisobutyl ketone	108-10-1	Ketone	Solvent; Synthetic flavor; Drycleaning	liquid	n.p.	100%	n.p.	4	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Methylisobutyl ketone	108-10-1	Ketone	Solvent; Synthetic flavor; Drycleaning	liquid	n.p.	100%	n.p.	5	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Methylisobutyl ketone	108-10-1	Ketone	Solvent; Synthetic flavor; Drycleaning	liquid	n.p.	100%	n.p.	6	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Methylisobutyl ketone	108-10-1	Ketone	Solvent; Synthetic flavor; Drycleaning	liquid	n.p.	100%	n.p.	7	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Methylisobutyl ketone	108-10-1	Ketone	Solvent; Synthetic flavor; Drycleaning	liquid	n.p.	100%	n.p.	8	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Methylisobutyl ketone	108-10-1	Ketone	Solvent; Synthetic flavor; Drycleaning	liquid	n.p.	100%	n.p.	9	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Methylisobutyl ketone	108-10-1	Ketone	Solvent; Synthetic flavor; Drycleaning	liquid	n.p.	100%	n.p.	10	n.a.	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Methylisobutyl ketone	108-10-1	Ketone	Solvent; Synthetic flavor; Drycleaning	liquid	n.p.	100%	n.p.	11	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Methylisobutyl ketone	108-10-1	Ketone	Solvent; Synthetic flavor; Drycleaning	liquid	n.p.	100%	n.p.	12	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
MYRJ-45	-	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	surfactant	n.p.	10%	n.p.	1	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
MYRJ-45	-	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	surfactant	n.p.	10%	n.p.	2	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
MYRJ-45	-	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	surfactant	n.p.	10%	n.p.	3	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
MYRJ-45	-	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	surfactant	n.p.	10%	n.p.	4	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
MYRJ-45	-	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	surfactant	n.p.	10%	n.p.	5	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
MYRJ-45	-	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	surfactant	n.p.	10%	n.p.	6	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
MYRJ-45	-	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	surfactant	n.p.	10%	n.p.	7	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
MYRJ-45	-	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	surfactant	n.p.	10%	n.p.	8	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
MYRJ-45	-	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	surfactant	n.p.	10%	n.p.	9	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
MYRJ-45	-	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	surfactant	n.p.	10%	n.p.	10	n.a.	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
MYRJ-45	-	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	surfactant	n.p.	10%	n.p.	11	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
MYRJ-45	-	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	surfactant	n.p.	10%	n.p.	12	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
1-Nitropropane	108-03-2	Hydrocarbon (acyclic), Nitro compound	Solvent, Chemical intermediate	liquid	n.p.	100%	n.p.	1	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
1-Nitropropane	108-03-2	Hydrocarbon (acyclic), Nitro compound	Solvent, Chemical intermediate	liquid	n.p.	100%	n.p.	2	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
1-Nitropropane	108-03-2	Hydrocarbon (acyclic), Nitro compound	Solvent, Chemical intermediate	liquid	n.p.	100%	n.p.	3	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
1-Nitropropane	108-03-2	Hydrocarbon (acyclic), Nitro compound	Solvent, Chemical intermediate	liquid	n.p.	100%	n.p.	4	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
1-Nitropropane	108-03-2	Hydrocarbon (acyclic), Nitro compound	Solvent, Chemical intermediate	liquid	n.p.	100%	n.p.	5	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
1-Nitropropane	108-03-2	Hydrocarbon (acyclic), Nitro compound	Solvent, Chemical intermediate	liquid	n.p.	100%	n.p.	6	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)

Substance	CASRN[1]	Chemical Class	Product Class	Form Tested	Solubility	Concentration Tested	Purity (%)	Lab No.	In VitroTest Call[2]	In Vitro Consensus Call[2]	In Vivo GHS[4,5]	GHS Category 1 SubClass[6]	In Vivo EPA[7,8]	In Vivo EU[9,10]	Reference
1-Nitropropane	108-03-2	Hydrocarbon (acyclic), Nitro compound	Solvent, Chemical intermediate	liquid	n.p.	100%	n.p.	7	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
1-Nitropropane	108-03-2	Hydrocarbon (acyclic), Nitro compound	Solvent, Chemical intermediate	liquid	n.p.	100%	n.p.	8	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
1-Nitropropane	108-03-2	Hydrocarbon (acyclic), Nitro compound	Solvent, Chemical intermediate	liquid	n.p.	100%	n.p.	9	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
1-Nitropropane	108-03-2	Hydrocarbon (acyclic), Nitro compound	Solvent, Chemical intermediate	liquid	n.p.	100%	n.p.	10	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
1-Nitropropane	108-03-2	Hydrocarbon (acyclic), Nitro compound	Solvent, Chemical intermediate	liquid	n.p.	100%	n.p.	11	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
1-Nitropropane	108-03-2	Hydrocarbon (acyclic), Nitro compound	Solvent, Chemical intermediate	liquid	n.p.	100%	n.p.	12	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Octanol	111-87-5	Alcohol	Solvent; Fragrance	liquid	water insoluble*	100%	n.p.	1	Severe	Moderate	Category 2B		Category III	R36	Gautheron et al. (1994)
Octanol	111-87-5	Alcohol	Solvent; Fragrance	liquid	water insoluble*	100%	n.p.	2	Moderate	Moderate	Category 2B		Category III	R36	Gautheron et al. (1994)
Octanol	111-87-5	Alcohol	Solvent; Fragrance	liquid	water insoluble*	100%	n.p.	3	Moderate	Moderate	Category 2B		Category III	R36	Gautheron et al. (1994)
Octanol	111-87-5	Alcohol	Solvent; Fragrance	liquid	water insoluble*	100%	n.p.	4	Moderate	Moderate	Category 2B		Category III	R36	Gautheron et al. (1994)
Octanol	111-87-5	Alcohol	Solvent; Fragrance	liquid	water insoluble*	100%	n.p.	5	Severe	Moderate	Category 2B		Category III	R36	Gautheron et al. (1994)
Octanol	111-87-5	Alcohol	Solvent; Fragrance	liquid	water insoluble*	100%	n.p.	6	Moderate	Moderate	Category 2B		Category III	R36	Gautheron et al. (1994)
Octanol	111-87-5	Alcohol	Solvent; Fragrance	liquid	water insoluble*	100%	n.p.	7	Moderate	Moderate	Category 2B		Category III	R36	Gautheron et al. (1994)
Octanol	111-87-5	Alcohol	Solvent; Fragrance	liquid	water insoluble*	100%	n.p.	8	Mild	Moderate	Category 2B		Category III	R36	Gautheron et al. (1994)
Octanol	111-87-5	Alcohol	Solvent; Fragrance	liquid	water insoluble*	100%	n.p.	9	Severe	Moderate	Category 2B		Category III	R36	Gautheron et al. (1994)
Octanol	111-87-5	Alcohol	Solvent; Fragrance	liquid	water insoluble*	100%	n.p.	10	n.a.	Moderate	Category 2B		Category III	R36	Gautheron et al. (1994)
Octanol	111-87-5	Alcohol	Solvent; Fragrance	liquid	water insoluble*	100%	n.p.	11	Moderate	Moderate	Category 2B		Category III	R36	Gautheron et al. (1994)
Octanol	111-87-5	Alcohol	Solvent; Fragrance	liquid	water insoluble*	100%	n.p.	12	Severe	Moderate	Category 2B		Category III	R36	Gautheron et al. (1994)
2,4-Pentanedione	123-54-6	Alcohol	Solvent; Plasticizer	liquid	n.p.	100%	n.p.	1	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2,4-Pentanedione	123-54-6	Alcohol	Solvent; Plasticizer	liquid	n.p.	100%	n.p.	2	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2,4-Pentanedione	123-54-6	Alcohol	Solvent; Plasticizer	liquid	n.p.	100%	n.p.	3	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2,4-Pentanedione	123-54-6	Alcohol	Solvent; Plasticizer	liquid	n.p.	100%	n.p.	4	Moderate	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2,4-Pentanedione	123-54-6	Alcohol	Solvent; Plasticizer	liquid	n.p.	100%	n.p.	5	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2,4-Pentanedione	123-54-6	Alcohol	Solvent; Plasticizer	liquid	n.p.	100%	n.p.	6	Moderate	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2,4-Pentanedione	123-54-6	Alcohol	Solvent; Plasticizer	liquid	n.p.	100%	n.p.	7	Moderate	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2,4-Pentanedione	123-54-6	Alcohol	Solvent; Plasticizer	liquid	n.p.	100%	n.p.	8	Moderate	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2,4-Pentanedione	123-54-6	Alcohol	Solvent; Plasticizer	liquid	n.p.	100%	n.p.	9	Moderate	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2,4-Pentanedione	123-54-6	Alcohol	Solvent; Plasticizer	liquid	n.p.	100%	n.p.	10	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2,4-Pentanedione	123-54-6	Alcohol	Solvent; Plasticizer	liquid	n.p.	100%	n.p.	11	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
2,4-Pentanedione	123-54-6	Alcohol	Solvent; Plasticizer	liquid	n.p.	100%	n.p.	12	Severe	Severe	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Petroleum ether	8032-32-4	Hydrocarbon (acyclic)	Solvent	liquid	n.p.	100%	n.p.	1	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Petroleum ether	8032-32-4	Hydrocarbon (acyclic)	Solvent	liquid	n.p.	100%	n.p.	2	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Petroleum ether	8032-32-4	Hydrocarbon (acyclic)	Solvent	liquid	n.p.	100%	n.p.	3	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Petroleum ether	8032-32-4	Hydrocarbon (acyclic)	Solvent	liquid	n.p.	100%	n.p.	4	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Petroleum ether	8032-32-4	Hydrocarbon (acyclic)	Solvent	liquid	n.p.	100%	n.p.	5	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Petroleum ether	8032-32-4	Hydrocarbon (acyclic)	Solvent	liquid	n.p.	100%	n.p.	6	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Petroleum ether	8032-32-4	Hydrocarbon (acyclic)	Solvent	liquid	n.p.	100%	n.p.	7	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Petroleum ether	8032-32-4	Hydrocarbon (acyclic)	Solvent	liquid	n.p.	100%	n.p.	8	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Petroleum ether	8032-32-4	Hydrocarbon (acyclic)	Solvent	liquid	n.p.	100%	n.p.	9	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Petroleum ether	8032-32-4	Hydrocarbon (acyclic)	Solvent	liquid	n.p.	100%	n.p.	10	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Petroleum ether	8032-32-4	Hydrocarbon (acyclic)	Solvent	liquid	n.p.	100%	n.p.	11	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Petroleum ether	8032-32-4	Hydrocarbon (acyclic)	Solvent	liquid	n.p.	100%	n.p.	12	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Phenylbutazone	50-33-9	Heterocyclic	Pharmaceutical	solid	n.p.	20%	n.p.	1	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Phenylbutazone	50-33-9	Heterocyclic	Pharmaceutical	solid	n.p.	20%	n.p.	2	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Phenylbutazone	50-33-9	Heterocyclic	Pharmaceutical	solid	n.p.	20%	n.p.	3	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Phenylbutazone	50-33-9	Heterocyclic	Pharmaceutical	solid	n.p.	20%	n.p.	4	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Phenylbutazone	50-33-9	Heterocyclic	Pharmaceutical	solid	n.p.	20%	n.p.	5	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Phenylbutazone	50-33-9	Heterocyclic	Pharmaceutical	solid	n.p.	20%	n.p.	6	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Phenylbutazone	50-33-9	Heterocyclic	Pharmaceutical	solid	n.p.	20%	n.p.	7	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Phenylbutazone	50-33-9	Heterocyclic	Pharmaceutical	solid	n.p.	20%	n.p.	8	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Phenylbutazone	50-33-9	Heterocyclic	Pharmaceutical	solid	n.p.	20%	n.p.	9	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Phenylbutazone	50-33-9	Heterocyclic	Pharmaceutical	solid	n.p.	20%	n.p.	10	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Phenylbutazone	50-33-9	Heterocyclic	Pharmaceutical	solid	n.p.	20%	n.p.	11	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Phenylbutazone	50-33-9	Heterocyclic	Pharmaceutical	solid	n.p.	20%	n.p.	12	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
1-Phenyl-3-pyrazolidone	92-43-3	Heterocyclic	Photographic agent	solid	n.p.	20%	n.p.	1	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1-Phenyl-3-pyrazolidone	92-43-3	Heterocyclic	Photographic agent	solid	n.p.	20%	n.p.	2	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1-Phenyl-3-pyrazolidone	92-43-3	Heterocyclic	Photographic agent	solid	n.p.	20%	n.p.	3	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1-Phenyl-3-pyrazolidone	92-43-3	Heterocyclic	Photographic agent	solid	n.p.	20%	n.p.	4	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1-Phenyl-3-pyrazolidone	92-43-3	Heterocyclic	Photographic agent	solid	n.p.	20%	n.p.	5	Moderate	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1-Phenyl-3-pyrazolidone	92-43-3	Heterocyclic	Photographic agent	solid	n.p.	20%	n.p.	6	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1-Phenyl-3-pyrazolidone	92-43-3	Heterocyclic	Photographic agent	solid	n.p.	20%	n.p.	7	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1-Phenyl-3-pyrazolidone	92-43-3	Heterocyclic	Photographic agent	solid	n.p.	20%	n.p.	8	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1-Phenyl-3-pyrazolidone	92-43-3	Heterocyclic	Photographic agent	solid	n.p.	20%	n.p.	9	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1-Phenyl-3-pyrazolidone	92-43-3	Heterocyclic	Photographic agent	solid	n.p.	20%	n.p.	10	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1-Phenyl-3-pyrazolidone	92-43-3	Heterocyclic	Photographic agent	solid	n.p.	20%	n.p.	11	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1-Phenyl-3-pyrazolidone	92-43-3	Heterocyclic	Photographic agent	solid	n.p.	20%	n.p.	12	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Promethazine hydrochloride	58-33-3	Amine/Amidine, Heterocyclic, Organic sulfur compound	Antihistamine; Anti-nausea drug	solid	water soluble*	20%	n.p.	1	Severe	Severe	Category 1	3	Category I	R41	Gautheron et al. (1994)
Promethazine hydrochloride	58-33-3	Amine/Amidine, Heterocyclic, Organic sulfur compound	Antihistamine; Anti-nausea drug	solid	water soluble*	20%	n.p.	2	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Promethazine hydrochloride	58-33-3	Amine/Amidine, Heterocyclic, Organic sulfur compound	Antihistamine; Anti-nausea drug	solid	water soluble*	20%	n.p.	3	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Promethazine hydrochloride	58-33-3	Amine/Amidine, Heterocyclic, Organic sulfur compound	Antihistamine; Anti-nausea drug	solid	water soluble*	20%	n.p.	4	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Promethazine hydrochloride	58-33-3	Amine/Amidine, Heterocyclic, Organic sulfur compound	Antihistamine; Anti-nausea drug	solid	water soluble*	20%	n.p.	5	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Promethazine hydrochloride	58-33-3	Amine/Amidine, Heterocyclic, Organic sulfur compound	Antihistamine; Anti-nausea drug	solid	water soluble*	20%	n.p.	6	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Promethazine hydrochloride	58-33-3	Amine/Amidine, Heterocyclic, Organic sulfur compound	Antihistamine; Anti-nausea drug	solid	water soluble*	20%	n.p.	7	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Promethazine hydrochloride	58-33-3	Amine/Amidine, Heterocyclic, Organic sulfur compound	Antihistamine; Anti-nausea drug	solid	water soluble*	20%	n.p.	8	Moderate	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Promethazine hydrochloride	58-33-3	Amine/Amidine, Heterocyclic, Organic sulfur compound	Antihistamine; Anti-nausea drug	solid	water soluble*	20%	n.p.	9	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Promethazine hydrochloride	58-33-3	Amine/Amidine, Heterocyclic, Organic sulfur compound	Antihistamine; Anti-nausea drug	solid	water soluble*	20%	n.p.	10	n.a.	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Promethazine hydrochloride	58-33-3	Amine/Amidine, Heterocyclic, Organic sulfur compound	Antihistamine; Anti-nausea drug	solid	water soluble*	20%	n.p.	11	Severe	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Promethazine hydrochloride	58-33-3	Amine/Amidine, Heterocyclic, Organic sulfur compound	Antihistamine; Anti-nausea drug	solid	water soluble*	20%	n.p.	12	Mild	Severe	Category 1		Category I	R41	Gautheron et al. (1994)
Propyl-4-hydroxybenzoate	94-13-3	Carboxylic acid, Phenol	Antimicrobial	solid	n.p.	20%	n.p.	1	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Propyl-4-hydroxybenzoate	94-13-3	Carboxylic acid, Phenol	Antimicrobial	solid	n.p.	20%	n.p.	2	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)

Substance	CASRN[1]	Chemical Class	Product Class	Form Tested	Solubility	Concentration Tested	Purity (%)	Lab No.	In VitroTest Call[2]	In Vitro Consensus Call[2]	In Vivo GHS[4,5]	GHS Category 1 SubClass[6]	In Vivo EPA[7,8]	In Vivo EU[5,10]	Reference
Propyl-4-hydroxybenzoate	94-13-3	Carboxylic acid, Phenol	Antimicrobial	solid	n.p.	20%	n.p.	3	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Propyl-4-hydroxybenzoate	94-13-3	Carboxylic acid, Phenol	Antimicrobial	solid	n.p.	20%	n.p.	4	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Propyl-4-hydroxybenzoate	94-13-3	Carboxylic acid, Phenol	Antimicrobial	solid	n.p.	20%	n.p.	5	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Propyl-4-hydroxybenzoate	94-13-3	Carboxylic acid, Phenol	Antimicrobial	solid	n.p.	20%	n.p.	6	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Propyl-4-hydroxybenzoate	94-13-3	Carboxylic acid, Phenol	Antimicrobial	solid	n.p.	20%	n.p.	7	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Propyl-4-hydroxybenzoate	94-13-3	Carboxylic acid, Phenol	Antimicrobial	solid	n.p.	20%	n.p.	8	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Propyl-4-hydroxybenzoate	94-13-3	Carboxylic acid, Phenol	Antimicrobial	solid	n.p.	20%	n.p.	9	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Propyl-4-hydroxybenzoate	94-13-3	Carboxylic acid, Phenol	Antimicrobial	solid	n.p.	20%	n.p.	10	n.a.	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Propyl-4-hydroxybenzoate	94-13-3	Carboxylic acid, Phenol	Antimicrobial	solid	n.p.	20%	n.p.	11	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Propyl-4-hydroxybenzoate	94-13-3	Carboxylic acid, Phenol	Antimicrobial	solid	n.p.	20%	n.p.	12	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Pyridine	110-86-1	Heterocyclic	Solvent; Intermediate for pharmaceuticals, dyes, pesticides	liquid	water soluble	100%	n.p.	1	Severe	Severe	Category 1		Category II	R41	Gautheron et al. (1994)
Pyridine	110-86-1	Heterocyclic	Solvent; Intermediate for pharmaceuticals, dyes, pesticides	liquid	water soluble	100%	n.p.	2	Severe	Severe	Category 1		Category II	R41	Gautheron et al. (1994)
Pyridine	110-86-1	Heterocyclic	Solvent; Intermediate for pharmaceuticals, dyes, pesticides	liquid	water soluble	100%	n.p.	3	Severe	Severe	Category 1		Category II	R41	Gautheron et al. (1994)
Pyridine	110-86-1	Heterocyclic	Solvent; Intermediate for pharmaceuticals, dyes, pesticides	liquid	water soluble	100%	n.p.	4	Severe	Severe	Category 1		Category II	R41	Gautheron et al. (1994)
Pyridine	110-86-1	Heterocyclic	Solvent; Intermediate for pharmaceuticals, dyes, pesticides	liquid	water soluble	100%	n.p.	5	Severe	Severe	Category 1		Category II	R41	Gautheron et al. (1994)
Pyridine	110-86-1	Heterocyclic	Solvent; Intermediate for pharmaceuticals, dyes, pesticides	liquid	water soluble	100%	n.p.	6	Severe	Severe	Category 1		Category II	R41	Gautheron et al. (1994)
Pyridine	110-86-1	Heterocyclic	Solvent; Intermediate for pharmaceuticals, dyes, pesticides	liquid	water soluble	100%	n.p.	7	Severe	Severe	Category 1	4	Category II	R41	Gautheron et al. (1994)
Pyridine	110-86-1	Heterocyclic	Solvent; Intermediate for pharmaceuticals, dyes, pesticides	liquid	water soluble	100%	n.p.	8	Severe	Severe	Category 1		Category II	R41	Gautheron et al. (1994)
Pyridine	110-86-1	Heterocyclic	Solvent; Intermediate for pharmaceuticals, dyes, pesticides	liquid	water soluble	100%	n.p.	9	Severe	Severe	Category 1		Category II	R41	Gautheron et al. (1994)
Pyridine	110-86-1	Heterocyclic	Solvent; Intermediate for pharmaceuticals, dyes, pesticides	liquid	water soluble	100%	n.p.	10	n.a.	Severe	Category 1		Category II	R41	Gautheron et al. (1994)
Pyridine	110-86-1	Heterocyclic	Solvent; Intermediate for pharmaceuticals, dyes, pesticides	liquid	water soluble	100%	n.p.	11	Severe	Severe	Category 1		Category II	R41	Gautheron et al. (1994)
Pyridine	110-86-1	Heterocyclic	Solvent; Intermediate for pharmaceuticals, dyes, pesticides	liquid	water soluble	100%	n.p.	12	Severe	Severe	Category 1		Category II	R41	Gautheron et al. (1994)
Quinacrine	69-05-6	Heterocyclic	Drug/Therapeutic agent	solid	water soluble*	20%	n.p.	1	Mild	Moderate	Category 1		Category I	R41	Gautheron et al. (1994)
Quinacrine	69-05-6	Heterocyclic	Drug/Therapeutic agent	solid	water soluble*	20%	n.p.	2	Moderate	Moderate	Category 1		Category I	R41	Gautheron et al. (1994)
Quinacrine	69-05-6	Heterocyclic	Drug/Therapeutic agent	solid	water soluble*	20%	n.p.	3	Mild	Moderate	Category 1		Category I	R41	Gautheron et al. (1994)
Quinacrine	69-05-6	Heterocyclic	Drug/Therapeutic agent	solid	water soluble*	20%	n.p.	4	Moderate	Moderate	Category 1		Category I	R41	Gautheron et al. (1994)
Quinacrine	69-05-6	Heterocyclic	Drug/Therapeutic agent	solid	water soluble*	20%	n.p.	5	Moderate	Moderate	Category 1		Category I	R41	Gautheron et al. (1994)
Quinacrine	69-05-6	Heterocyclic	Drug/Therapeutic agent	solid	water soluble*	20%	n.p.	6	Mild	Moderate	Category 1		Category I	R41	Gautheron et al. (1994)
Quinacrine	69-05-6	Heterocyclic	Drug/Therapeutic agent	solid	water soluble*	20%	n.p.	7	Moderate	Moderate	Category 1	1	Category I	R41	Gautheron et al. (1994)
Quinacrine	69-05-6	Heterocyclic	Drug/Therapeutic agent	solid	water soluble*	20%	n.p.	8	Moderate	Moderate	Category 1		Category I	R41	Gautheron et al. (1994)
Quinacrine	69-05-6	Heterocyclic	Drug/Therapeutic agent	solid	water soluble*	20%	n.p.	9	Severe	Moderate	Category 1		Category I	R41	Gautheron et al. (1994)
Quinacrine	69-05-6	Heterocyclic	Drug/Therapeutic agent	solid	water soluble*	20%	n.p.	10	n.a.	Moderate	Category 1		Category I	R41	Gautheron et al. (1994)
Quinacrine	69-05-6	Heterocyclic	Drug/Therapeutic agent	solid	water soluble*	20%	n.p.	11	Mild	Moderate	Category 1		Category I	R41	Gautheron et al. (1994)
Quinacrine	69-05-6	Heterocyclic	Drug/Therapeutic agent	solid	water soluble*	20%	n.p.	12	Severe	Moderate	Category 1		Category I	R41	Gautheron et al. (1994)
Sodium oxalate	62-76-0	Carboxylic acid (salt)	Textile finishing; Pyrotechnic, Industrial byproduct	solid	water soluble	20%	n.p.	1	Mild	Mild	Category 1		Category I	R41	Gautheron et al. (1994)
Sodium oxalate	62-76-0	Carboxylic acid (salt)	Textile finishing; Pyrotechnic, Industrial byproduct	solid	water soluble	20%	n.p.	2	Mild	Mild	Category 1		Category I	R41	Gautheron et al. (1994)
Sodium oxalate	62-76-0	Carboxylic acid (salt)	Textile finishing; Pyrotechnic, Industrial byproduct	solid	water soluble	20%	n.p.	3	Mild	Mild	Category 1		Category I	R41	Gautheron et al. (1994)
Sodium oxalate	62-76-0	Carboxylic acid (salt)	Textile finishing; Pyrotechnic, Industrial byproduct	solid	water soluble	20%	n.p.	4	Mild	Mild	Category 1		Category I	R41	Gautheron et al. (1994)
Sodium oxalate	62-76-0	Carboxylic acid (salt)	Textile finishing; Pyrotechnic, Industrial byproduct	solid	water soluble	20%	n.p.	5	Mild	Mild	Category 1		Category I	R41	Gautheron et al. (1994)
Sodium oxalate	62-76-0	Carboxylic acid (salt)	Textile finishing; Pyrotechnic, Industrial byproduct	solid	water soluble	20%	n.p.	6	Mild	Mild	Category 1		Category I	R41	Gautheron et al. (1994)
Sodium oxalate	62-76-0	Carboxylic acid (salt)	Textile finishing; Pyrotechnic, Industrial byproduct	solid	water soluble	20%	n.p.	7	Mild	Mild	Category 1	4	Category I	R41	Gautheron et al. (1994)
Sodium oxalate	62-76-0	Carboxylic acid (salt)	Textile finishing; Pyrotechnic, Industrial byproduct	solid	water soluble	20%	n.p.	8	Mild	Mild	Category 1		Category I	R41	Gautheron et al. (1994)
Sodium oxalate	62-76-0	Carboxylic acid (salt)	Textile finishing; Pyrotechnic, Industrial byproduct	solid	water soluble	20%	n.p.	9	Mild	Mild	Category 1		Category I	R41	Gautheron et al. (1994)
Sodium oxalate	62-76-0	Carboxylic acid (salt)	Textile finishing; Pyrotechnic, Industrial byproduct	solid	water soluble	20%	n.p.	10	Mild	Mild	Category 1		Category I	R41	Gautheron et al. (1994)
Sodium oxalate	62-76-0	Carboxylic acid (salt)	Textile finishing; Pyrotechnic, Industrial byproduct	solid	water soluble	20%	n.p.	11	Mild	Mild	Category 1		Category I	R41	Gautheron et al. (1994)
Sodium oxalate	62-76-0	Carboxylic acid (salt)	Textile finishing; Pyrotechnic, Industrial byproduct	solid	water soluble	20%	n.p.	12	Mild	Mild	Category 1		Category I	R41	Gautheron et al. (1994)
Tetraaminopyrimidine sulfate	5392-28-9	Amine, Heterocycle, Inorganic salt	Not classified	solid	n.p.	20%	n.p.	1	Mild	Mild	Nonirritant		Category II	Nonirritant	Gautheron et al. (1994)
Tetraaminopyrimidine sulfate	5392-28-9	Amine, Heterocycle, Inorganic salt	Not classified	solid	n.p.	20%	n.p.	2	Mild	Mild	Nonirritant		Category II	Nonirritant	Gautheron et al. (1994)
Tetraaminopyrimidine sulfate	5392-28-9	Amine, Heterocycle, Inorganic salt	Not classified	solid	n.p.	20%	n.p.	3	Mild	Mild	Nonirritant		Category II	Nonirritant	Gautheron et al. (1994)
Tetraaminopyrimidine sulfate	5392-28-9	Amine, Heterocycle, Inorganic salt	Not classified	solid	n.p.	20%	n.p.	4	Mild	Mild	Nonirritant		Category II	Nonirritant	Gautheron et al. (1994)
Tetraaminopyrimidine sulfate	5392-28-9	Amine, Heterocycle, Inorganic salt	Not classified	solid	n.p.	20%	n.p.	5	Mild	Mild	Nonirritant		Category II	Nonirritant	Gautheron et al. (1994)
Tetraaminopyrimidine sulfate	5392-28-9	Amine, Heterocycle, Inorganic salt	Not classified	solid	n.p.	20%	n.p.	6	Mild	Mild	Nonirritant		Category II	Nonirritant	Gautheron et al. (1994)
Tetraaminopyrimidine sulfate	5392-28-9	Amine, Heterocycle, Inorganic salt	Not classified	solid	n.p.	20%	n.p.	7	Mild	Mild	Nonirritant		Category II	Nonirritant	Gautheron et al. (1994)
Tetraaminopyrimidine sulfate	5392-28-9	Amine, Heterocycle, Inorganic salt	Not classified	solid	n.p.	20%	n.p.	8	Mild	Mild	Nonirritant		Category II	Nonirritant	Gautheron et al. (1994)

Substance	CASRN[1]	Chemical Class	Product Class	Form Tested	Solubility	Concentration Tested	Purity (%)	Lab No.	In VitroTest Call[2]	In Vitro Consensus Call[2]	In Vivo GHS[4,5]	GHS Category 1 SubClass[6]	In Vivo EPA[7,8]	In Vivo EU[9,10]	Reference
Tetraaminopyrimidine sulfate	5392-28-9	Amine, Heterocycle, Inorganic salt	Not classified	solid	n.p.	20%	n.p.	9	Mild	Mild	Nonirritant		Category II	Nonirritant	Gautheron et al. (1994)
Tetraaminopyrimidine sulfate	5392-28-9	Amine, Heterocycle, Inorganic salt	Not classified	solid	n.p.	20%	n.p.	10	n.a.	Mild	Nonirritant		Category II	Nonirritant	Gautheron et al. (1994)
Tetraaminopyrimidine sulfate	5392-28-9	Amine, Heterocycle, Inorganic salt	Not classified	solid	n.p.	20%	n.p.	11	Mild	Mild	Nonirritant		Category II	Nonirritant	Gautheron et al. (1994)
Tetraaminopyrimidine sulfate	5392-28-9	Amine, Heterocycle, Inorganic salt	Not classified	solid	n.p.	20%	n.p.	12	Mild	Mild	Nonirritant		Category II	Nonirritant	Gautheron et al. (1994)
Thiourea	62-56-6	Organic sulfur compound	Photographic agent; Flame-retardant; Chelation reagent and catalyst; Chemical intermediate; Pesticide; Drug/Therapeutic agent	solid	n.p.	20%	n.p.	1	Severe	Severe	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Thiourea	62-56-6	Organic sulfur compound	Photographic agent; Flame-retardant; Chelation reagent and catalyst; Chemical intermediate; Pesticide; Drug/Therapeutic agent	solid	n.p.	20%	n.p.	2	Severe	Severe	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Thiourea	62-56-6	Organic sulfur compound	Photographic agent; Flame-retardant; Chelation reagent and catalyst; Chemical intermediate; Pesticide; Drug/Therapeutic agent	solid	n.p.	20%	n.p.	3	Severe	Severe	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Thiourea	62-56-6	Organic sulfur compound	Photographic agent; Flame-retardant; Chelation reagent and catalyst; Chemical intermediate; Pesticide; Drug/Therapeutic agent	solid	n.p.	20%	n.p.	4	Severe	Severe	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Thiourea	62-56-6	Organic sulfur compound	Photographic agent; Flame-retardant; Chelation reagent and catalyst; Chemical intermediate; Pesticide; Drug/Therapeutic agent	solid	n.p.	20%	n.p.	5	Severe	Severe	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Thiourea	62-56-6	Organic sulfur compound	Photographic agent; Flame-retardant; Chelation reagent and catalyst; Chemical intermediate; Pesticide; Drug/Therapeutic agent	solid	n.p.	20%	n.p.	6	Severe	Severe	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Thiourea	62-56-6	Organic sulfur compound	Photographic agent; Flame-retardant; Chelation reagent and catalyst; Chemical intermediate; Pesticide; Drug/Therapeutic agent	solid	n.p.	20%	n.p.	7	Severe	Severe	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Thiourea	62-56-6	Organic sulfur compound	Photographic agent; Flame-retardant; Chelation reagent and catalyst; Chemical intermediate; Pesticide; Drug/Therapeutic agent	solid	n.p.	20%	n.p.	8	Severe	Severe	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Thiourea	62-56-6	Organic sulfur compound	Photographic agent; Flame-retardant; Chelation reagent and catalyst; Chemical intermediate; Pesticide; Drug/Therapeutic agent	solid	n.p.	20%	n.p.	9	Severe	Severe	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Thiourea	62-56-6	Organic sulfur compound	Photographic agent; Flame-retardant; Chelation reagent and catalyst; Chemical intermediate; Pesticide; Drug/Therapeutic agent	solid	n.p.	20%	n.p.	10	n.a.	Severe	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Thiourea	62-56-6	Organic sulfur compound	Photographic agent; Flame-retardant; Chelation reagent and catalyst; Chemical intermediate; Pesticide; Drug/Therapeutic agent	solid	n.p.	20%	n.p.	11	Severe	Severe	SCNM		SCNM	SCNM	Gautheron et al. (1994)
Thiourea	62-56-6	Organic sulfur compound	Photographic agent; Flame-retardant; Chelation reagent and catalyst; Chemical intermediate; Pesticide; Drug/Therapeutic agent	solid	n.p.	20%	n.p.	12	Severe	Severe	SCNM		SCNM	SCNM	Gautheron et al. (1994)
1,2,3-Trichloropropane	96-18-4	Hydrocarbon (halogenated)	Solvent	liquid	n.p.	100%	n.p.	1	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1,2,3-Trichloropropane	96-18-4	Hydrocarbon (halogenated)	Solvent	liquid	n.p.	100%	n.p.	2	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1,2,3-Trichloropropane	96-18-4	Hydrocarbon (halogenated)	Solvent	liquid	n.p.	100%	n.p.	3	Severe	Moderate	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1,2,3-Trichloropropane	96-18-4	Hydrocarbon (halogenated)	Solvent	liquid	n.p.	100%	n.p.	4	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1,2,3-Trichloropropane	96-18-4	Hydrocarbon (halogenated)	Solvent	liquid	n.p.	100%	n.p.	5	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1,2,3-Trichloropropane	96-18-4	Hydrocarbon (halogenated)	Solvent	liquid	n.p.	100%	n.p.	6	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1,2,3-Trichloropropane	96-18-4	Hydrocarbon (halogenated)	Solvent	liquid	n.p.	100%	n.p.	7	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1,2,3-Trichloropropane	96-18-4	Hydrocarbon (halogenated)	Solvent	liquid	n.p.	100%	n.p.	8	Mild	Moderate	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1,2,3-Trichloropropane	96-18-4	Hydrocarbon (halogenated)	Solvent	liquid	n.p.	100%	n.p.	9	Severe	Moderate	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1,2,3-Trichloropropane	96-18-4	Hydrocarbon (halogenated)	Solvent	liquid	n.p.	100%	n.p.	10	n.a.	Moderate	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1,2,3-Trichloropropane	96-18-4	Hydrocarbon (halogenated)	Solvent	liquid	n.p.	100%	n.p.	11	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1,2,3-Trichloropropane	96-18-4	Hydrocarbon (halogenated)	Solvent	liquid	n.p.	100%	n.p.	12	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Triethanolamine	102-71-6	Amine, Alcohol	Antimicrobial, Chemical intermediate	liquid	n.p.	100%	n.p.	1	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Triethanolamine	102-71-6	Amine, Alcohol	Antimicrobial, Chemical intermediate	liquid	n.p.	100%	n.p.	2	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Triethanolamine	102-71-6	Amine, Alcohol	Antimicrobial, Chemical intermediate	liquid	n.p.	100%	n.p.	3	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Triethanolamine	102-71-6	Amine, Alcohol	Antimicrobial, Chemical intermediate	liquid	n.p.	100%	n.p.	4	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Triethanolamine	102-71-6	Amine, Alcohol	Antimicrobial, Chemical intermediate	liquid	n.p.	100%	n.p.	5	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Triethanolamine	102-71-6	Amine, Alcohol	Antimicrobial, Chemical intermediate	liquid	n.p.	100%	n.p.	6	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Triethanolamine	102-71-6	Amine, Alcohol	Antimicrobial, Chemical intermediate	liquid	n.p.	100%	n.p.	7	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Triethanolamine	102-71-6	Amine, Alcohol	Antimicrobial, Chemical intermediate	liquid	n.p.	100%	n.p.	8	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Triethanolamine	102-71-6	Amine, Alcohol	Antimicrobial, Chemical intermediate	liquid	n.p.	100%	n.p.	9	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Triethanolamine	102-71-6	Amine, Alcohol	Antimicrobial, Chemical intermediate	liquid	n.p.	100%	n.p.	10	n.a.	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)

Substance	CASRN[1]	Chemical Class	Product Class	Form Tested	Solubility	Concentration Tested	Purity (%)	Lab No.	In VitroTest Call[2]	In Vitro Consensus Call[2]	In Vivo GHS[4,5]	GHS Category 1 SubClass[6]	In Vivo EPA[7,8]	In Vivo EU[5,10]	Reference
Triethanolamine	102-71-6	Amine, Alcohol	Antimicrobial, Chemical intermdiate	liquid	n.p.	100%	n.p.	11	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Triethanolamine	102-71-6	Amine, Alcohol	Antimicrobial, Chemical intermdiate	liquid	n.p.	100%	n.p.	12	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
1,2,4-Trimethylbenzene	95-63-6	Hydrocarbon (cyclic)	Chemical intermediate	liquid	n.p.	100%	n.p.	1	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1,2,4-Trimethylbenzene	95-63-6	Hydrocarbon (cyclic)	Chemical intermediate	liquid	n.p.	100%	n.p.	2	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1,2,4-Trimethylbenzene	95-63-6	Hydrocarbon (cyclic)	Chemical intermediate	liquid	n.p.	100%	n.p.	3	Moderate	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1,2,4-Trimethylbenzene	95-63-6	Hydrocarbon (cyclic)	Chemical intermediate	liquid	n.p.	100%	n.p.	4	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1,2,4-Trimethylbenzene	95-63-6	Hydrocarbon (cyclic)	Chemical intermediate	liquid	n.p.	100%	n.p.	5	Moderate	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1,2,4-Trimethylbenzene	95-63-6	Hydrocarbon (cyclic)	Chemical intermediate	liquid	n.p.	100%	n.p.	6	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1,2,4-Trimethylbenzene	95-63-6	Hydrocarbon (cyclic)	Chemical intermediate	liquid	n.p.	100%	n.p.	7	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1,2,4-Trimethylbenzene	95-63-6	Hydrocarbon (cyclic)	Chemical intermediate	liquid	n.p.	100%	n.p.	8	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1,2,4-Trimethylbenzene	95-63-6	Hydrocarbon (cyclic)	Chemical intermediate	liquid	n.p.	100%	n.p.	9	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1,2,4-Trimethylbenzene	95-63-6	Hydrocarbon (cyclic)	Chemical intermediate	liquid	n.p.	100%	n.p.	10	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1,2,4-Trimethylbenzene	95-63-6	Hydrocarbon (cyclic)	Chemical intermediate	liquid	n.p.	100%	n.p.	11	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
1,2,4-Trimethylbenzene	95-63-6	Hydrocarbon (cyclic)	Chemical intermediate	liquid	n.p.	100%	n.p.	12	Mild	Mild	Nonirritant		Category III	Nonirritant	Gautheron et al. (1994)
Triton X-155	9010-44-0	Ether	Surfactant (nonionic)	surfactant	n.p.	10%	n.p.	1	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Triton X-155	9010-44-0	Ether	Surfactant (nonionic)	surfactant	n.p.	10%	n.p.	2	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Triton X-155	9010-44-0	Ether	Surfactant (nonionic)	surfactant	n.p.	10%	n.p.	3	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Triton X-155	9010-44-0	Ether	Surfactant (nonionic)	surfactant	n.p.	10%	n.p.	4	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Triton X-155	9010-44-0	Ether	Surfactant (nonionic)	surfactant	n.p.	10%	n.p.	5	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Triton X-155	9010-44-0	Ether	Surfactant (nonionic)	surfactant	n.p.	10%	n.p.	6	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Triton X-155	9010-44-0	Ether	Surfactant (nonionic)	surfactant	n.p.	10%	n.p.	7	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Triton X-155	9010-44-0	Ether	Surfactant (nonionic)	surfactant	n.p.	10%	n.p.	8	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Triton X-155	9010-44-0	Ether	Surfactant (nonionic)	surfactant	n.p.	10%	n.p.	9	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Triton X-155	9010-44-0	Ether	Surfactant (nonionic)	surfactant	n.p.	10%	n.p.	10	n.a.	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Triton X-155	9010-44-0	Ether	Surfactant (nonionic)	surfactant	n.p.	10%	n.p.	11	Nonirritant	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Triton X-155	9010-44-0	Ether	Surfactant (nonionic)	surfactant	n.p.	10%	n.p.	12	Mild	Mild	Nonirritant		Category IV	Nonirritant	Gautheron et al. (1994)
Ammonium nitrate	6484-52-2	Inorganic salt; Onium compound	Fertilizer, Chemical intermediate; Industrial explosive	n.p.	n.p.	100%	n.p.	1 (1)	Mild	Mild	Category 2B		Category III	R36	Southee (1998)
Ammonium nitrate	6484-52-2	Inorganic salt; Onium compound	Fertilizer, Chemical intermediate; Industrial explosive	n.p.	n.p.	100%	n.p.	1 (2)	Mild	Mild	Category 2B		Category III	R36	Southee (1998)
Ammonium nitrate	6484-52-2	Inorganic salt; Onium compound	Fertilizer, Chemical intermediate; Industrial explosive	n.p.	n.p.	100%	n.p.	2 (1)	Mild	Mild	Category 2B		Category III	R36	Southee (1998)
Ammonium nitrate	6484-52-2	Inorganic salt; Onium compound	Fertilizer, Chemical intermediate; Industrial explosive	n.p.	n.p.	100%	n.p.	2 (2)	Mild	Mild	Category 2B		Category III	R36	Southee (1998)
Ammonium nitrate	6484-52-2	Inorganic salt; Onium compound	Fertilizer, Chemical intermediate; Industrial explosive	n.p.	n.p.	100%	n.p.	3 (1)	Mild	Mild	Category 2B		Category III	R36	Southee (1998)
Ammonium nitrate	6484-52-2	Inorganic salt; Onium compound	Fertilizer, Chemical intermediate; Industrial explosive	n.p.	n.p.	100%	n.p.	3 (2)	Mild	Mild	Category 2B		Category III	R36	Southee (1998)
Benzalkonium chloride (100%)	8001-54-5	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	liquid	surfactant	10%	n.p.	1 (1)	Very severe	Very Severe	Category 1		SCNM	R41	Southee (1998)
Benzalkonium chloride (100%)	8001-54-5	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	liquid	surfactant	10%	n.p.	1 (2)	Very severe	Very Severe	Category 1		SCNM	R41	Southee (1998)
Benzalkonium chloride (100%)	8001-54-5	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	liquid	surfactant	10%	n.p.	1 (3)	Very severe	Very Severe	Category 1		SCNM	R41	Southee (1998)
Benzalkonium chloride (100%)	8001-54-5	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	liquid	surfactant	10%	n.p.	1 (4)	Very severe	Very Severe	Category 1		SCNM	R41	Southee (1998)
Benzalkonium chloride (100%)	8001-54-5	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	liquid	surfactant	10%	n.p.	1 (5)	Very severe	Very Severe	Category 1		SCNM	R41	Southee (1998)
Benzalkonium chloride (100%)	8001-54-5	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	liquid	surfactant	10%	n.p.	1 (6)	Very severe	Very Severe	Category 1		SCNM	R41	Southee (1998)
Benzalkonium chloride (100%)	8001-54-5	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	liquid	surfactant	10%	n.p.	1 (7)	Very severe	Very Severe	Category 1		SCNM	R41	Southee (1998)
Benzalkonium chloride (100%)	8001-54-5	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	liquid	surfactant	10%	n.p.	1 (8)	Very severe	Very Severe	Category 1		SCNM	R41	Southee (1998)
Benzalkonium chloride (100%)	8001-54-5	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	liquid	surfactant	10%	n.p.	2 (1)	Very severe	Very Severe	Category 1		SCNM	R41	Southee (1998)
Benzalkonium chloride (100%)	8001-54-5	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	liquid	surfactant	10%	n.p.	2 (2)	Very severe	Very Severe	Category 1		SCNM	R41	Southee (1998)
Benzalkonium chloride (100%)	8001-54-5	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	liquid	surfactant	10%	n.p.	2 (3)	Very severe	Very Severe	Category 1		SCNM	R41	Southee (1998)
Benzalkonium chloride (100%)	8001-54-5	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	liquid	surfactant	10%	n.p.	2 (4)	Very severe	Very Severe	Category 1		SCNM	R41	Southee (1998)
Benzalkonium chloride (100%)	8001-54-5	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	liquid	surfactant	10%	n.p.	2 (5)	Very severe	Very Severe	Category 1	4	SCNM	R41	Southee (1998)
Benzalkonium chloride (100%)	8001-54-5	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	liquid	surfactant	10%	n.p.	2 (6)	Very severe	Very Severe	Category 1		SCNM	R41	Southee (1998)
Benzalkonium chloride (100%)	8001-54-5	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	liquid	surfactant	10%	n.p.	2 (7)	Very severe	Very Severe	Category 1		SCNM	R41	Southee (1998)
Benzalkonium chloride (100%)	8001-54-5	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	liquid	surfactant	10%	n.p.	3 (1)	Very severe	Very Severe	Category 1		SCNM	R41	Southee (1998)
Benzalkonium chloride (100%)	8001-54-5	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	liquid	surfactant	10%	n.p.	3 (2)	Very severe	Very Severe	Category 1		SCNM	R41	Southee (1998)
Benzalkonium chloride (100%)	8001-54-5	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	liquid	surfactant	10%	n.p.	3 (3)	Very severe	Very Severe	Category 1		SCNM	R41	Southee (1998)
Benzalkonium chloride (100%)	8001-54-5	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	liquid	surfactant	10%	n.p.	3 (4)	Very severe	Very Severe	Category 1		SCNM	R41	Southee (1998)
Benzalkonium chloride (100%)	8001-54-5	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	liquid	surfactant	10%	n.p.	3 (5)	Very severe	Very Severe	Category 1		SCNM	R41	Southee (1998)
Benzalkonium chloride (100%)	8001-54-5	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	liquid	surfactant	10%	n.p.	3 (6)	Very severe	Very Severe	Category 1		SCNM	R41	Southee (1998)

Substance	CASRN[1]	Chemical Class	Product Class	Form Tested	Solubility	Concentration Tested	Purity (%)	Lab No.	In VitroTest Call[2]	In Vitro Consensus Call[2]	In Vivo GHS[4,5]	GHS Category 1 SubClass[6]	In Vivo EPA[7,8]	In Vivo EU[5,10]	Reference
Benzalkonium chloride (100%)	8001-54-5	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	liquid	surfactant	10%	n.p.	3 (7)	Very severe	Very Severe	Category 1		SCNM	R41	Southee (1998)
Benzalkonium chloride (100%)	8001-54-5	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	liquid	surfactant	10%	n.p.	3 (8)	Very severe	Very Severe	Category 1		SCNM	R41	Southee (1998)
Benzalkonium chloride (100%)	8001-54-5	Onium compound	Surfactant (cationic), Bactericide, Fungicide, Preservative	liquid	surfactant	10%	n.p.	3 (9)	Very severe	Very Severe	Category 1		SCNM	R41	Southee (1998)
Butyl cellusolve	111-76-2	Alcohol, Ester	Solvent	liquid	n.p.	100%	n.p.	1 (1)	Very severe	Very Severe	Category 1		Category II	R41	Southee (1998)
Butyl cellusolve	111-76-2	Alcohol, Ester	Solvent	liquid	n.p.	100%	n.p.	1 (2)	Very severe	Very Severe	Category 1		Category II	R41	Southee (1998)
Butyl cellusolve	111-76-2	Alcohol, Ester	Solvent	liquid	n.p.	100%	n.p.	2 (1)	Very severe	Very Severe	Category 1		Category II	R41	Southee (1998)
Butyl cellusolve	111-76-2	Alcohol, Ester	Solvent	liquid	n.p.	100%	n.p.	2 (2)	Very severe	Very Severe	Category 1	1	Category II	R41	Southee (1998)
Butyl cellusolve	111-76-2	Alcohol, Ester	Solvent	liquid	n.p.	100%	n.p.	3 (1)	Very severe	Very Severe	Category 1		Category II	R41	Southee (1998)
Butyl cellusolve	111-76-2	Alcohol, Ester	Solvent	liquid	n.p.	100%	n.p.	3 (2)	Very severe	Very Severe	Category 1		Category II	R41	Southee (1998)
4-Carboxybenzaldehyde	619-66-9	Carboxylic acid, Aldehyde	Not classified	solid	water insoluble*	20%	95	1 (1)	Moderate	Moderate	Category 2A		Category II	R36	Southee (1998)
4-Carboxybenzaldehyde	619-66-9	Carboxylic acid, Aldehyde	Not classified	solid	water insoluble*	20%	95	1 (2)	Moderate	Moderate	Category 2A		Category II	R36	Southee (1998)
4-Carboxybenzaldehyde	619-66-9	Carboxylic acid, Aldehyde	Not classified	solid	water insoluble*	20%	95	2 (1)	Moderate	Moderate	Category 2A		Category II	R36	Southee (1998)
4-Carboxybenzaldehyde	619-66-9	Carboxylic acid, Aldehyde	Not classified	solid	water insoluble*	20%	95	2 (2)	Moderate	Moderate	Category 2A		Category II	R36	Southee (1998)
4-Carboxybenzaldehyde	619-66-9	Carboxylic acid, Aldehyde	Not classified	solid	water insoluble*	20%	95	3 (1)	Moderate	Moderate	Category 2A		Category II	R36	Southee (1998)
4-Carboxybenzaldehyde	619-66-9	Carboxylic acid, Aldehyde	Not classified	solid	water insoluble*	20%	95	3 (2)	Moderate	Moderate	Category 2A		Category II	R36	Southee (1998)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	1 (1)	Moderate	Moderate	Category 2A		Category III	Nonirritant	Southee (1998)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	1 (2)	Moderate	Moderate	Category 2A		Category III	Nonirritant	Southee (1998)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	1 (3)	Moderate	Moderate	Category 2A		Category III	Nonirritant	Southee (1998)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	1 (4)	Moderate	Moderate	Category 2A		Category III	Nonirritant	Southee (1998)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	1 (5)	Moderate	Moderate	Category 2A		Category III	Nonirritant	Southee (1998)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	1 (6)	Moderate	Moderate	Category 2A		Category III	Nonirritant	Southee (1998)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	1 (7)	Severe	Moderate	Category 2A		Category III	Nonirritant	Southee (1998)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	2 (1)	Moderate	Moderate	Category 2A		Category III	Nonirritant	Southee (1998)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	2 (2)	Moderate	Moderate	Category 2A		Category III	Nonirritant	Southee (1998)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	2 (3)	Severe	Moderate	Category 2A		Category III	Nonirritant	Southee (1998)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	2 (4)	Severe	Moderate	Category 2A		Category III	Nonirritant	Southee (1998)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	2 (5)	Moderate	Moderate	Category 2A		Category III	Nonirritant	Southee (1998)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	2 (6)	Severe	Moderate	Category 2A		Category III	Nonirritant	Southee (1998)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	2 (7)	Severe	Moderate	Category 2A		Category III	Nonirritant	Southee (1998)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	2 (8)	Moderate	Moderate	Category 2A		Category III	Nonirritant	Southee (1998)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	3 (1)	Moderate	Moderate	Category 2A		Category III	Nonirritant	Southee (1998)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	3 (2)	Moderate	Moderate	Category 2A		Category III	Nonirritant	Southee (1998)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	3 (3)	Moderate	Moderate	Category 2A		Category III	Nonirritant	Southee (1998)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	3 (4)	Moderate	Moderate	Category 2A		Category III	Nonirritant	Southee (1998)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	3 (5)	Moderate	Moderate	Category 2A		Category III	Nonirritant	Southee (1998)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	3 (6)	Moderate	Moderate	Category 2A		Category III	Nonirritant	Southee (1998)
Ethanol	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	water soluble	100%	n.p.	3 (7)	Moderate	Moderate	Category 2A		Category III	Nonirritant	Southee (1998)
Glycerol	56-81-5	Alcohol	Solvent; Plasticizer; Lubricant; Emollient; Drug vehicle	liquid	water soluble	100%	>99.5	1 (1)	Mild	Nonirritant	Nonirritant		Category IV	Nonirritant	Southee (1998)
Glycerol	56-81-5	Alcohol	Solvent; Plasticizer; Lubricant; Emollient; Drug vehicle	liquid	water soluble	100%	>99.5	1 (2)	Mild	Nonirritant	Nonirritant		Category IV	Nonirritant	Southee (1998)
Glycerol	56-81-5	Alcohol	Solvent; Plasticizer; Lubricant; Emollient; Drug vehicle	liquid	water soluble	100%	>99.5	2 (1)	Nonirritant	Nonirritant	Nonirritant		Category IV	Nonirritant	Southee (1998)
Glycerol	56-81-5	Alcohol	Solvent; Plasticizer; Lubricant; Emollient; Drug vehicle	liquid	water soluble	100%	>99.5	2 (2)	Nonirritant	Nonirritant	Nonirritant		Category IV	Nonirritant	Southee (1998)
Glycerol	56-81-5	Alcohol	Solvent; Plasticizer; Lubricant; Emollient; Drug vehicle	liquid	water soluble	100%	>99.5	3 (1)	Nonirritant	Nonirritant	Nonirritant		Category IV	Nonirritant	Southee (1998)
Glycerol	56-81-5	Alcohol	Solvent; Plasticizer; Lubricant; Emollient; Drug vehicle	liquid	water soluble	100%	>99.5	3 (2)	Nonirritant	Nonirritant	Nonirritant		Category IV	Nonirritant	Southee (1998)
Hexadecyltrimethylammonium bromide	57-09-0	Organic salt, Onium compound	Agricultural chemical; Germicide; Drug/Therapeutic agent	surfactant	n.p.	10%	n.p.	1 (1)	Mild	Moderate	Category 1		Category I	R41	Southee (1998)
Hexadecyltrimethylammonium bromide	57-09-0	Organic salt, Onium compound	Agricultural chemical; Germicide; Drug/Therapeutic agent	surfactant	n.p.	10%	n.p.	1 (2)	Mild	Moderate	Category 1		Category I	R41	Southee (1998)
Hexadecyltrimethylammonium bromide	57-09-0	Organic salt, Onium compound	Agricultural chemical; Germicide; Drug/Therapeutic agent	surfactant	n.p.	10%	n.p.	2 (1)	Moderate	Moderate	Category 1		Category I	R41	Southee (1998)
Hexadecyltrimethylammonium bromide	57-09-0	Organic salt, Onium compound	Agricultural chemical; Germicide; Drug/Therapeutic agent	surfactant	n.p.	10%	n.p.	2 (2)	Moderate	Moderate	Category 1	4	Category I	R41	Southee (1998)
Hexadecyltrimethylammonium bromide	57-09-0	Organic salt, Onium compound	Agricultural chemical; Germicide; Drug/Therapeutic agent	surfactant	n.p.	10%	n.p.	3 (1)	Moderate	Moderate	Category 1		Category I	R41	Southee (1998)
Hexadecyltrimethylammonium bromide	57-09-0	Organic salt, Onium compound	Agricultural chemical; Germicide; Drug/Therapeutic agent	surfactant	n.p.	10%	n.p.	3 (2)	Moderate	Moderate	Category 1		Category I	R41	Southee (1998)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	1 (1)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	1 (2)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	1 (3)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	1 (4)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	1 (5)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)

Substance	CASRN[1]	Chemical Class	Product Class	Form Tested	Solubility	Concentration Tested	Purity (%)	Lab No.	In VitroTest Call[2]	In Vitro Consensus Call[2]	In Vivo GHS[4,5]	GHS Category 1 SubClass[6]	In Vivo EPA[7,8]	In Vivo EU[9,10]	Reference
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	1 (6)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	1 (7)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	2 (1)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	2 (2)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	2 (3)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	2 (4)	Very severe	Very Severe	Category 1	4	Category I	R41	Southee (1998)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	2 (5)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	2 (6)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	2 (7)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	3 (1)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	3 (2)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	3 (3)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	3 (4)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	3 (5)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	3 (6)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)
Imidazole	288-32-4	Heterocyclic	Anti-fungal; Enzyme inhibitor	solid	water soluble	20%	n.p.	3 (7)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)
Methyl ethyl ketone	78-93-3	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	liquid	water soluble	100%	99	1 (1)	Severe	Severe	Category 2B		Category III	R36	Southee (1998)
Methyl ethyl ketone	78-93-3	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	liquid	water soluble	100%	99	1 (2)	Severe	Severe	Category 2B		Category III	R36	Southee (1998)
Methyl ethyl ketone	78-93-3	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	liquid	water soluble	100%	99	2 (1)	Very severe	Severe	Category 2B		Category III	R36	Southee (1998)
Methyl ethyl ketone	78-93-3	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	liquid	water soluble	100%	99	2 (2)	Very severe	Severe	Category 2B		Category III	R36	Southee (1998)
Methyl ethyl ketone	78-93-3	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	liquid	water soluble	100%	99	3 (1)	Severe	Severe	Category 2B		Category III	R36	Southee (1998)
Methyl ethyl ketone	78-93-3	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	liquid	water soluble	100%	99	3 (2)	Severe	Severe	Category 2B		Category III	R36	Southee (1998)
Parafluoraniline	371-40-4	Amine/Amidine	Intermediate for herbicides, Dyes	liquid	water insoluble	100%	99	1 (1)	Moderate	Moderate	SCNM		SCNM	SCNM	Southee (1998)
Parafluoraniline	371-40-4	Amine/Amidine	Intermediate for herbicides, Dyes	liquid	water insoluble	100%	99	1 (2)	Moderate	Moderate	SCNM		SCNM	SCNM	Southee (1998)
Parafluoraniline	371-40-4	Amine/Amidine	Intermediate for herbicides, Dyes	liquid	water insoluble	100%	99	2 (1)	Moderate	Moderate	SCNM		SCNM	SCNM	Southee (1998)
Parafluoraniline	371-40-4	Amine/Amidine	Intermediate for herbicides, Dyes	liquid	water insoluble	100%	99	2 (2)	Moderate	Moderate	SCNM		SCNM	SCNM	Southee (1998)
Parafluoraniline	371-40-4	Amine/Amidine	Intermediate for herbicides, Dyes	liquid	water insoluble	100%	99	3 (1)	Mild	Moderate	SCNM		SCNM	SCNM	Southee (1998)
Parafluoraniline	371-40-4	Amine/Amidine	Intermediate for herbicides, Dyes	liquid	water insoluble	100%	99	3 (2)	Moderate	Moderate	SCNM		SCNM	SCNM	Southee (1998)
Propyl-4-hydroxybenzoate	94-13-3	Carboxylic acid, Phenol	Antimicrobial	solid	n.p.	20%	100	1 (1)	Mild	Mild	Nonirritant		Category III	Nonirritant	Southee (1998)
Propyl-4-hydroxybenzoate	94-13-3	Carboxylic acid, Phenol	Antimicrobial	solid	n.p.	20%	100	1 (2)	Mild	Mild	Nonirritant		Category III	Nonirritant	Southee (1998)
Propyl-4-hydroxybenzoate	94-13-3	Carboxylic acid, Phenol	Antimicrobial	solid	n.p.	20%	100	2 (1)	Mild	Mild	Nonirritant		Category III	Nonirritant	Southee (1998)
Propyl-4-hydroxybenzoate	94-13-3	Carboxylic acid, Phenol	Antimicrobial	solid	n.p.	20%	100	2 (2)	Mild	Mild	Nonirritant		Category III	Nonirritant	Southee (1998)
Propyl-4-hydroxybenzoate	94-13-3	Carboxylic acid, Phenol	Antimicrobial	solid	n.p.	20%	100	3 (1)	Mild	Mild	Nonirritant		Category III	Nonirritant	Southee (1998)
Propyl-4-hydroxybenzoate	94-13-3	Carboxylic acid, Phenol	Antimicrobial	solid	n.p.	20%	100	3 (2)	Mild	Mild	Nonirritant		Category III	Nonirritant	Southee (1998)
Sodium hydroxide (10%)	1310-73-2	Alkali	Caustic agent	liquid	water soluble	10%	n.p.	1 (1)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)
Sodium hydroxide (10%)	1310-73-2	Alkali	Caustic agent	liquid	water soluble	10%	n.p.	1 (2)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)
Sodium hydroxide (10%)	1310-73-2	Alkali	Caustic agent	liquid	water soluble	10%	n.p.	2 (1)	Very severe	Very Severe	Category 1	4	Category I	R41	Southee (1998)
Sodium hydroxide (10%)	1310-73-2	Alkali	Caustic agent	liquid	water soluble	10%	n.p.	2 (2)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)
Sodium hydroxide (10%)	1310-73-2	Alkali	Caustic agent	liquid	water soluble	10%	n.p.	3 (1)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)
Sodium hydroxide (10%)	1310-73-2	Alkali	Caustic agent	liquid	water soluble	10%	n.p.	3 (2)	Very severe	Very Severe	Category 1		Category I	R41	Southee (1998)
Sodium lauryl sulfate (15%)	151-21-3	Carboxylic acid (salt)	Surfactant (anionic), Detergent	liquid	surfactant	10%	98	1 (1)	Mild	Mild	Category 1		Category I	SCNM	Southee (1998)
Sodium lauryl sulfate (15%)	151-21-3	Carboxylic acid (salt)	Surfactant (anionic), Detergent	liquid	surfactant	10%	98	1 (2)	Mild	Mild	Category 1		Category I	SCNM	Southee (1998)
Sodium lauryl sulfate (15%)	151-21-3	Carboxylic acid (salt)	Surfactant (anionic), Detergent	liquid	surfactant	10%	98	2 (1)	Mild	Mild	Category 1		Category I	SCNM	Southee (1998)
Sodium lauryl sulfate (15%)	151-21-3	Carboxylic acid (salt)	Surfactant (anionic), Detergent	liquid	surfactant	10%	98	2 (2)	Mild	Mild	Category 1	NC	Category I	SCNM	Southee (1998)
Sodium lauryl sulfate (15%)	151-21-3	Carboxylic acid (salt)	Surfactant (anionic), Detergent	liquid	surfactant	10%	98	3 (1)	Mild	Mild	Category 1		Category I	SCNM	Southee (1998)
Sodium lauryl sulfate (15%)	151-21-3	Carboxylic acid (salt)	Surfactant (anionic), Detergent	liquid	surfactant	10%	98	3 (2)	Mild	Mild	Category 1		Category I	SCNM	Southee (1998)
Sodium oxalate	62-76-0	Carboxylic acid (salt)	Textile finishing; Pyrotechnic, Industrial byproduct	solid	water soluble	20%	99	1 (1)	Mild	Nonirritant	Category 1		Category I	R41	Southee (1998)
Sodium oxalate	62-76-0	Carboxylic acid (salt)	Textile finishing; Pyrotechnic, Industrial byproduct	solid	water soluble	20%	99	1 (2)	Mild	Nonirritant	Category 1		Category I	R41	Southee (1998)
Sodium oxalate	62-76-0	Carboxylic acid (salt)	Textile finishing; Pyrotechnic, Industrial byproduct	solid	water soluble	20%	99	2 (1)	Nonirritant	Nonirritant	Category 1		Category I	R41	Southee (1998)
Sodium oxalate	62-76-0	Carboxylic acid (salt)	Textile finishing; Pyrotechnic, Industrial byproduct	solid	water soluble	20%	99	2 (2)	Nonirritant	Nonirritant	Category 1	4	Category I	R41	Southee (1998)
Sodium oxalate	62-76-0	Carboxylic acid (salt)	Textile finishing; Pyrotechnic, Industrial byproduct	solid	water soluble	20%	99	3 (1)	Nonirritant	Nonirritant	Category 1		Category I	R41	Southee (1998)
Sodium oxalate	62-76-0	Carboxylic acid (salt)	Textile finishing; Pyrotechnic, Industrial byproduct	solid	water soluble	20%	99	3 (2)	Mild	Nonirritant	Category 1		Category I	R41	Southee (1998)
Triton X-100 (5%)	9002-93-1	Ether	Surfactant (nonionic)	liquid	surfactant	10%	98	1 (1)	Mild	Mild	Category 2B		Category III	R36	Southee (1998)
Triton X-100 (5%)	9002-93-1	Ether	Surfactant (nonionic)	liquid	surfactant	10%	98	1 (2)	Mild	Mild	Category 2B		Category III	R36	Southee (1998)

Substance	CASRN[1]	Chemical Class	Product Class	Form Tested	Solubility	Concentration Tested	Purity (%)	Lab No.	In VitroTest Call[2]	In Vitro Consensus Call[3]	In Vivo GHS[4,5]	GHS Category 1 SubClass[6]	In Vivo EPA[7,8]	In Vivo EU[9,10]	Reference
Triton X-100 (5%)	9002-93-1	Ether	Surfactant (nonionic)	liquid	surfactant	10%	98	2 (1)	Mild	Mild	Category 2B		Category III	R36	Southee (1998)
Triton X-100 (5%)	9002-93-1	Ether	Surfactant (nonionic)	liquid	surfactant	10%	98	2 (2)	Mild	Mild	Category 2B		Category III	R36	Southee (1998)
Triton X-100 (5%)	9002-93-1	Ether	Surfactant (nonionic)	liquid	surfactant	10%	98	3 (1)	Nonirritant	Mild	Category 2B		Category III	R36	Southee (1998)
Triton X-100 (5%)	9002-93-1	Ether	Surfactant (nonionic)	liquid	surfactant	10%	98	3 (2)	Nonirritant	Mild	Category 2B		Category III	R36	Southee (1998)
Tween 20	9005-64-5	Ester, Polyether	Surfactant (nonionic), Detergent	liquid	surfactant	100%	98	1 (1)	Mild	Nonirritant	Nonirritant		Category III	Nonirritant	Southee (1998)
Tween 20	9005-64-5	Ester, Polyether	Surfactant (nonionic), Detergent	liquid	surfactant	100%	98	1 (2)	Mild	Nonirritant	Nonirritant		Category III	Nonirritant	Southee (1998)
Tween 20	9005-64-5	Ester, Polyether	Surfactant (nonionic), Detergent	liquid	surfactant	100%	98	2 (1)	Mild	Nonirritant	Nonirritant		Category III	Nonirritant	Southee (1998)
Tween 20	9005-64-5	Ester, Polyether	Surfactant (nonionic), Detergent	liquid	surfactant	100%	98	2 (2)	Nonirritant	Nonirritant	Nonirritant		Category III	Nonirritant	Southee (1998)
Tween 20	9005-64-5	Ester, Polyether	Surfactant (nonionic), Detergent	liquid	surfactant	100%	98	3 (1)	Nonirritant	Nonirritant	Nonirritant		Category III	Nonirritant	Southee (1998)
Tween 20	9005-64-5	Ester, Polyether	Surfactant (nonionic), Detergent	liquid	surfactant	100%	98	3 (2)	Nonirritant	Nonirritant	Nonirritant		Category III	Nonirritant	Southee (1998)
Anti-Dandruff Shampoo (HZY) 100%	-	-	-	n.p.	n.p.	10%	n.p.	-	Severe	Severe	Category 1	1	Category I	R41	Gettings et al. (1996)
Baby Shampoo No. 1 (HZP) 100%	-	-	-	n.p.	n.p.	10%	n.p.	-	Nonsevere	Nonsevere	Nonirritant		Category III	Nonirritant	Gettings et al. (1996)
Baby Shampoo No. 2 (HZF) 100%	-	-	-	n.p.	n.p.	10%	n.p.	-	Nonsevere	Nonsevere	Category 1	1	Category I	R41	Gettings et al. (1996)
Bubble Bath (HZK) 100%	-	-	-	n.p.	n.p.	10%	n.p.	-	Severe	Severe	Category 1	1	Category I	R41	Gettings et al. (1996)
Cleansing Gel (HZO) 100%	-	-	-	n.p.	n.p.	10%	n.p.	-	Nonsevere	Nonsevere	Nonirritant		Category III	Nonirritant	Gettings et al. (1996)
Eye Make-Up Remover (HZH) 100%	-	-	-	n.p.	n.p.	10%	n.p.	-	Nonsevere	Nonsevere	Nonirritant		Category IV	Nonirritant	Gettings et al. (1996)
Facial Cleaning Foam (HZR) 25%	-	-	-	n.p.	n.p.	10%	n.p.	-	Nonsevere	Nonsevere	SCNM		Category I	SCNM	Gettings et al. (1996)
Facial Cleanser (HZZ) 100%	-	-	-	n.p.	n.p.	10%	n.p.	-	Nonsevere	Nonsevere	Nonirritant		Category IV	Nonirritant	Gettings et al. (1996)
Foam Bath (HZL) 100%	-	-	-	n.p.	n.p.	10%	n.p.	-	Severe	Severe	Category 1	1	Category I	R41	Gettings et al. (1996)
Gel Cleanser (HZE) 100%	-	-	-	n.p.	n.p.	10%	n.p.	-	Nonsevere	Nonsevere	SCNM		Category I	SCNM	Gettings et al. (1996)
Hand Soap (HZU) 25%	-	-	-	n.p.	n.p.	10%	n.p.	-	Nonsevere	Nonsevere	Nonirritant		Category III	Nonirritant	Gettings et al. (1996)
Liquid Soap No. 2 (HZW) 25%	-	-	-	n.p.	n.p.	10%	n.p.	-	Nonsevere	Nonsevere	Category 2B		Category III	Nonirritant	Gettings et al. (1996)
Liquid Soap No. 1 (HZB) 25%	-	-	-	n.p.	n.p.	10%	n.p.	-	Nonsevere	Nonsevere	Nonirritant		Category III	Nonirritant	Gettings et al. (1996)
Mild Shampoo (HZJ) 25%	-	-	-	n.p.	n.p.	10%	n.p.	-	Nonsevere	Nonsevere	Nonirritant		Category IV	Nonirritant	Gettings et al. (1996)
Polishing Scrub (HZT) 100%	-	-	-	n.p.	n.p.	10%	n.p.	-	Nonsevere	Nonsevere	Nonirritant		Category IV	Nonirritant	Gettings et al. (1996)
Shampoo No. 1 (HZ) 25%	-	-	-	n.p.	n.p.	10%	n.p.	-	Severe	Severe	Nonirritant		Category III	Nonirritant	Gettings et al. (1996)
Shampoo No. 2 (HZX)	-	-	-	n.p.	n.p.	10%	n.p.	-	Severe	Severe	Category 1	1	Category I	R41	Gettings et al. (1996)
Shampoo No. 3 (HZM) 25%	-	-	-	n.p.	n.p.	10%	n.p.	-	Nonsevere	Nonsevere	Nonirritant		Category III	Nonirritant	Gettings et al. (1996)
Shampoo No. 4 (HZV) 25%	-	-	-	n.p.	n.p.	10%	n.p.	-	Nonsevere	Nonsevere	Nonirritant		Category III	Nonirritant	Gettings et al. (1996)
Shampoo No. 5 (HZD) 25%	-	-	-	n.p.	n.p.	10%	n.p.	-	Nonsevere	Nonsevere	Nonirritant		Category III	Nonirritant	Gettings et al. (1996)
Shampoo No. 6 (HZN) 25%	-	-	-	n.p.	n.p.	10%	n.p.	-	Nonsevere	Nonsevere	Nonirritant		Category III	Nonirritant	Gettings et al. (1996)
Shampoo No. 7 (HZA) 100%	-	-	-	n.p.	n.p.	10%	n.p.	-	Nonsevere	Nonsevere	Category 1	1	Category I	R41	Gettings et al. (1996)
Shampoo No. 8 (HZG) 25%	-	-	-	n.p.	n.p.	10%	n.p.	-	Nonsevere	Nonsevere	Nonirritant		Category III	Nonirritant	Gettings et al. (1996)
Shower Gel (HZS) 100%	-	-	-	n.p.	n.p.	10%	n.p.	-	Severe	Severe	Category 1	1	Category I	R41	Gettings et al. (1996)
Skin Cleanser (HZI) 100%	-	-	-	n.p.	n.p.	10%	n.p.	-	Severe	Severe	Category 1	1	Category I	R41	Gettings et al. (1996)
Anti-Dandruff Shampoo (HZY)	-	-	-	n.p.	n.p.	100%	n.p.	-	Moderate	Moderate	Category 1	1	Category I	R41	Casterton et al. (1996)
Baby Shampoo No. 1 (HZP)	-	-	-	n.p.	n.p.	100%	n.p.	-	Mild	Mild	Nonirritant		Category III	Nonirritant	Casterton et al. (1996)
Baby Shampoo No. 2 (HZF)	-	-	-	n.p.	n.p.	100%	n.p.	-	Moderate	Moderate	Category 1	1	Category I	R41	Casterton et al. (1996)
Bubble Bath (HZK)	-	-	-	n.p.	n.p.	100%	n.p.	-	Moderate	Moderate	Category 1	1	Category I	R41	Casterton et al. (1996)
Cleansing Gel (HZO)	-	-	-	n.p.	n.p.	100%	n.p.	-	Mild	Mild	Nonirritant		Category III	Nonirritant	Casterton et al. (1996)
Eye Make-Up Remover (HZH)	-	-	-	n.p.	n.p.	100%	n.p.	-	Mild	Mild	Nonirritant		Category IV	Nonirritant	Casterton et al. (1996)
Facial Cleanser (HZZ)	-	-	-	n.p.	n.p.	100%	n.p.	-	Mild	Mild	Nonirritant		Category IV	Nonirritant	Casterton et al. (1996)
Foam Bath (HZL)	-	-	-	n.p.	n.p.	100%	n.p.	-	Moderate	Moderate	Category 1	1	Category I	R41	Casterton et al. (1996)
Gel Cleanser (HZE)	-	-	-	n.p.	n.p.	100%	n.p.	-	Mild	Mild	SCNM		Category I	SCNM	Casterton et al. (1996)
Mild Shampoo (HZJ)	-	-	-	n.p.	n.p.	100%	n.p.	-	Mild	Mild	Nonirritant		Category IV	Nonirritant	Casterton et al. (1996)
Polishing Scrub (HZT)	-	-	-	n.p.	n.p.	100%	n.p.	-	Mild	Mild	Nonirritant		Category IV	Nonirritant	Casterton et al. (1996)
Shampoo No. 2 (HZX)	-	-	-	n.p.	n.p.	100%	n.p.	-	Moderate	Moderate	Category 1	1	Category I	R41	Casterton et al. (1996)
Shampoo No. 7 (HZA)	-	-	-	n.p.	n.p.	100%	n.p.	-	Moderate	Moderate	Category 1	1	Category I	R41	Casterton et al. (1996)
Shower Gel (HZS)	-	-	-	n.p.	n.p.	100%	n.p.	-	Moderate	Moderate	Category 1	1	Category I	R41	Casterton et al. (1996)
Skin Cleanser (HZI)	-	-	-	n.p.	n.p.	100%	n.p.	-	Moderate	Moderate	Category 1	1	Category I	R41	Casterton et al. (1996)
Acetone	67-64-1	Ketone	Solvent; Antiseptic; Chemical intermediate; Raw material	liquid	water soluble	100%	n.p.	-	Severe	Severe	Category 2A		Category II	R36	Casterton et al. (1996)
Benzalkonium chloride (1%)	8001-54-5	Inorganic salt; Onium compound	Surfactant (cationic); Bactericide; Fungicide; Preservative	liquid	surfactant	1%	n.p.	-	Severe	Severe	Category 1	1	Category I	R41	Casterton et al. (1996)
Benzalkonium chloride (10%)	8001-54-5	Inorganic salt; Onium compound	Surfactant (cationic); Bactericide; Fungicide; Preservative	liquid	surfactant	10%	n.p.	-	Severe	Severe	Category 1	4	Category I	R41	Casterton et al. (1996)
Benzalkonium chloride (5%)	8001-54-5	Inorganic salt; Onium compound	Surfactant (cationic); Bactericide; Fungicide; Preservative	liquid	surfactant	5%	n.p.	-	Severe	Severe	Category 1	2	Category I	R41	Casterton et al. (1996)
4-Bromophenetole	-	Not classified	Not classified	n.p.	n.p.	100%	n.p.	-	Mild	Mild					Casterton et al. (1996)
n-Butanol	71-36-3	Alcohol	Ingredient of spray paint, nail polish	liquid	n.p.	100%	n.p.	-	Severe	Severe					Casterton et al. (1996)
2-Butoxyethanol	111-76-2	Ether	Solvent	liquid	n.p.	100%	n.p.	-	Severe	Severe					Casterton et al. (1996)
4-Carboxybenzaldehyde	619-66-9	Carboxylic acid, Aldehyde	Not classified	solid	water insoluble*	100%	n.p.	-	Mild	Mild	Category 2A		Category II	R36	Casterton et al. (1996)
Cetylpyridinium bromide (0.1%)	140-72-7	Heterocyclic, Onium compound	Surfactant (cationic), Germicide, Laboratory reagent	liquid	surfactant	0%	n.p.	-	Mild	Mild	Nonirritant		Category III	Nonirritant	Casterton et al. (1996)
Cetylpyridinium bromide (1%)	140-72-7	Heterocyclic, Onium compound	Surfactant (cationic), Germicide, Laboratory reagent	liquid	surfactant	1%	n.p.	-	Moderate	Moderate					Casterton et al. (1996)
Cetylpyridinium bromide (10%)	140-72-7	Heterocyclic, Onium compound	Surfactant (cationic), Germicide, Laboratory reagent	liquid	surfactant	10%	n.p.	-	Severe	Severe	Category 1	4	Category I	R41	Casterton et al. (1996)
Cetylpyridinium bromide (6%)	140-72-7	Heterocyclic, Onium compound	Surfactant (cationic), Germicide, Laboratory reagent	liquid	surfactant	6%	n.p.	-	Severe	Severe	Category 1	2	SCNM	R41	Casterton et al. (1996)
Cyclohexanol	108-93-0	Alcohol	Sovent; Chemical intermediate	liquid	water soluble	100%	n.p.	-	Severe	Severe	Category 1	2	Category I	R41	Casterton et al. (1996)
2,6-Dichlorobenzoyl chloride	4659-45-4	Acyl Halide	Anti-Fungal, Anti-Infective	liquid	water insoluble*	100%	n.p.	-	Mild	Mild	Category 2A		Category II	SCNM	Casterton et al. (1996)
2,4-Difluoronitrobenzene	446-35-5	Hydrocarbon (halogenated)	Pesticide, Pharmaceutical Intermediate	liquid	n.p.	100%	n.p.	-	Mild	Mild					Casterton et al. (1996)
1,3-Diisopropylbenzene	99-62-7	Hydrocarbon (cyclic)	Chemical Intermediate, Solvent	liquid	n.p.	100%	n.p.	-	Mild	Mild					Casterton et al. (1996)
2,2-Dimethylbutanoic acid	595-37-9	Carboxylic acid	Pharmaceutical metabolite	liquid	water insoluble	100%	n.p.	-	Severe	Severe	SCNM		Category I	SCNM	Casterton et al. (1996)
Dodecane	112-40-3	Hydrocarbon, acyclic	Industrial chemical	liquid	n.p.	100%	n.p.	-	Mild	Mild					Casterton et al. (1996)
2-Ethylhexanol	104-76-7	Alcohol	Solvent	liquid	water soluble	100%	n.p.	-	Moderate	Moderate	Category 2A		Category II	R36	Casterton et al. (1996)
3-Ethyltoluene	620-14-4	Hydrocarbon (cyclic)	Industrial Chemical, Laboratory Chemical	liquid	n.p.	100%	n.p.	-	Mild	Mild					Casterton et al. (1996)
Ethyl trimethyl acetate	3938-95-2	Ester	Solvent	liquid	water insoluble*	100%	n.p.	-	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Casterton et al. (1996)
Glycerol	56-81-5	Alcohol	Solvent; Plasticizer; Lubricant; Emollient; Drug vehicle	liquid	water soluble	100%	n.p.	-	Mild	Mild	Nonirritant		Category IV	Nonirritant	Casterton et al. (1996)
1,5-Hexadiene	592-42-7	Hydrocarbon (acyclic)	Chemical Intermediate, Industrial Chemical	liquid	n.p.	100%	n.p.	-	Mild	Mild					Casterton et al. (1996)
Isobutanol	78-83-1	Alcohol	Solvent; Chemical intermediate; Flavor ingredient	liquid	water insoluble*	100%	n.p.	-	Severe	Severe	Category 2A		Category II	R36	Casterton et al. (1996)
Isopropanol	67-63-0	Alcohol	Solvent; Aerosol formulations (ingredient)	liquid	water soluble	100%	n.p.	-	Moderate	Moderate	Category 2A		Category III	SCNM	Casterton et al. (1996)

Substance	CASRN[1]	Chemical Class	Product Class	Form Tested	Solubility	Concentration Tested	Purity (%)	Lab No.	In VitroTest Call[2]	In Vitro Consensus Call[2]	In Vivo GHS[4,5]	GHS Category 1 SubClass[6]	In Vivo EPA[7,8]	In Vivo EU[5,10]	Reference
Methyl acetate	79-20-9	Ester	Solvent; Chemical intermediate; Synthetic flavor ingredient	liquid	water soluble	100%	n.p.	-	Moderate	Moderate	Category 2A		Category II	R36	Casterton et al. (1996)
Methyl ethyl ketone	78-93-3	Ketone	Solvent; Manufacture of lacquers, varnishes, cosmetics, pharmaceuticals	liquid	water soluble	100%	n.p.	-	Moderate	Moderate	Category 2A		Category III	R36	Casterton et al. (1996)
Methyl isobutyl ketone	108-10-1	Ketone	Solvent; Synthetic flavor; Drycleaning	liquid	water insoluble*	100%	n.p.	-	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Casterton et al. (1996)
1-Methylpropyl benzene	135-98-8	Hydrocarbon (cyclic)	Solvent	liquid	n.p.	100%	n.p.	-	Mild	Mild					Casterton et al. (1996)
Parafluoraniline	371-40-4	Amine/Amidine	Intermediate for herbicides Dyes	liquid	water insoluble	100%	n.p.	-	Moderate	Moderate	SCNM		SCNM	SCNM	Casterton et al. (1996)
Polyethylene glycol 400	25322-68-3	Alcohol, Polyether	Surfactant (nonionic), Lubricant, Plasticizer, Solvent	liquid	surfactant	100%	n.p.	-	Mild	Mild	Nonirritant		Category IV	Nonirritant	Casterton et al. (1996)
Polyethylene glycol 600	-	Alcohol, Polyether	Surfactant (nonionic), Lubricant, Plasticizer, Solvent	liquid	surfactant	100%	n.p.	-	Mild	Mild					Casterton et al. (1996)
Propylene glycol	57-55-6	Alcohol	Solvent	liquid	n.p.	100%	n.p.	-	Mild	Mild					Casterton et al. (1996)
Sodium hydroxide (1%)	1310-73-2	Alkali	Caustic agent	liquid	water soluble	1%	n.p.	-	Severe	Severe	Category 2B		Category III	R36	Casterton et al. (1996)
Sodium hydroxide (10%)	1310-73-2	Alkali	Caustic agent	liquid	water soluble	10%	n.p.	-	Severe	Severe	Category 1	4	Category I	R41	Casterton et al. (1996)
Sodium lauryl sulfate (15 %)	151-21-3	Carboxylic acid (salt)	Surfactant (anionic), Detergent	liquid	surfactant	15%	n.p.	-	Moderate	Moderate	Category 1	NC	Category I	R36	Casterton et al. (1996)
Sodium lauryl sulfate (3 %)	151-21-3	Carboxylic acid (salt)	Surfactant (anionic), Detergent	liquid	surfactant	3%	n.p.	-	Mild	Mild	Nonirritant		Category III	Nonirritant	Casterton et al. (1996)
Sodium lauryl sulfate (30 %)	151-21-3	Carboxylic acid (salt)	Surfactant (anionic), Detergent	liquid	surfactant	30%	n.p.	-	Moderate	Moderate					Casterton et al. (1996)
Toluene	108-88-3	Hydrocarbon (cyclic)	Solvent	liquid	water insoluble*	100%	n.p.	-	Severe	Severe	Nonirritant		Category III	Nonirritant	Casterton et al. (1996)
Trichloroacetic acid (3%)	76-03-9	Carboxylic acid	Caustic agent; Fixative; Herbicide	liquid	water soluble	3%	n.p.	-	Mild	Mild	Nonirritant		Category III	Nonirritant	Casterton et al. (1996)
Trichloroacetic acid (30%)	76-03-9	Carboxylic acid	Caustic agent; Fixative; Herbicide	liquid	water soluble	30%	n.p.	-	Severe	Severe	Category 1	4	Category I	R41	Casterton et al. (1996)
Triton X-100 (5%)	9002-93-1	Ether	Surfactant (nonionic)	liquid	surfactant	5%	n.p.	-	Moderate	Moderate	Category 2A		Category III	Nonirritant	Casterton et al. (1996)
Triton X-100 (1%)	9002-93-1	Ether	Surfactant (nonionic)	liquid	surfactant	1%	n.p.	-	Mild	Mild					Casterton et al. (1996)
Triton X-100 (10%)	9002-93-1	Ether	Surfactant (nonionic)	liquid	surfactant	10%	n.p.	-	Severe	Severe	Category 1	NC	Category II	R41	Casterton et al. (1996)
Tween 20	9005-64-5	Ester, Polyether	Surfactant (nonionic), Detergent	liquid	surfactant	100%	n.p.	-	Mild	Mild	Nonirritant		Category III	Nonirritant	Casterton et al. (1996)
Xylene	1330-20-7	Hydrocarbon (cyclic)	Industrial Chemical, Laboratory Chemical, Pharmaceutical Intermediate, Solvent	liquid	n.p.	100%	n.p.	-	Moderate	Moderate	Nonirritant		Category II	Nonirritant	Casterton et al. (1996)
Amway all fabric bleach	-	Formulation	Bleach (laundry)	n.p.	n.p.	100%	n.p.	-	Severe	Severe	Category 1	4	Category I	R41	Casterton et al. (1996)
Amway automatic dishwashing compound for soft water	-	Formulation	Detergent	n.p.	n.p.	100%	n.p.	-	Severe	Severe	Category 1	4	Category I	R41	Casterton et al. (1996)
Amway automatic dishwashing compound, standard formula	-	Formulation	Detergent	n.p.	n.p.	100%	n.p.	-	Moderate	Moderate	Category 1	4	Category I	R41	Casterton et al. (1996)
Amway concrete floor cleaner	-	Formulation	Cleaner	n.p.	n.p.	100%	n.p.	-	Severe	Severe	Category 1	4	SCNM	R41	Casterton et al. (1996)
Amway Dish Drops dishwashing liquid	-	Formulation	Detergent	n.p.	n.p.	100%	n.p.	-	Moderate	Moderate					Casterton et al. (1996)
Amway dry chlorine bleach	-	Formulation	Bleach	n.p.	n.p.	100%	n.p.	-	Moderate	Moderate	Category 1	4	Category I	R41	Casterton et al. (1996)
Amway fabric softener	-	Formulation	Fabric softener	n.p.	n.p.	100%	n.p.	-	Mild	Mild	Nonirritant		Category III	Nonirritant	Casterton et al. (1996)
Amway Kool Wash delicate fabric detergent	-	Formulation	Detergent	n.p.	n.p.	100%	n.p.	-	Moderate	Moderate	Category 1	4	Category I	R36	Casterton et al. (1996)
Amway LOC all purpose cleaner	-	Formulation	Cleaner	n.p.	n.p.	100%	n.p.	-	Mild	Mild	SCNM		SCNM	Nonirritant	Casterton et al. (1996)
Amway prewash liquid	-	Formulation	Detergent	liquid	n.p.	100%	n.p.	-	Mild	Mild	SCNM		Category I	SCNM	Casterton et al. (1996)
Amway Purge disinfectant cleaner	-	Formulation	Cleaner	n.p.	n.p.	100%	n.p.	-	Severe	Severe	Category 1	4	Category I	R41	Casterton et al. (1996)
Amway Redu dye stain remover	-	Formulation	Stain remover	n.p.	n.p.	100%	n.p.	-	Mild	Mild	Category 2A		Category II	Nonirritant	Casterton et al. (1996)
Amway SA8 laundry liquid	-	Formulation	Detergent	liquid	n.p.	100%	n.p.	-	Moderate	Moderate	Category 1	1	Category I	R41	Casterton et al. (1996)
Amway SA8 limited phos laundry powder	-	Formulation	Detergent	solid	n.p.	100%	n.p.	-	Moderate	Moderate	Category 1	4	Category I	R41	Casterton et al. (1996)
Toilet Bowl Cleaner (#1)	-	Formulation	Cleaner	liquid	n.p.	100%	n.p.	-	Mild	Mild	Nonirritant		Category IV	Nonirritant	Swanson et al. (1995)
Floor Cleaner (#2)	-	Formulation	Cleaner	liquid	n.p.	100%	n.p.	-	Nonirritant	Nonirritant					Swanson et al. 1995
Meat Room Degreaser (#3)	-	Formulation	Degreaser	liquid	n.p.	100%	n.p.	-	Severe	Severe					Swanson et al. 1995
Toilet Bowl Cleaner (#4)	-	Formulation	Cleaner	liquid	n.p.	100%	n.p.	-	Mild	Mild	Nonirritant		SCNM	Nonirritant	Swanson et al. (1995)
All Purpose Cleaner (#5)	-	Formulation	Cleaner	liquid	n.p.	100%	n.p.	-	Severe	Severe					Swanson et al. (1995)
Bathroom Cleaner (#6)	-	Formulation	Cleaner	liquid	n.p.	100%	n.p.	-	Severe	Severe	SCNM		Category III	Nonirritant	Swanson et al. (1995)
All Purpose Cleaner (#7)	-	Formulation	Cleaner	liquid	n.p.	100%	n.p.	-	Severe	Severe					Swanson et al. (1995)
Pot and Pan Cleaner (#8)	-	Formulation	Cleaner	liquid	n.p.	100%	n.p.	-	Nonirritant	Nonirritant					Swanson et al. (1995)
Heavy Duty Cleaner/Degreaser (#9)	-	Formulation	Cleaner	liquid	n.p.	100%	n.p.	-	Severe	Severe					Swanson et al. (1995)
Floor Cleaner (#10)	-	Formulation	Cleaner	liquid	n.p.	100%	n.p.	-	Severe	Severe					Swanson et al. (1995)
General Cleaner (#11)	-	Formulation	Cleaner	liquid	n.p.	100%	n.p.	-	Severe	Severe					Swanson et al. (1995)
General Cleaner (#12)	-	Formulation	Cleaner	liquid	n.p.	100%	n.p.	-	Severe	Severe					Swanson et al. (1995)
Cleaner/Degreaser (#13)	-	Formulation	Cleaner	liquid	n.p.	100%	n.p.	-	Severe	Severe					Swanson et al. (1995)
Floor Stripper (#14)	-	Formulation	Floor stripper	liquid	n.p.	100%	n.p.	-	Severe	Severe					Swanson et al. (1995)
Heavy Duty Cleaner (#15)	-	Formulation	Cleaner	liquid	n.p.	100%	n.p.	-	Severe	Severe	Category 1	NC	Category I	R41	Swanson et al. (1995)
Degreaser (#16)	-	Formulation	Degreaser	liquid	n.p.	100%	n.p.	-	Severe	Severe	Category 1	4	Category I	R41	Swanson et al. (1995)
Floor Stripper (#17)	-	Formulation	Floor stripper	liquid	n.p.	100%	n.p.	-	Severe	Severe	Category 1	NC	Category I	R41	Swanson et al. (1995)
Floor Stripper (#18)	-	Formulation	Floor stripper	liquid	n.p.	100%	n.p.	-	Severe	Severe	Category 1	4	Category I	R41	Swanson et al. (1995)
Glass Cleaner (#19)	-	Formulation	Cleaner	liquid	n.p.	100%	n.p.	-	Severe	Severe	Category 1	4	Category I	R41	Swanson et al. (1995)
Metal Cleaner (#20)	-	Formulation	Cleaner	liquid	n.p.	100%	n.p.	-	Severe	Severe	Category 1	4	Category I	R41	Swanson et al. (1995)
1-1 (#1)	-	Formulation	Insect repellent	liquid	n.p.	100%	n.p.	-	Severe	Severe	Category 2A		Category I	R36	Swanson and Harbell (2000)
1-2 (#2)	-	Formulation	Insect repellent	liquid	n.p.	100%	n.p.	-	Mild	Mild	Category 2A		Category II	R36	Swanson and Harbell (2000)
1-3 (#3)	-	Formulation	Insect repellent	liquid	n.p.	100%	n.p.	-	Moderate	Moderate	Category 2A		Category II	R36	Swanson and Harbell (2000)
2-4 (#4)	-	Formulation	Insect repellent	liquid	n.p.	100%	n.p.	-	Mild	Mild	Nonirritant		Category IV	Nonirritant	Swanson and Harbell (2000)
2-7 (#7)	-	Formulation	Insect repellent	liquid	n.p.	100%	n.p.	-	Moderate	Moderate	Nonirritant		Category IV	Nonirritant	Swanson and Harbell (2000)
2-8 (#8)	-	Formulation	Insect repellent	liquid	n.p.	100%	n.p.	-	Moderate	Moderate	Nonirritant		Category III	Nonirritant	Swanson and Harbell (2000)
Benchmark-Group 1 (#12)	-	Formulation	Insect repellent	liquid	n.p.	100%	n.p.	-	Severe	Severe	Category 2A		Category I	R36	Swanson and Harbell (2000)

Substance	CASRN[1]	Chemical Class	Product Class	Form Tested	Solubility	Concentration Tested	Purity (%)	Lab No.	In VitroTest Call[2]	In Vitro Consensus Call[3]	In Vivo GHS[4,5]	GHS Category 1 SubClass[6]	In Vivo EPA[7,8]	In Vivo EU[9,10]	Reference
Benchmark-Group 2 (#13)	-	Formulation	Insect repellent	liquid	n.p.	100%	n.p.	-	Severe	Severe	Category 1	1	Category I	R41	Swanson and Harbell (2000)
Ethanol (#14)	64-17-5	Alcohol	Solvent; Beverages; Antifreeze agent	liquid	n.p.	100%	n.p.	-	Moderate	Moderate	Category 2A		Category I	R36	Swanson and Harbell (2000)
Alkyl phosphoric acid ester/amine salt	-	Formulation, petrochemical	Lubricant additive; Petrochemical product	liquid	moderate	100%	n.p.	-	Severe	Severe	Category 1	4	SCNM	R41	Bailey et al. (2004)
Aromatic hydrocarbon #1	-	Aromatic hydrocarbon	Solvent/industrial chemical; Petrochemical product	liquid	negligible	100%	n.p.	-	Mild	Mild	Nonirritant		Category IV	Nonirritant	Bailey et al. (2004)
Aromatic hydrocarbon #2	-	Aromatic hydrocarbon	Solvent/industrial chemical; Petrochemical product	liquid	negligible	100%	n.p.	-	Mild	Mild	Nonirritant		Category IV	Nonirritant	Bailey et al. (2004)
Aryl phosponates	-	Formulation, petrochemical	Lubricant additive; Petrochemical product	liquid	moderate	100%	n.p.	-	Moderate	Moderate	Category 2B		SCNM	SCNM	Bailey et al. (2004)
Carboxylic acid amides	-	Formulation, petrochemical	Lubricant additive; Petrochemical product	solid	moderate	100%	n.p.	-	Moderate	Moderate	Category 1	4	Category I	R41	Bailey et al. (2004)
2-Chloro-2,4,4-trimethylpentane	-	Chlorinated hydrocarbon	Solvent/industrial chemical; Petrochemical product	liquid	negligible	100%	n.p.	-	Mild	Mild	Nonirritant		Category IV	Nonirritant	Bailey et al. (2004)
Clarified slurry oil	-	Oil	Petrochemical product	liquid	negligible	100%	n.p.	-	Mild	Mild	Nonirritant		Category IV	Nonirritant	Bailey et al. (2004)
Cutting fluid (conc.) #1	-	-	Cutting fluid; Petrochemical product	liquid	emulsifies	100%	n.p.	-	Mild	Mild	Nonirritant		Category IV	Nonirritant	Bailey et al. (2004)
Cutting fluid (conc.) #2	-	-	Cutting fluid; Petrochemical product	liquid	emulsifies	100%	n.p.	-	Mild	Mild	Nonirritant		Category III	Nonirritant	Bailey et al. (2004)
Ethylhexyl acid phosphate ester	-	Formulation, petrochemical	Lubricant additive; Petrochemical product	liquid	moderate	100%	n.p.	-	Severe	Severe	Category 1	4	SCNM	R41	Bailey et al. (2004)
5-Ethylidene-2-norbornene	16219-75-3	Terpene	Solvent/industrial chemical; Petrochemical product	liquid	negligible	100%	n.p.	-	Mild	Mild	Nonirritant		Category IV	Nonirritant	Bailey et al. (2004)
Methyl cyclopentadiene dimer	-	Cyclic hydrocarbon	Solvent/industrial chemical; Petrochemical product	liquid	negligible	100%	n.p.	-	Mild	Mild	Nonirritant		Category IV	Nonirritant	Bailey et al. (2004)
Petroleum wax	-	Wax	Petrochemical product	solid	negligible	100%	n.p.	-	Mild	Mild	Nonirritant		Category IV	Nonirritant	Bailey et al. (2004)
Polyalkenylsuccinate ester/amine salt	-	Formulation, petrochemical	Lubricant additive; Petrochemical product	liquid	moderate	100%	n.p.	-	Mild	Mild	SCNM		Category III	SCNM	Bailey et al. (2004)
Process oil	-	Oil	Petrochemical product	liquid	negligible	100%	n.p.	-	Mild	Mild	Nonirritant		Category IV	Nonirritant	Bailey et al. (2004)
Thiadiazole alkyl derivative	-	Formulation, petrochemical	Lubricant additive; Petrochemical product	liquid	negligible	100%	n.p.	-	Moderate	Moderate	SCNM		Category III	SCNM	Bailey et al. (2004)

[1]CASRN=Chemical Abstract Services Registry Number

[2]In Vitro Test Call represents the BCOP ocular irritancy classification assigned for each chemical in the study for each test for a specific substance

[3]Concensus call represents the overall BCOP ocular irritancy classification assigned for each chemical in the study based on the majority of ocular irritancy classification calls

[4]GHS=Globally Harmonized System (UN [2003])

[5]Eye Irritant Category 1 = irreversible effects on the eye/serious damage to the eye; Category 2A = reversible effects on the eye/irritating to the eyes; Category 2B = reversible effects on the eye/mildly irritating to the eyes; Nonirritant = not an eye irritant

[6]NICEATM-defined subgroups assigned based on the lesions that drove classification of a GHS Category 1 substance. 1: based on lesions that are persistent; 2: based on lesions that are severe (not including corneal opacity score equal to 4); 3: based on lesions that are severe (not including corneal opacity score equal to 4) and persistent; 4: corneal opacity score equal to 4 at any time; NC: No subclassification could be made based on the data.

[7]EPA=U.S. Environmental Protection Agency (EPA [1996]).

[8]Toxicity Category I for the Primary Eye Irritation Study = Corrosive, or corneal involvement or irritation not reversible within 21 days; Category II = Corneal involvement or irritation clearing in 8-21 days; Category III = Corneal involvement or irritation clearing in 7 days or less; Category IV = Minimal effects clearing within 24 hr.

[9]EU=European Union (EU [2001]).

[10]Risk phrase R41 = risk of serious damage to the eyes; R36 = irritating to the eyes; nonirritant = not an eye irritant.

[11]SCNM=Study Crtieria Not Met

[12]n.p.=not provided

[13]n.a.=not applicable

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SECTION IV

HEN'S EGG TEST - CHORIOALLANTOIC MEMBRANE (HET-CAM) TEST METHOD ACCURACY AND RELIABILITY REANALYSIS

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1.0 INTRODUCTION

On November 1, 2004, NICEATM released draft BRDs on the current status of four *in vitro* test methods for detecting ocular corrosives and severe irritants (see http://iccvam.niehs.nih.gov/methods/ocudocs/ocu_brd.htm). The test methods reviewed were the BCOP, the HET-CAM, the IRE, and the ICE assays. On January 11-12, 2005, ICCVAM convened an Expert Panel to independently evaluate the validation status of these four *in vitro* test methods for identifying ocular corrosives or severe irritants. The Expert Panel Report, *Evaluation of the Current Validation Status of In Vitro Test Methods for Identifying Ocular Corrosives and Severe Irritants*, can be obtained by contacting NICEATM or electronically from http://iccvam.niehs.nih.gov/methods/eyeirrit.htm. Public comments at the meeting revealed that additional data could be made available that had not yet been provided in response to earlier requests for data. The Expert Panel subsequently recommended that the additional data be requested and that a reanalysis of the accuracy and reliability of each test method be conducted, to the extent possible.

In response to this recommendation, a second *FR* notice was published on February 28, 2005 (*FR* Vol. 70, No. 38, pp. 9661-9662; http://iccvam.niehs.nih.gov/methods/eyeirrit.htm) requesting all available *in vitro* data on these four *in vitro* ocular irritancy test methods and corresponding *in vivo* rabbit eye test method data, as well as any human exposure data (either via ethical human studies or accidental exposure). The first *FR* notice requesting these data had been published on March 24, 2004 (*FR* Vol. 69, No. 57, pp. 13859-13861; http://iccvam.niehs.nih.gov/methods/eyeirrit.htm). Also, a request for relevant data was re-sent directly to the primary developers or users of each test method, and sent to other scientists who participated in or attended the Expert Panel Meeting on January 11-12, 2005 and who had indicated a desire to provide additional data. No human exposure data was obtained for the substances evaluated in the HET-CAM test method, and therefore no calculations could be made for the accuracy of the HET-CAM test method for predicting human severe ocular irritancy.

Other factors also necessitated a reanalysis of the accuracy of HET-CAM for detecting ocular corrosives and severe irritants. First, clarification regarding the rules for classification of severe irritants was obtained subsequent to the release of the four BRDs that resulted in changes to the hazard classification of some of the substances used in the original analysis. For the original analysis, reversibility of ocular effects for all EU and GHS hazard classification systems was considered to be achieved if, by post-exposure day 21, the endpoint scores fell below the threshold that resulted in a test substance being classified as a severe irritant (EU [2001]; UN [2003]). The new information obtained indicated that reversibility of ocular effects is achieved only when all scores reach zero on post-exposure day 21. This change resulted in two substances previously classified as GHS nonsevere irritants now being classified as GHS severe irritants.

Second, the chemical classes assigned to each test substance were revised to reflect a standardized classification scheme (based on MeSH [www.nlm.nih.gov/mesh]) that would ensure consistency in classifying substances among all *in vitro* ocular test methods under consideration. This resulted in some chemicals being reclassified. The accuracy of the HET-

CAM test method, by chemical class and using the GHS classification system (UN [2003]), has been reanalyzed to reflect these changes.

Finally, an additional accuracy analysis was conducted. In this analysis, the accuracy of each *in vitro* ocular irritancy test method for detecting ocular corrosives or severe irritants, depending on whether the classification was based on the severity of the response and/or its persistence to day 21 post-treatment, was determined.

For the HET-CAM test method, the changes to the existing database that resulted from using the appropriate persistence classification criteria and any new data and/or information received subsequent to the release of the draft BRD are summarized in **Table IV-1**. Additional HET-CAM test method data and corresponding *in vivo* rabbit eye test data were received from the German Center for Documentation and Evaluation of Alternative Methods to Animal Experiments (ZEBET) for substances that were originally described in Spielmann et al. (1996) (Spielmann and Liebsch [2005a]). HET-CAM test data previously discussed in Section 9.0 of the draft HET-CAM BRD also were included in this reanalysis (Gilleron et al. [1996, 1997]). Results from control studies run concurrently with HET-CAM studies also were provided (Vanparys and VanGoethem [2005b]; Spielmann and Liebsch [2005b]). In addition, replicate intralaboratory and interlaboratory HET-CAM test data were obtained (Vanparys and VanGoethem [2005a]). The efforts of Dr. P. Vanparys, Dr. F. Van Goethem, Dr. M. Liebsch, and Dr. med. H. Spielmann who provided additional data and/or information are gratefully acknowledged.

2.0 ACCURACY OF THE HET-CAM TEST METHOD - REANALYSIS

The ability of the HET-CAM test method to correctly identify ocular corrosives and severe irritants, as defined by the GHS, EPA, and EU classification systems was evaluated (EPA [1996]; EU [2001]; UN [2003])[1]. The three regulatory ocular hazard classification systems considered during this analysis use different classification systems and decision criteria to identify ocular corrosives and severe irritants based on *in vivo* rabbit eye test results. All three classification systems are based on individual animal data in terms of the magnitude of the response and on the extent to which induced ocular lesions fail to reverse by day 21. However, there are differences among the three classifications systems with regard to the criteria used by NICEATM for distinguishing between a severe and a nonsevere response (See **Appendix A**). Thus, to evaluate the accuracy of the HET-CAM test method for identifying ocular corrosives and severe irritants, individual rabbit data collected at the different observation times was needed for each substance.

[1] For the purposes of this analysis, an ocular corrosive or severe irritant was defined as a substance that would be classified as Category 1 according to the GHS classification system (UN [2003]), as Category I according to the EPA classification system (EPA [1996]), or as R41 according to the EU classification system (EU [2001]).

2697 **Table IV-1. Summary of HET-CAM Database Changes**
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Data Source	Data Set	Analysis Method	Number of Available Substances	Number of Acceptable Substances by Ocular Irritancy Classification System			Comments
				EPA[1]	EU[2]	GHS[3]	
				Cat I/Total	R41/Total	Cat 1/Total	
Bagley et al. (1992)	New[4]	IS(A)[5]	32	0/2[6]	0/2	0/2	
	Old[4]	IS(A)	32	0/3	0/3	0/3	
Balls et al. (1995)	New	Q-Score[5] S-Score[5]	59	14/45 9/15	13/39 4/14	12/43 4/16	The decrease, where present, in the total number of usable substances is due to excluding substances from consideration due to insufficient rabbit eye test data for classification (See **Appendix A)**. The increase, where present, in the number of corrosives and severe irritants is due to reclassification of substances.
	Old	Q-Score S-Score	59	10/40 2/12	14/48 4/19	15/45 4/17	
CEC (1991)	New	IS(B)[5]		-	15/21	-	Data previously described in an Addendum to the draft HET-CAM BRD which was released to the public on November 16, 2004. The decrease, where present, in the total number of usable substances is due to excluding substances from consideration due to insufficient rabbit eye test data for classification (See **Appendix A)**.
	Old	IS(B)		-	21/21	-	
Gettings et al. (1991)	New	IS(B)	9	3/9	3/8	3/9	The decrease, where present, in the total number of usable substances is due to excluding substances from consideration due to insufficient rabbit eye test data for classification (See **Appendix A)**. The increase, where present, in the number of corrosives and severe irritants is due to reclassification of substances.
	Old	IS(B)	9	3/9	2/9	3/9	
Gettings et al. (1994)	New	IS(A) IS(B)	18	1/18 1/18	1/18 1/18	1/18 1/18	

Data Source	Data Set	Analysis Method	Number of Available Substances	Number of Acceptable Substances by Ocular Irritancy Classification System			Comments
				EPA[1]	EU[2]	GHS[3]	
				Cat I/Total	R41/Total	Cat 1/Total	
	Old	IS(A) IS(B)	18	1/18 1/18	1/18 1/18	1/18 1/18	
Gettings et al. (1996)	New	IS(A) IS(B)	25	3/25 9/25	3/23 8/23	3/23 8/23	The decrease, where present, in the total number of usable substances reflects the exclusion of substances from consideration due to insufficient rabbit eye test data for classification (See **Appendix A)**. The increase, where present, in the number of corrosives and severe irritants is due to reclassification of substances.
	Old	IS(A) IS(B)	25	3/25 9/25	1/25 6/25	3/23 8/23	
Gilleron et al. (1996)	New	IS(B)		-	2/43	-	Data previously described in Section 9.0 of the draft HET-CAM BRD. Data were included in the reanalysis for the ability of the test method to accurately classify test substances according to the EU classification system.
	Old	IS(B)	0	-	-	-	
Gilleron et al. (1997)	New	IS(B)	60	16/53	16/48	19/54	Data previously described in Section 9.0 of the draft HET-CAM BRD. Data were included in the reanalysis for the ability of the test method to accurately classify test substances according to the GHS, EPA, and EU classification system.
	Old	IS(B)	0	-	-	-	
Hagino et al. (1999)	New	IS(A)	17	7/15	7/15	8/12	The decrease, where present, in the total number of usable substances reflects the exclusion of substances from consideration due to insufficient rabbit eye test data for classification (See **Appendix A)**. The increase, where present, in the number of corrosives and severe irritants is due to reclassification of substances.
	Old	IS(A)	17	6/14	7/17	8/16	
Kojima et al. (1995)	New	IS(A)	24	2/5	2/4	2/5	The decrease, where present, in the total number of usable substances is due to excluding substances from consideration due to insufficient rabbit eye test data for
	Old	IS(A)	24	2/5	2/5	2/5	

Data Source	Data Set	Analysis Method	Number of Available Substances	Number of Acceptable Substances by Ocular Irritancy Classification System			Comments
				EPA[1]	EU[2]	GHS[3]	
				Cat I/Total	R41/Total	Cat 1/Total	
							classification (See **Appendix A)**.
Spielmann et al. (1996)	New	mtc10[5]	142	-	25/142	-	
	New	mtc10	189	-	30/189	-	
	New	IS(B)-10[5] IS(B)-100[5]	120 120	11/73 13/70	14/71 16/69	19/77 21/75	Previous ocular irritancy calls only available for EU classification system. Additional *in vivo* and *in vitro* data received which allowed for an accuracy evaluation when compared to all three classification systems.
	Old	IS(B)-10 IS(B)-100	0 0	- -	- -	- -	
Vinardell and Macián (1994)	New	IS(B)	13	0/2	0/2	0/2	
	Old	IS(B)	13	0/2	0/2	0/2	

[1]EPA = U.S. Environmental Protection Agency (EPA [1996]).
[2]EU = European Union (EU [2001]).
[3]GHS = Globally Harmonized System (UN [2003]).
[4]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on the previous analysis included in the draft HET-CAM BRD.
[5]IS(A) = method described in Luepke (1985); IS(B), IS(B)-10, and IS(B)-100 = method described in Kalweit et al. (1987); Q = Q-Score, method described in Balls et al. (1995); S = S-Score, method described in Balls et al. (1995); mtc10 = mean time to coagulation after administration of a 10% solution, method described in Spielmann et al. (1996).
[6]First number (before forward slash) refers to the number of substances in each study that were classified as a severe irritant according to each classification system (EPA, EU, and GHS). The second number (after the forward slash) refers to the number of substances in were classified, based on animal data, for each classification system (EPA, EU, GHS).

The ability of the HET-CAM test method to correctly identify ocular corrosives and severe irritants, as defined by the GHS, EPA, and EU classification systems (EPA [1996]; EU [2001]; UN [2003]), was evaluated using two approaches. In the first approach, the accuracy of HET-CAM was assessed separately for each *in vitro-in vivo* comparative study (i.e., publication) reviewed in Sections 4.0 and 5.0 and some studies reviewed in Section 9.0 of the draft HET-CAM BRD. For this accuracy analysis, the HET-CAM ocular irritancy potential of each substance in each report was determined. When the same substance was evaluated in multiple laboratories within the same study (e.g., Balls et al. [1995]), the HET-CAM ocular irritancy potential for each independent test result was determined. Subsequently, an overall HET-CAM ocular irritancy classification was assigned for each substance in the study based on the majority of ocular irritancy classification calls (e.g., if two laboratories classified a substance as a nonirritant and three laboratories classified a substance as a severe irritant; the overall *in vitro* irritancy classification for the substance would be severe irritant). When there was an even number of different irritancy classifications for substances (e.g., two laboratories classified a substance as a nonirritant and two laboratories classified a substance as a severe irritant), the more severe irritancy classification was used for the overall classification for the substance (severe irritant, in this case; see **Appendix IV-A**). Once the ocular irritancy potential classification was determined for each substance in each of the studies, the ability of the HET-CAM test method to identify ocular corrosives and severe irritants, as defined by the GHS (UN [2003]), EPA (1996), and EU (2001) classification systems.

In the second approach to evaluating the accuracy of HET-CAM, results from the different studies using the same HET-CAM analysis approach were combined. As noted in the draft HET-CAM BRD There is no standardized data collection method for HET-CAM studies and several different data collection methods have been developed (i.e., IS, Q-Score, S-Score). Since conversion of the values obtained by one data collection method to another method (i.e., conversion of Q-Score to IS) was not possible, the accuracy assessments conducted in this section were evaluated according to each of the data collection methods described. Once the ocular irritancy classification was determined for each substance, the ability of the HET-CAM test method to identify ocular corrosives and severe irritants, as defined by the GHS (UN [2003]), EPA (1996), and EU (2001) classification systems, was determined for each analysis method (**Appendix IV-A**). Since the test methods protocols used in different studies to generate HET-CAM test results are not identical, care should be used when interpreting the results of these analyses.

Based on the revisions made to the HET-CAM test method database, a revised accuracy analysis has been conducted. The calculations were performed as described previously in Section 6.0 of the draft HET-CAM BRD. To allow for a comparison of the results obtained in the revised analysis relative to those obtained previously, the data tables include accuracy statistics from both analyses. However, the discussion of the results in the sections that follow relate to the revised analysis only.

2.1 GHS Ocular Hazard Classification System

Ten studies (Gettings et al. [1991, 1994, 1996]; Bagley et al. [1992]; Vinardell and Macián [1994]; Balls et al. [1995]; Kojima et al. [1995]; Spielmann et al. [1996]; Gilleron et al.

[1997]; Hagino et al. [1999]) contained HET-CAM test data on 376 substances, 260 of which had sufficient *in vivo* data to be assigned an ocular irritancy classification as defined by the GHS classification system (UN [2003])[2]. Based on results from *in vivo* rabbit eye experiments, 92[3] of the 260 substances were classified as severe irritants (i.e., Category 1) and 119 substances were classified as nonsevere irritants (either Category 2A, 2B) or nonirritants. The remaining 49 substances that could not be classified according to the GHS classification system due to the lack of adequate animal data are noted in **Appendix IV-A**.

For one set of data (Spielmann et al. [1996]) a large number of substances were available to compare the accuracy of the test method when substances were evaluated at a 10% and 100% concentration *in vitro* and 100% *in vivo*. Therefore, a comparison of the accuracy statistics of these two *in vitro* concentrations was possible. To include the additional HET-CAM test data, which were tested at 10% and 100% concentrations, appropriate data were combined with each of the Spielmann et al. (1996) data sets. These combined data sets were used to evaluate the overall accuracy of the IS(B) test method, when using a 10% (IS(B)-10) and 100% (IS(B)-100) concentration *in vitro*, in predicting the effect produced *in vivo* at 100% concentration. As a corollary to this evaluation, the accuracy of the IS(A) method, when substances were tested at 10% or 100% concentration *in vitro*, in predicting the effect produced *in vivo* at 100% concentration also was evaluated.

Based on the data provided in the ten reports and when results across multiply tested substances were combined to generate a single consensus call per test substance, the HET-CAM test method has an accuracy in predicting substances classified as corrosives or severe irritants, according to the GHS classification system (UN [2003]), of 41% to 83%, a sensitivity of 20% to 100%, a specificity of 33% to 100%, a false positive rate of 0% to 67%, and a false negative rate of 0% to 80%. The performance characteristics for each report are provided in **Table IV-2**.

The overall performance statistics, arranged by HET-CAM data analysis method, are provided in **Table IV-3**. Based on the combined test result approach, the HET-CAM test method has an accuracy in predicting substances classified as corrosives or severe irritants, according to the GHS classification system (UN [2003]), of 44% to 85%, a sensitivity of 25% to 100%, a specificity of 39% to 100%, a false positive rate of 0% to 61%, and a false negative rate of 0% to 75%.

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[2] For the purpose of this accuracy analysis, *in vivo* rabbit study results were used to identify GHS Category 1 irritants (i.e., severe irritants); substances classified as GHS Category 2A and 2B irritants were identified as nonsevere irritants.

[3] Two chemicals (benzalkonium chloride and sodium lauryl sulfate) were tested *in vivo* twice. The results from these studies were discordant with respect to GHS classification. According to one test, the classification was Category 1, while results from the other test yielded a Category 2B for both chemicals. The accuracy analysis was performed with the substances classified as Category 1.

Table IV-2. Evaluation of the Performance of the HET-CAM Test Method in Predicting Ocular Corrosives and Severe Irritants Compared to the *In Vivo* Rabbit Eye Test Method, as Defined by the GHS[1] Classification System, by Study

Data Source	Data Set	Anal.[2]	N[3]	Accuracy		Sensitivity		Specificity		Positive Predictivity		Negative Predictivity		False Positive Rate		False Negative Rate	
				%	No.[4]	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Gettings et al. (1991)	New[5]	IS(B)	9/10	78	7/9	100	3/3	67	4/6	60	3/5	100	4/4	33	2/6	0	0/3
	Old[5]	IS(B)	9/10	78	7/9	100	3/3	67	4/6	60	3/5	100	4/4	33	2/6	0	0/3
Gettings et al. (1994)	New	IS(A)	18/18	83	15/18	25	1/4	100	14/14	100	1/1	82	14/17	0	0/14	75	3/4
	Old	IS(A)	18/18	83	15/18	100	1/1	82	14/17	25	1/4	100	14/14	18	3/17	0	0/1
Gettings et al. (1994)	New	IS(B)	18/18	78	14/18	20	1/5	100	13/13	100	1/1	76	13/17	0	0/13	80	4/5
	Old	IS(B)	18/18	78	14/18	100	1/1	76	13/17	20	1/5	100	13/13	24	4/17	0	0/1
Gettings et al. (1996)	New	IS(A)	24/25	50	12/24	25	4/12	100	8/8	100	4/4	40	8/12	0	0/8	75	12/16
	Old	IS(A)	23/25	78	18/23	38	3/8	100	15/15	100	3/3	75	15/20	0	0/15	63	5/8
Gettings et al. (1996)	New	IS(B)	24/25	71	17/24	56	9/16	100	8/8	100	9/9	53	8/15	0	0/8	44	7/16
	Old	IS(B)	23/25	100	23/23	100	8/8	93	14/15	89	8/9	100	14/14	7	1/15	0	0/8
Bagley et al. (1992)	New	IS(A)	2/32	0	0/2	-	-	0	0/2	0	0/2	-	-	100	2/2	-	-
	Old	IS(A)	2/32	0	0/2	-	-	0	0/2	0	0/2	-	-	100	2/2	-	-
Vinardell and Macián (1994)	New	IS(B)	2/13	50	1/2	0	0/1	100	1/1	0	0/1	-	-	0	0/1	100	1/1
	Old	IS(B)	2/13	50	1/2	-	-	50	1/2	0	0/1	100	1/1	50	1/2	-	-
Balls et al. (1995)	New	Q	43/59	63	27/43	100	12/12	43	12/28	48	15/31	100	12/12	57	16/28	0	0/12
	Old	Q	45/59	62	28/45	100	15/15	43	13/30	47	15/32	100	13/13	57	17/30	0	0/15
Balls et al. (1995)	New	S	16/59	44	7/16	36	4/11	60	3/5	67	4/6	30	3/10	40	2/5	64	7/11
	Old	S	17/59	47	8/17	36	4/11	67	4/6	67	4/6	36	4/11	33	2/6	64	7/11
Kojima et al. (1995)	New	IS(A)	5/24	60	3/5	100	2/2	33	1/3	50	2/4	100	1/1	67	2/3	0	0/2
	Old	IS(A)	5/24	80	4/5	67	2/3	100	2/2	100	2/2	67	2/3	0	0/2	33	1/3
Spielmann et al. (1996)	New	IS(B)-10	77/120	68	52/77	79	19/24	62	33/53	49	19/39	87	33/38	38	20/53	21	5/24
	New	IS(B)-100	75/120	55	41/75	88	21/24	39	20/51	40	21/52	87	20/23	61	31/51	13	3/24
Gilleron et al. (1997)	New	IS(B)	54/60	41	22/54	40	19/48	50	3/6	86	19/22	9	3/32	50	3/6	60	29/48
Hagino et al. (1999)	New	IS(A)	15/17	80	12/15	73	8/11	100	4/4	100	8/8	57	4/7	0	0/4	27	3/11
	Old	IS(A)	16/17	75	12/16	100	8/8	50	4/8	67	8/12	100	4/4	50	4/8	0	0/8

[1]GHS = Globally Harmonized System (UN [2003]).

[2]Anal. = data collection/analysis method used to transform the sample data into HET-CAM scores. IS(A) = method described in Luepke (1985); IS(B), IS(B)-10, and IS(B)-100 = method described in Kalweit et al. (1987); Q = Q-Score, method described in Balls et al. (1995); S = S-Score, method described in Balls et al. (1995).

[3]N = number of substances included in this analysis/the total number of substances in the study.

[4]Data used to calculate the percentage.

[5]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on the previous analysis included in the draft HET-CAM BRD.

Table IV-3. Evaluation of the Performance of the HET-CAM Test Method in Predicting Ocular Corrosives and Severe Irritants Compared to the *In Vivo* Rabbit Eye Test Method, as Defined by the GHS[1] Classification System, by HET-CAM Analysis Method

Analysis Method[2]	Data Set	N[3]	Accuracy		Sensitivity		Specificity		Positive Predictivity		Negative Predictivity		False Positive Rate		False Negative Rate	
			%	No.[4]	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
IS(A)-100[5]	New[6]	20	85	17/20	100	2/2	83	15/18	40	2/5	100	15/15	17	3/18	0	0/2
IS(A)-10[5]	New	24	50	12/24	25	4/12	100	8/8	100	4/4	40	8/20	0	0/8	75	12/16
IS(A)	New	64	66	42/64	52	14/29	77	27/35	65	15/23	66	27/41	23	8/35	48	15/29
IS(A)	Old[6]	61	75	46/61	67	12/18	79	34/43	57	12/21	85	34/40	21	9/43	33	6/18
IS(B)-100[5] (Entire database)	New	143	53	76/143	85	35/41	40	41/102	36	35/96	87	41/47	60	61/102	15	6/41
IS(B)-100[5] (Spielmann et al. 1996)	New	75	55	41/75	88	21/24	39	20/51	40	21/31	87	20/23	61	31/51	13	3/24
IS(B)-10[5](Entire database)	New	101	68	69/101	70	28/40	67	41/61	58	28/48	77	41/53	33	20/61	30	12/40
IS(B)-10[4] (Spielmann et al. 1996)	New	77	68	52/77	79	19/24	62	33/53	49	19/39	87	33/38	38	20/53	21	5/24
IS(B)	New	107	57	61/107	76	32/42	45	29/65	47	32/68	74	29/39	55	36/65	24	10/42
IS(B)	Old	52	85	44/52	100	12/12	80	32/40	60	12/20	100	32/32	20	8/40	0	0/12
Q-Score	New	43	63	27/43	100	12/12	43	12/28	48	15/31	100	12/12	57	16/28	0	0/12
	Old	45	63	28/45	100	15/15	43	13/30	47	15/32	100	13/13	57	17/30	0	0/15
S-Score	New	16	44	7/16	36	4/11	60	3/5	67	4/6	30	3/10	40	2/5	64	7/11
	Old	17	47	8/17	36	4/11	67	4/6	67	4/6	36	4/11	33	2/6	64	7/11

[1]GHS = Globally Harmonized System (UN [2003]).
[2]IS(A), IS(A)-10, IS(A)-100 = method described in Luepke (1985); IS(B), IS(B)-10, IS(B)-100 = method described in Kalweit et al. (1987); Q = Q-Score, method described in Balls et al. (1995); S = S-Score, method described in Balls et al. (1995).
[3]N = number of substances evaluated in each study.
[4]Data used to calculate the percentage.

[5]The analysis compares the ability of the specified concentration tested *in vitro* (IS(A)-10 represents the 10% concentration tested *in vitro*) to predict the effect produced by the undiluted test substance tested *in vivo*.

[6]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on the previous analysis included in the draft HET-CAM BRD.

The IS(A)-100 analysis method (substances were tested *in vitro* at a concentration of 100% and compared to substances tested *in vivo* at 100%) had the highest accuracy for predicting ocular corrosives and severe irritants (85%; 17/20. It is noted that for the IS(A)-100 analysis method evaluation represents 20 substances that are mostly formulations. Comparatively, the IS(B) approach (which has a larger database and contains many individual chemicals) had the highest accuracy when 10% concentration tested *in vitro* was compared to 100% concentration tested *in vivo*. The false positive and false negative rates for this analysis method were 33% (20/41) and 30% (12/40), respectively.

2.2 EPA Ocular Hazard Classification System

Ten studies (Gettings et al. [1991, 1994, 1996]; Bagley et al. [1992]; Vinardell and Macián [1994]; Balls et al. [1995]; Kojima et al. [1995]; Spielmann et al. [1996]; Gilleron et al. [1997]; Hagino et al. [1999]) contained HET-CAM test data on 376 substances, 256 of which had sufficient *in vivo* data to be assigned an ocular irritancy classification as defined by the EPA classification system (EPA [1996])[4]. Based on results from the *in vivo* rabbit eye test, 76[5] of these 256 substances were classified as severe irritants (i.e., Category I), while the other 127 substances were classified as nonsevere irritants or nonirritants (Categories II, III, or IV). The remaining 127 substances that could not be classified according to the EPA classification system are so noted in **Appendix IV-A**.

As described in the previous section (see **Section IV-2.1**), a large number of substances were available to compare the accuracy of the test method when substances were evaluated at a 10% and 100% concentration *in vitro* and 100% *in vivo*. As conducted previously, appropriate data, which were tested at 10% and 100% concentration, were combined with each of the Spielmann et al. (1996) data sets. These combined data sets were used to evaluate the overall accuracy of the IS(B) test method, when using a 10% (IS(B)-10) and 100% (IS(B)-100) concentration *in vitro*, in predicting the effect produced *in vivo* at 100% concentration. As a corollary to this evaluation, the accuracy of the IS(A) method, when substances were tested at 10% or 100% concentration *in vitro*, in predicting the effect produced *in vivo* at 100% concentration was evaluated.

Based on the data provided in the ten reports and when results across multiply tested substances were combined to generate a single consensus call per test substance, the HET-CAM test method has an accuracy in predicting substances classified as corrosives or severe irritants, according to the EPA classification system (EPA [1996]), of 57% to 83%, a sensitivity of 24% to 100%, a specificity of 39% to 100%, a false positive rate of 0% to 61%, and a false negative rate of 0% to 80%. The performance characteristics for each report are provided in **Table IV-4**.

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[4] For the purpose of this accuracy analysis, *in vivo* rabbit study results were used to identify GHS Category I irritants (i.e., severe irritants); substances classified as EPA Category II, III, and IV were identified as nonsevere irritants.

[5] One chemical (sodium lauryl sulfate) was tested *in vivo* twice. The results from these studies were discordant with respect to EPA classification. According to one test, the classification was Category I, while results from the other test yielded a Category II. The accuracy analysis was performed with the substances classified as Category I.

The overall performance statistics, arranged by HET-CAM data analysis method, are provided in **Table IV-5**. Based on the combined test result approach, the HET-CAM test method has an accuracy in predicting substances classified as corrosives or severe irritants, according to the EPA classification system (EPA [1996]), of 51% to 85%, a sensitivity of 24% to 100%, a specificity of 39% to100%, a false positive rate of 0% to 61%, and a false negative rate of 0% to 76%.

The IS(A)-100 analysis approach, when substances were tested *in vitro* at a concentration of 100% and compared to substances tested *in vivo* at 100%, had the highest accuracy for predicting ocular corrosives and severe irritants (85%; 17/20), as classified by the EPA (EPA [1996]). It is noted that the database used for the IS(A)-100 analysis method evaluation represents 20 substances that are mostly formulations. Comparatively, the IS(B) approach (which has a larger database and contains many individual chemicals) had the highest accuracy when 10% concentration tested *in vitro* was compared to 100% concentration tested *in vivo*. The false positive and false negative rates for this analysis method were 36% (24/67) and 32% (10/31), respectively.

2.3 EU Ocular Hazard Classification System

Twelve studies (CEC [1991]; Gettings et al. [1991, 1994, 1996]; Bagley et al. [1992]; Vinardell and Macián [1994]; Balls et al. [1995]; Kojima et al. [1995]; Spielmann et al. [1996]; Gilleron et al. [1996, 1997]; Hagino et al. [1999]) contained HET-CAM test data on 381 substances, 312[6] of which had sufficient *in vivo* data to be assigned an ocular irritancy classification as defined by the EU classification system (EU [2001])[7]. Based on results from the *in vivo* rabbit eye test, 85 of these 312 substances were classified as severe irritants (i.e., R41), while the other 156 substances were classified as nonsevere irritants (i.e., R36) or nonirritants. The remaining 71 substances that could not be classified according to the EU classification system are so noted in **Appendix IV-A**.

As described in **Section IV-2.1** of this addendum, a large number of substances were available to compare the accuracy of the test method when substances were evaluated at a 10% and 100% concentration *in vitro* and 100% *in vivo*. As conducted previously, appropriate data, which were tested at 10% and 100% concentrations, were combined with each of the Spielmann et al. (1996) data sets. These combined data sets were used to evaluate the overall accuracy of the IS(B) test method, when using a 10% (IS(B)-10) and 100% (IS(B)-100) concentration *in vitro*, in predicting the effect produced *in vivo* at 100% concentration. As a corollary to this evaluation, the accuracy of the IS(A) method, when

[6] Two chemicals (benzalkonium chloride and sodium lauryl sulfate) were tested *in vivo* twice. The results from these studies were discordant with respect to EU classification. According to one test, the classification was R41, while results from the other test yielded a nonsevere (R36 or nonirritant) for both chemicals. The accuracy analysis was performed with the substances classified as R41.

[7] For the purpose of this accuracy analysis, *in vivo* rabbit study results were used to identify EU R41 irritants (i.e., severe irritants); substances classified R36 and nonirritants were identified as nonsevere irritants.

Table IV-4. Evaluation of the Performance of the HET-CAM Test Method in Predicting Ocular Corrosives and Severe Irritants Compared to the *In Vivo* Rabbit Eye Test Method, as Defined by the EPA[1] Classification System, by Study

Data Source	Data Set	Anal.[2]	N[3]	Accuracy		Sensitivity		Specificity		Positive Predictivity		Negative Predictivity		False Positive Rate		False Negative Rate	
				%	No.[4]	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Gettings et al. (1991)	New[5]	IS(B)	9/10	78	7/9	100	3/3	67	4/6	60	3/5	100	4/4	33	2/6	0	0/3
	Old[5]	IS(B)	9/10	78	7/9	100	3/3	67	4/6	60	3/5	100	4/4	33	2/6	0	0/3
Gettings et al. (1994)	New	IS(A)	18/18	83	15/18	25	1/4	100	14/14	100	1/1	82	14/17	0	0/14	75	3/4
	Old	IS(A)	18/18	83	15/18	100	1/1	82	14/17	25	1/4	100	14/14	18	3/17	0	0/1
Gettings et al. (1994)	New	IS(B)	18/18	78	14/18	20	1/5	100	13/13	100	1/1	76	13/17	0	0/13	80	4/5
	Old	IS(B)	18/18	78	14/18	100	1/1	76	13/17	20	1/5	100	13/13	24	4/17	0	0/1
Gettings et al. (1996)	New	IS(A)	25/25	48	12/25	24	4/17	100	8/8	100	4/4	38	8/21	0	0/8	76	13/17
	Old	IS(A)	25/25	68	17/25	30	3/10	93	14/15	75	3/4	67	14/21	7	1/15	70	7/10
Gettings et al. (1996)	New	IS(B)	25/25	72	18/25	59	10/17	100	8/8	100	10/10	53	8/15	0	0/8	41	7/17
	Old	IS(B)	25/25	92	23/25	90	9/10	93	14/15	90	9/10	93	14/15	7	1/15	10	1/10
Bagley et al. (1992)	New	IS(A)	2/32	0	0/2	-	-	0	0/2	0	0/2	-	-	100	2/2	-	-
	Old	IS(A)	3/32	0	0/3	-	-	0	0/3	0	0/3	-	-	100	3/3	-	-
Vinardell and Macián (1994)	New	IS(B)	2/13	50	1/2	0		100	1/1	-	-	50	1/2	0	0/2	100	1/1
	Old	IS(B)	2/13	50	1/2	-	-	50	1/2	0	0/1	100	1/1	50	1/2	-	-
Balls et al. (1995)	New	Q	44/59	61	27/44	100	14/14	43	13/30	45	14/17	100	13/13	57	17/30	0	0/14
	Old	Q	40/59	58	23/40	100	10/10	43	13/30	37	10/27	100	13/13	57	17/30	0	0/14
Balls et al. (1995)	New	S	14/59	57	8/14	50	4/8	67	4/6	67	4/6	50	4/8	33	2/6	50	4/8
	Old	S	12/59	50	6/12	33	2/6	67	4/6	50	2/4	50	4/8	33	2/6	67	4/6
Kojima et al. (1995)	New	IS(A)	5/24	80	4/5	100	2/2	67	2/3	67	2/3	100	2/2	33	1/3	0	0/2
	Old	IS(A)	5/24	80	4/5	67	2/3	100	2/2	100	2/2	67	2/3	0	0/2	33	1/3
Spielmann et al. (1996)	New	IS(B)-10	73/120	63	46/73	79	11/14	59	35/59	31	11/35	92	35/38	41	24/59	21	3/14
	New	IS(B)-100	70/120	50	35/70	93	13/14	39	22/56	28	13/34	96	22/23	61	34/56	7	1/14
Gilleron et al. (1997)	New	IS(B)	53/60	38	20/53	35	16/46	57	4/7	84	16/19	12	4/34	43	3/7	65	30/46
Hagino et al.	New	IS(A)	15/17	73	11/15	64	7/11	100	4/4	100	7/7	50	4/8	0	0/4	36	4/7

Data Source	Data Set	Anal.[2]	N[3]	Accuracy		Sensitivity		Specificity		Positive Predictivity		Negative Predictivity		False Positive Rate		False Negative Rate	
				%	No.[4]	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
(1999)	Old	IS(A)	14/17	71	10/14	100	6/6	50	4/8	60	6/10	100	4/4	50	4/8	0	0/6

[1]EPA = U.S. Environmental Protection Agency (EPA [1996]).
[2]Anal. = data collection/analysis method used to transform the sample data into HET-CAM scores. IS(A) = method described in Luepke (1985); IS(B), IS(B)-10, and IS(B)-100 = method described in Kalweit et al. (1987); Q = Q-Score, method described in Balls et al. (1995); S = S-Score, method described in Balls et al. (1995).
[3]N = number of substances included in this analysis/the total number of substances in the study.
[4]Data used to calculate the percentage.
[5]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on the previous analysis included in the draft HET-CAM BRD.

Table IV-5 Evaluation of the Performance of the HET-CAM Test Method in Predicting Ocular Corrosives and Severe Irritants Compared to the *In Vivo* Rabbit Eye Test Method, as Defined by the EPA[1] Classification System, by HET-CAM Analysis Method

Analysis Method[2]	Data Set	N[3]	Accuracy		Sensitivity		Specificity		Positive Predictivity		Negative Predictivity		False Positive Rate		False Negative Rate	
			%	No.[4]	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
IS(A)-100[5]	New[6]	20	85	17/20	100	2/2	83	15/18	40	2/5	100	15/15	17	3/18	0	0/2
IS(A)-10[5]	New	25	48	12/25	24	4/17	100	8/8	100	4/4	38	8/13	0	0/8	76	13/17
IS(A)	New	65	65	42/65	50	14/28	76	28/37	61	14/23	67	28/42	24	9/37	50	14/28
	Old[6]	61	70	43/61	56	10/18	77	33/43	50	10/20	80	33/41	23	10/43	44	8/18
IS(B)-100[5] (Entire database)	New	138	51	70/138	87	26/30	41	44/108	29	26/90	92	44/48	59	64/108	13	4/30
IS(B)-100[5](Spielmann et al. 1996)	New	70	50	35/70	93	13/14	39	22/56	28	13/47	96	22/23	61	34/56	7	1/14
IS(B)-10[5] (Entire database)	New	98	65	64/98	68	21/31	64	43/67	47	21/45	81	43/53	36	24/67	32	10/31
IS(B)-10[5] (Spielmann et al. 1996)	New	73	63	46/73	79	11/14	59	35/59	31	11/35	92	35/38	41	24/59	21	3/14
IS(B)	New	107	56	60/107	75	30/40	45	30/67	45	30/67	75	30/40	55	30/67	25	10/40
IS(B)	Old	54	83	45/54	93	13/14	80	32/40	62	13/21	97	32/33	20	8/40	7	1/14
Q-Score	New	44	61	27/44	100	14/14	43	13/30	45	14/17	100	13/13	57	17/30	0	0/14
	Old	40	58	23/40	100	10/10	43	13/30	37	10/27	10	13/13	57	17/30	0	0/10
S-Score	New	14	57	8/14	50	4/8	67	4/6	67	4/6	50	4/8	33	2/6	50	4/8
	Old	12	50	6/12	33	2/6	67	4/6	50	2/4	50	4/8	33	2/6	67	4/6

[1]EPA=U.S. Environmental Protection Agency (EPA [1996])

[2]IS(A), IS(A)-10, IS(A)-100 = Method described in Luepke (1985); IS(B), IS(B)-10, IS(B)-100 = Method described in Kalweit et al. (1987); Q = Q-Score, Method described in Balls et al. (1995); S = S-Score, Method described in Balls et al. (1995).

[3]N = Number of substances evaluated in each study.

[4]Data used to calculate the percentage.

[5]The analysis compares the ability of the specified concentration tested *in vitro* (IS(A)-10 represents the 10% concentration tested *in vitro*) to predict the effect produced by the undiluted test substance tested *in vivo*.

2910 [6]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on the previous analysis included in the draft HET-CAM BRD.

substances were tested at 10% or 100% concentration *in vitro*, in predicting the effect produced *in vivo* at 100% concentration was evaluated.

Based on the data provided in the twelve reports and when results across multiply tested substances were combined to generate a single consensus call per test substance, the HET-CAM test method has an accuracy in predicting substances classified as corrosives or severe irritants, according to the EU classification system (EU [2001]), of 40% to 96%, a sensitivity of 20% to 100%, a specificity of 38% to 100%, a false positive rate of 0% to 62%, and a false negative rate of 0% to 90%. The performance characteristics for each report are provided in **Table IV-6**.

The overall performance statistics, arranged by HET-CAM data analysis method, are provided in **Table IV-7**. Based on the combined test result approach, the HET-CAM test method has an accuracy in predicting substances classified as corrosives or severe irritants, according to the EU classification system (EU [2001]), of 50% to 83%, a sensitivity of 25% to 100%, a specificity of 38% to 100%, a false positive rate of 0% to 62%, and a false negative rate of 0% to 80%.

The IS(A)-100 analysis approach, when substances were tested *in vitro* at a concentration of 100% and compared to substances tested *in vivo* at 100%, had the highest accuracy for predicting ocular corrosives and severe irritants (85%; 17/20), as classified by the EU (EU [2001]). It is noted that the database used for the IS(A)-100 analysis method evaluation represents 20 substances that are mostly formulations. Comparatively, the IS(B) approach (which has a larger database and contains many individual chemicals) had the highest accuracy when 10% concentration tested *in vitro* was compared to 100% concentration tested *in vivo*. The false positive and false negative rates for this analysis method were 34% (21/61) and 30% (10/53), respectively.

In addition to the accuracy evaluations conducted as previously described in Section 6.0 of the draft HET-CAM BRD, accuracy analyses conducted using a different HET-CAM endpoint are included in **Table IV-6** and **IV-7**[8]. In the study by Spielmann et al. (1996), discriminant analyses were used to select HET-CAM endpoints with the highest power and to develop models for the prediction of severe irritants as classified by the EU classification system (EU [1996]). In this evaluation, it was shown that the mean detection time for the appearance of coagulation on the chorioallantoic membrane (CAM) obtained with a 10% solution of the test substance (termed mtc10) was the endpoint with the greatest power in distinguishing severe irritants from nonsevere test substances.

[8] Data described in these rows were taken directly from Spielmann et al. (1996); no additional analyses of these studies were conducted.

Table IV-6. Evaluation of the Performance of the HET-CAM Test Method In Predicting Ocular Corrosives and Severe Irritants Compared to the *In Vivo* Rabbit Eye Test Method, as Defined by the EU[1] Classification System, by Study

Data Source	Data Set	Anal.[2]	N[3]	Accuracy		Sensitivity		Specificity		Positive Predictivity		Negative Predictivity		False Positive Rate		False Negative Rate	
				%	No.[4]	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
CEC (1991)	New[5]	IS(B)	26/32	62	16/26	86	6/7	53	10/19	40	6/15	91	10/11	47	9/19	14	1/7
	Old[5]	IS(B)	32/32	65	21/32	91	10/11	52	11/21	50	10/20	92	11/12	48	10/21	9	1/11
Gettings et al. (1991)	New	IS(B)	8/10	88	7/8	100	3/3	80	4/5	75	3/4	100	4/4	20	1/5	0	0/3
	Old	IS(B)	9/10	67	6/9	100	2/2	57	4/7	40	2/5	100	4/4	43	3/7	0	0/2
Gettings et al. (1994)	New	IS(A)	18/18	83	15/18	25	1/4	100	14/14	100	1/1	82	14/17	0	0/14	75	3/4
	Old	IS(A)	18/18	83	15/18	100	1/1	82	14/17	25	1/4	100	14/14	18	3/17	0	0/1
Gettings et al. (1994)	New	IS(B)	18/18	78	14/18	20	1/5	100	13/13	100	1/1	76	13/17	0	0/13	80	4/5
	Old	IS(B)	18/18	78	14/18	100	1/1	76	13/17	20	1/5	100	13/13	24	4/17	0	0/1
Gettings et al. (1996)	New	IS(A)	24/25	50	12/24	25	4/16	100	8/8	100	4/4	40	8/20	0	0/8	75	12/16
	Old	IS(A)	25/25	68	17/25	17	1/6	84	16/19	25	1/4	76	16/21	16	3/19	83	5/6
Gettings et al. (1996)	New	IS(B)	24/25	71	17/24	56	9/16	100	8/8	100	9/9	53	8/15	0	0/8	44	7/16
	Old	IS(B)	25/25	84	21/25	100	6/6	79	15/19	60	6/10	100	15/15	21	4/19	0	0/6
Bagley et al. (1992)	New	IS(A)	2/32	0	0/2	-	-	0	0/2	0	0/2	-	-	100	2/2	-	-
	Old	IS(A)	3/32	0	0/3	-	-	0	0/3	0	0/3	-	-	100	3/3	-	-
Vinardell and Macián (1994)	New	IS(B)	2/13	50	1/2	0	0/1	100	1/1	-	-	50	1/2	0	0/1	100	1/1
	Old	IS(B)	2/13	50	1/2	-	-	50	1/2	0	0/2	100	1/1	50	1/2	-	-
Balls et al. (1995)	New	Q	39/49	64	25/39	100	13/13	46	12/26	48	13/27	100	12/12	54	14/26	0	0/13
	Old	Q	48/59	58	28/48	100	14/14	41	14/34	41	14/34	100	14/14	59	20/34	0	0/14
Balls et al. (1995)	New	S	14/59	50	7/14	44	4/5	60	3/5	67	4/6	38	3/8	40	2/5	56	5/9
	Old	S	19/59	47	9/19	36	4/11	63	5/8	57	4/7	42	7/11	38	3/8	64	7/11
Kojima et al. (1995)	New	IS(A)	4/24	75	3/4	100	2/2	50	1/2	67	1/3	100	1/1	50	1/2	0	0/2
	Old	IS(A)	5/24	80	4/5	67	2/3	100	2/2	100	2/2	67	2/3	0	0/2	33	1/3
Spielmann et al. (1996)	New	IS(B)-10	71/120	66	47/71	82	14/17	61	33/54	40	14/35	92	33/36	39	21/54	18	3/17
	New	IS(B)-100	69/120	52	32/69	94	16/17	38	20/52	33	16/48	95	20/21	62	32/52	6	1/17
	New[6]	mtc10	142	76	108/142	52	25/48	88	83/94	70	25/36	78	83/106	12	11/94	48	23/48
	New[6]	mtc10	189	77	145/189	53	30/57	87	115/132	64	30/47	81	115/142	13	17/132	47	27/57

Data Source	Data Set	Anal.[2]	N[3]	Accuracy		Sensitivity		Specificity		Positive Predictivity		Negative Predictivity		False Positive Rate		False Negative Rate	
				%	No.[4]	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Gilleron et al. (1996)	New	IS(B)	43/46	57	26/43	10	2/21	96	24/25	67	2/3	56	24/43	4	1/25	90	19/21
Gilleron et al. (1997)	New	IS(B)	48/60	40	19/48	37	16/43	60	3/5	89	16/18	10	3/30	40	2/5	63	27/43
Hagino et al. (1999)	New	IS(A)	15/17	73	11/15	64	7/11	100	4/4	100	7/7	50	4/8	0	0/4	36	4/11
	Old	IS(A)	17/17	65	11/17	100	7/7	40	4/10	54	7/13	100	4/4	60	6/10	0	0/7

[1]EU = European Union (EU [2001]).
[2]Anal. = data collection/analysis method used to transform the sample data into HET-CAM scores. IS(A) = method described in Luepke (1985); IS(B), IS(B)-10, and IS(B)-100 = method described in Kalweit et al. (1987); Q = Q-Score, method described in Balls et al. (1995); S = S-Score, method described in Balls et al. (1995).
[3]N = number of substances included in this analysis/the total number of substances in the study.
[4]Data used to calculate the percentage.
[5]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on the previous analysis included in the draft HET-CAM BRD.
[6]Results were calculated based on the results presented in Spielmann et al. (1996)(pages 765 and 767). Classification of *in vivo* results is described in Spielmann et al. (1996).

Table IV-7. Evaluation of the Performance of the HET-CAM Test Method In Predicting Ocular Corrosives and Severe Irritants Compared to the *In Vivo* Rabbit Eye Test Method, as Defined by the EU[1] Classification System, by HET-CAM Analysis Method

Analysis Method[2]	Data Set	N[3]	Accuracy		Sensitivity		Specificity		Positive Predictivity		Negative Predictivity		False Positive Rate		False Negative Rate	
			%	No.[4]	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
IS(A)-100[5]	New[6]	20	85	17/20	100	2/2	83	15/18	40	2/5	100	15/15	17	3/18	0	0/2
IS(A)-10[5]	New	24	50	12/24	25	4/16	100	8/8	100	4/4	40	8/16	0	0/8	75	12/16
IS(A)	New	62	66	41/62	54	14/26	75	27/36	61	14/23	69	27/39	25	9/36	46	14/26
	Old[6]	64	69	44/64	60	9/15	71	35/49	39	9/23	85	35/41	29	14/49	40	6/15
IS(B)-100[5] (Entire database)	New	178	54	96/178	89	81/35	45	65/143	28	31/109	94	65/69	55	78/143	11	4/35
IS(B)-100[5](Spielmann et al. 1996)	New	69	52	36/69	94	16/17	38	20/52	33	16/48	95	20/21	62	32/52	6	1/17
IS(B)-10[5] (Entire database)	New	95	67	64/95	70	23/33	66	41/62	52	23/44	80	41/51	34	21/61	30	10/53
IS(B)-10[5] (Spielmann et al. 1996)	New	71	66	47/71	82	14/17	61	33/54	40	17/35	92	33/36	39	21/54	18	3/17
IS(B)	New	173	58	101/173	77	37/48	51	64/125	38	37/98	85	64/75	49	61/125	23	11/48
IS(B)	Old	86	73	63/86	95	19/20	67	44/66	44	19/43	98	44/45	33	22/66	5	1/20
Q-Score	New	39	64	25/39	100	13/13	46	12/26	48	13/27	100	12/12	54	14/26	0	0/13
	Old	48	58	28/48	100	14/14	41	14/34	41	14/34	100	14/14	59	20/34	0	0/14
S-Score	New	14	50	7/14	44	4/5	60	3/5	67	4/6	38	3/8	40	2/5	56	5/9
	Old	19	47	9/19	36	4/11	63	5/8	57	4/7	42	7/11	38	3/8	64	7/11
mtc10[7]	New	142	76%	108/142	52	25/48	88	83/94	70	25/36	78	83/106	12	11/94	48	23/48
mtc10[7]	New	189	77%	145/189	53	30/57	87	115/132	64	30/47	81	115/142	13	17/132	47	27/57

[1]EU=European Union (EU [2001]).

[2]IS(A), IS(A)-10, IS(A)-100 = method described in Luepke (1985); IS(B), IS(B)-10, IS(B)-100 = method described in Kalweit et al. (1987); Q = Q-Score, method described in Balls et al. (1995); S = S-Score, method described in Balls et al. (1995).

[3]N = number of substances evaluated in each study.

[4]Data used to calculate the percentage.

[5]The analysis compares the ability of the specified concentration tested *in vitro* (IS(A)-10 represents the 10% concentration tested *in vitro*) to predict the effect produced by the undiluted test substance tested *in vivo*.

[6]New = accuracy statistics based on the revised analysis; Old = accuracy statistics based on the previous analysis included in the draft HET-CAM BRD.

[7]Results were calculated based on the results presented in Spielmann et al. (1996) (pages 765 and 767). Classification of *in vivo* results is described in Spielmann et al. (1996).

2.4 Accuracy of the HET-CAM IS(B) Analysis Method for the GHS Ocular Hazard Classification System, by Chemical Class and Property of Interest - Reanalysis

In order to further evaluate discordant responses of the HET-CAM test method relative to the *in vivo* hazard classification, several accuracy sub-analyses were performed. These included specific classes of chemicals with sufficiently robust numbers of substances ($n \geq 5$), as well as certain properties of interest considered relevant to ocular toxicity testing (e.g., pesticides, surfactants, pH, physical form). Because the international community will soon adopt the GHS classification system for hazard labeling (UN [2003]), and considering that there were only modest differences in overall HET-CAM test method accuracy among the three regulatory classification systems (i.e., EPA, EU, GHS), these sub-analyses were focused only on the GHS system.

Due to the various concentrations of test substances evaluated in this test method, different permutations of these sub-analyses are provided for comparative purposes. The overall false positive and false negative rates for the test substances evaluated are provided for two different groups: (a) substances tested at a 10% concentration in the entire database and (b) substances tested at a 100% concentration in the entire database. As is shown in **Table IV-8**, the false negative rate of the IS(B) analysis method is higher when test substances are tested at a 10% concentration (30%, 12/40) when compared to 100% (15%, 6/40). However, the false positive rate of the IS(B) analysis method is lower for the 10% concentration (33%, 20/61) compared to the 100% concentration (60%, 61/102).

As indicated in **Table IV-8**, there were some notable trends in the performance of the HET-CAM test method among subgroups of the tested substances. The chemical class of substances that was most consistently overpredicted according the GHS classification system (i.e., were false positives) by both analysis methods is alcohols. Nine out of 10 (90%) and 10 out of 11 alcohols (91%) were overpredicted by the IS(B)-10 and IS(B)-100 analysis methods, respectively. The remaining chemical classes represented among both analysis methods as being overpredicted were ethers, amines, organic salts, and heterocycles. Formulations appeared to have the lowest false positive rates for both analysis methods (0% [0/8] and 19% [6/31]). The chemical classes that were underpredicted by both the IS(B)-10 and IS(B)-100 analysis methods were amines and ethers. Generally, the false negative and false positive rates for the same chemical class were higher for the IS(B)-100 analysis method when compared to the IS(B)-10 analysis method.

With regard to physical form of the substances overpredicted by the IS(B)-10 analysis method, the false positive and false negative rates were 34% (12/62) and 30% (10/33), respectively for liquids. Since only diluted chemicals were tested for the IS(B)-10 analysis method, there were no solids to evaluate for this analysis method. For the IS(B)-100 analysis method liquids performed better than solids (see **Table IV-8**).

Table IV-8. False Negative and False Positive Rates of the HET-CAM Test Method, by Chemical Class and Properties of Interest, for the GHS[1] Classification System

Category	N[2]	False Positive Rate[3]		False Negative Rate[3]	
		%	No.	%	No.
Overall IS(B)-10 (Entire database)	101	33	20/61	30	12/40
Overall IS(B)-100 (Entire database)	143	60	61/102	15	6/41
Chemical Class[4]-IS(B)-10					
Alcohol	17	90	9/10	25	2/7
Amine	7	60	3/5	50	1/2
Ether	14	50	5/10	50	2/4
Formulation	24	0	0/8	44	7/16
Heterocycle	6	83	5/6	-	-
Organic salt	7	57	4/7	-	-
Chemical Class[4]-IS(B)-100					
Alcohol	20	91	10/11	11	1/9
Aldehyde	6	80	4/5	0	0/1
Amine	10	83	5/6	50	2/4
Ester	14	83	10/12	0	0/2
Ether	20	60	9/15	20	1/5
Formulation	51	19	6/31	35	7/13
Heterocycle	10	75	6/8	-	-
Inorganic salt	5	100	2/2	0	0/3
Ketone	6	67	4/6	-	-
Onium	7	100	2/2	0	0/5
Organic salt	8	88	7/8	-	-
Properties of Interest					
Physical Form: IS(B)-10					
Liquid	95	34	21/62	30	10/33
Solid	-	-	-	-	-
Physical Form: IS(B)-100					
Liquid	85	60	36/60	28	7/25
Solid	40	76	16/21	26	5/19
Surfactant – Total IS(B)-100	3	66	2/3	-	-
-nonionic	3	66	2/3	-	-
-anionic	0	-	-	-	-
-cationic	0	-	-	-	-
Surfactant-Based Formulation – IS(B)-10	24	0	0/8	44	7/16
pH – IS(B)-10[5]	35	58	11/19	13	2/16
- acidic (pH < 7.0)	24	50	7/14	20	2/10
- basic (pH > 7.0)	11	80	4/5	0	0/6
pH – IS(B)-100[5]	35	68	13/19	13	2/16
- acidic (pH < 7.0)	23	69	9/13	10	1/10
- basic (pH > 7.0)	12	67	4/6	17	1/6

Category	N[2]	False Positive Rate[3]		False Negative Rate[3]	
		%	No.	%	No.
Category 1 Subgroup-IS(B)-10[6]					
- Total	40	-	-	30	12/40
- 4 (CO=4 at any time)	13	-	-	15	2/13
- 3 (severity/persistence)	0	-	-	-	-
- 2 (severity)	0	-	-	-	-
- 2-4 combined[7]	*13*	-	-	15	2/11
- 1 (persistence)	27	-	-	37	10/27
Category 1 Subgroup-IS(B)-100[6]					
- Total	37	-	-	11	4/37
- 4 (CO=4 at any time)	19	-	-	11	2/19
- 3 (severity/persistence)	2	-	-	0	0/2
- 2 (severity)	2	-	-	0	0/2
- 2-4 combined[7]	*23*	-	-	9	2/23
- 1 (persistence)	18	-	-	11	2/18

[1]GHS = Globally Harmonized System (UN [2003]).
[2]N=number of substances
[3]False Positive Rate = the proportion of all negative substances that are falsely identified as positive in vitro; n = number of substances; False Negative Rate = the proportion of all positive substances that are falsely identified as negative in vitro.
[4]Chemical classes included in this table are represented by at least five substances tested in the HET-CAM test method and assignments are based on the MeSH categories (www.nlm.nih.gov/mesh). See **Appendix B**.
[5]Total number of GHS Category 1 substances for which pH information was obtained.
[6]NICEATM-defined subgroups assigned based on the lesions that drove classification of a GHS Category 1 substance. 1: based on lesions that are persistent; 2: based on lesions that are severe (not including Corneal Opacity [CO]=4); 3: based on lesions that are severe (not including CO=4) and persistent; 4: CO = 4 at any time.
[7]Subcategories 2 to 4 combined to allow for a direct comparison of GHS Category 1 substances classified *in vivo* based on some lesion severity component and those classified based on persistent lesions alone.

Information regarding the pH of test substances was only available for a subset of the substances evaluated by the IS(B)-10 and IS(B)-100 analysis methods. Among all the substances that were tested at a 10% concentration, 2 out of 35 test substances were underpredicted (false negative rate: 13%; 2/16). Among these two, both were acidic (pH < 7.0). For all substances tested at a 100% concentration, 2 out of 35 test substances were underpredicted. Of these substances, one was acidic (pH < 7.0) and one was basic (pH > 7.0). For substances that were overpredicted, basic substances were more overpredicted than acidic substances when tested at a 10% concentration *in vitro* (false positive rate of basic substances = 80% [4/5] vs. false positive rate of acidic substances: 50% [7/14]). The false positive rate of acidic and basic substances, when tested at 100% concentration *in vitro*, was approximately the same (see **Table IV-8**).

Finally, substances were more likely to be underpredicted if (a) the *in vivo* effect was based on a persistent lesion and (b) if the concentration of the test substance *in vitro* was 10% (**Table IV-8**).

2.5 Accuracy of the HET-CAM Test Method for Identifying Ocular Corrosives and Severe Irritants – Summary of Reanalysis

As detailed in **Section VI-1.0**, additional or new relevant HET-CAM test method data was received after the Expert Panel meeting on January 11 and 12, 2005 that increased the size of the comparative HET-CAM *in vivo* rabbit eye test database for the GHS classification system (UN [2003]), EPA classification system (EPA [1996]), and EU classification system (EU [2001]). The reanalysis of the accuracy of the HET-CAM test method for identifying ocular corrosives and severe irritants based on the additional data and the reclassification of some nonsevere irritants as severe irritants resulted in changes in the accuracy, sensitivity, and specificity of the HET-CAM test method.

The previous accuracy analysis of the IS(B) analysis method, which included substances used at a variety of concentrations, had an accuracy of 83% to 85%, a false positive rate from 20% to 27%, and a false negative rate from 0% to 7%. When the reanalysis was conducted, the accuracy rates decreased and the false positive and false negative rates increased for all three classification systems (see rows labeled IS(B)-10 and IS(B)-100 in **Tables IV-3**, **IV-5**, and **IV-7**).

When new analyses were conducted with the IS(A) and IS(B) methods, wherein substances tested at either 10% or 100% concentration were compared only against *in vivo* studies which were conducted with undiluted test substances, several interesting patterns were noted. For the IS(A) analysis method, these evaluations showed that accuracy increased when substances were evaluated at 100% concentration *in vitro* compared to the 10% concentration (e.g., 85% [17/20] for IS(A)-100 vs. 50% [12/24] for IS(A)-10; GHS classification system). Comparatively, the opposite was observed for the IS(B) analysis method. The IS(B)-10 method had a higher accuracy and lower false positive and false negative rate when compared to the IS(B)-100 analysis method.

Unlike the original analysis, where only formulations were evaluated by the IS(B) method, additional chemical classes were available for this assessment. The revised analysis indicated that several chemical classes are overpredicted by the HET-CAM IS(B) analysis methods. These chemical classes include alcohols, ethers, amines, organic salts, and heterocycles. Additionally, the IS(B)-100 analysis method overpredicted esters. The chemical class that was consistently underpredicted by the IS(B)-10 and IS(B)-100 analysis methods was formulations.

As noted in **Section IV-2.4**, an evaluation based on the physical form of the test substance was dependent on the analysis method being evaluated. Liquids could only be evaluated for the IS(B)-10 analysis method while solids and liquids could be evaluated for the IS(B)-100 analysis method. In the case of the IS(B)-100 evaluation, solids had a higher false positive rate than compared to liquids (76% [16/21] vs. 60% [36/60]). Comparatively, the false negative rates for solids and liquids were 26% (5/19) and 28% (7/25), respectively, for the IS(B)-100 analysis method (see **Table IV-5**). The false positive and false negative rate for liquids (when tested by the IS(B)-10 method) also were 34% (21/62) and 30% (10/33), respectively.

Using the expanded database, an analysis was conducted of the ability of the HET-CAM test method to identify ocular corrosives and severe irritants, depending on the nature of the *in vivo* ocular lesions (i.e., severity and/or persistence) responsible for classification of a substance as an ocular corrosive/severe irritant. As indicated in **Table IV-8**, the underpredicted substances were more likely to be substances classified *in vivo* based on persistent lesions (false negative rates = 37% [10/27] for IS(B)-10 and 11% [2/18] for IS(B)-100).

A new analysis not included original evaluation was an assessment of accuracy related to acidic or basic pH. For all the Category 1 substances in the database, pH information was only for 35 substances tested by the IS(B)-10 and IS(B)-100 methods. Among the two underpredicted substances that were tested at a 10% concentration for which pH information was available, both were acidic (pH < 7.0). Between the two underpredicted substances that were tested at a 100% concentration for which pH information was available, one was acidic and one was basic (pH > 7.0).

Tables IV-9 and **IV-10** provide a breakdown of the *in vivo* and *in vitro* irritancies of the substances tested using the IS(B)-10 and IS(B)-100 analysis methods. These tables indicate that the false positives for both analysis methods were typically nonirritants (18 substances for the IS(B)-10 method and 39 substances for the IS(B)-100 method). Category 2A and 2B substances made up a smaller proportion of the substances that were classified as false positives (2 and 22 substances for the IS(B)-10 and IS(B)-100 methods, respectively).

Table IV-9. Overall Accuracy of the HET-CAM Test Method in Predicting the Irritancy of a Substance as Defined by the GHS[1] Classification System (IS(B)-10 Analysis Method)

In Vivo **Classification**	***In Vitro*** **Classification**			
	Severe	**Moderate**	**Slight**	**Nonirritant**
Category 1	28	8	3	1
Category 2A	1	-	-	-
Category 2B	1	5	3	-
Nonirritant	18	8	18	7
Total	**48**	**21**	**24**	**8**

[1]GHS = Globally Harmonized System (UN [2003]).

Table IV-10. Overall Accuracy of the HET-CAM Test Method in Predicting the Irritancy of a Substance as Defined by the GHS[1] Classification System (IS(B)-100 Analysis Method)

In Vivo Classification	*In Vitro* Classification			
	Severe	**Moderate**	**Slight**	**Nonirritant**
Category 1	35	3	2	1
Category 2A	15	-	1	-
Category 2B	7	1	1	1
Nonirritant	39	15	16	6
Total	**96**	**19**	**20**	**8**

[1]GHS = Globally Harmonized System (UN [2003]).

Among the analysis methods re-evaluated, the IS(A)-100 had the greatest accuracy rate for the GHS classification system (85%; 17/20). Compared to the draft HET-CAM BRD, the IS(B) analysis method GHS classification system accuracy rate decreased (from 85% (44/25) to 57% (61/107) while the overall database increased.

3.0 RELIABILITY OF THE HET-CAM TEST METHOD - REANALYSIS

An assessment of test method reliability (intralaboratory repeatability and inter- and intra-laboratory reproducibility) is an essential element of any evaluation of the performance of an alternative test method (ICCVAM [2003]). Repeatability refers to the closeness of agreement between test results obtained within a single laboratory when the procedure is performed on the same substance under identical conditions within a given time period (ICCVAM [1997, 2003]). Intralaboratory reproducibility refers to the determination of whether qualified people within the same laboratory can successfully replicate results using a specific test protocol at different times (ICCVAM [1997, 2003]). Interlaboratory reproducibility refers to the extent to which a test method can be transferred successfully among laboratories (ICCVAM [1997, 2003)]. A reliability assessment includes determining the rationale for selecting the substances used to evaluate test method reliability, a discussion of the extent to which the substances tested represent the range of possible test outcomes, and a quantitative and/or qualitative analysis of repeatability and intra- and inter-laboratory reproducibility. In addition, measures of central tendency and variation are summarized for historical control data (negative, vehicle, positive), where applicable. This section provides the results of a more detailed analysis of HET-CAM test method reliability, based on the additional data provided subsequent to the previous analysis described in Section 7 of the draft HET-CAM BRD (http://iccvam.niehs.nih.gov/methods/ocudocs/ocu_brd.htm).

3.1 Substances Used to Re-evaluate the Reliability of the HET-CAM Test Method

There was limited information on the rationale for substance selection used in various multilaboratory studies to evaluate the reliability of the HET-CAM test method. Most reports indicated that substances were selected for inclusion based on available *in vivo* rabbit eye data for comparison, to cover the range of ocular irritation potential, and to include substances with different physicochemical properties (e.g., solids, liquids). The rationale for substance selection for CEC (1991), Balls et al. (1995), and Hagino et al. (1999) remain the same as in the draft HET-CAM BRD.

Gilleron et al. (1996, 1997) selected substances that had been tested previously and where existing data was available. Additionally, substances evaluated in the Gilleron et al. (1997) study were the same as those previously evaluated by Balls et al. (1995).

Spielmann et al. (1996) conducted an extensive evaluation of the accuracy of the HET-CAM test method. Substances selected for the evaluation were representative of the spectrum of chemicals produced by participating companies from the pharmaceutical and chemical industries.

3.2 Reanalysis of HET-CAM Test Method Intralaboratory Repeatability

An analysis of interlaboratory repeatability has included such approaches as:

- a CV analysis, which is a statistical measure of the deviation of a variable from its mean (e.g., Holzhütter et al. [1996])
- ANOVA methods (e.g., Holzhütter et al. [1996]; ASTM [1999]) that would detect whether there are significant differences among replicate (in this case) eggs within an experiment.

Two of the reports discussed in this section include intralaboratory repeatability data (Gilleron et al. [1996, 1997]). For both sets of reports, quantitative HET-CAM test method data were made available for replicate eggs within individual experiments. Using these data, the consistency of HET-CAM IS(B) results obtained among identically-treated eggs within an experiment was evaluated using a CV analysis. Considering the number of replicate eggs tested in each experiment, no attempt was made to use ANOVA to determine if any individual egg differed from any other egg.

3.2.1 Gilleron et al. (1996)

Individual egg results for 46 substances analyzed by the HET-CAM IS(B) analysis method and reported on by Gilleron et al. (1996) were received from Dr. P. Vanparys and Dr. F. Van Goethem in response to a request from NICEATM. In the data provided to NICEATM, the test results for nine of the 46 substances included in the 1996 publication (laurylsulfobetaine, deoxycholic acid, ethylacetoacetate, methyl isobutyl ketone, methanol, N-laurylsarcosine, promethazine hydrochloride, 2-methoxyethanol, benzethonium chloride, and imidazole) were no longer available. Since alternative HET-CAM test data generated by this laboratory were available for these substances, these data were provided to NICEATM. The overall replicate egg mean and median %CV values were evaluated with and without the inclusion of these data.

For each test substance, three different eggs were used in each of at least three replicate experiments. For this evaluation, the %CV values were determined for each endpoint evaluated (hemorrhage, lysis, coagulation) and for the overall *in vitro* IS(B) score. For each of the endpoints, there were a number of experiments where the test substance did not produce any effects (i.e., the average score of the three replicate eggs and standard deviation [SD] of the scores were both 0) (see **Table IV-11**). For the hemorrhage and lysis endpoints, 69 of 146 experiments (47%) resulted in an average score and SD of zero for the three replicate eggs, while, for the coagulation endpoint, 47 of 146 experiments (32%) resulted in an average score and SD of zero for the three replicate eggs. For the overall *in vitro* IS(B) score, 21 of 146 experiments (14%) resulted in an average score and SD of zero for the three replicate eggs. Three test substances (anthracene, ethylenediaminetetraacetic acid [EDTA] dipotassium, and iminodibenzyl) produced no response in any of the three endpoint evaluated in the three replicate eggs in each of three replicate experiments. The replicate egg repeatability %CV values for individual experiments, excluding studies where such values could not be calculated, ranged from 0.12 to 173.21 for hemorrhage, from 0.25 to 173.21 for lysis, from 0.00 to 173.21 for coagulation, and from 0.25 to 173.21 for the overall *in vitro* IS(B) score. The mean and median replicate egg repeatability %CV values for the overall *in*

3221 **Table IV-11. Intralaboratory Repeatibility Results for HET-CAM IS(B) Data of Gilleron et al. (1996)**
3222

Substance	Test Number	Hemorrhage			Lysis			Coagulation			Overall *In Vitro* Score		
		Mean for 3 Eggs	SD[1] for 3 Eggs	%CV[2] for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs
Allyl Alcohol	86	0.00	0.00		3.91	3.39	**86.63**	8.82	0.08	**0.90**	12.73	3.37	**26.44**
	95	0.62	1.07	**173.21**	1.38	2.38	**173.21**	8.03	0.18	**2.19**	10.02	3.52	**35.09**
	99	0.00	0.00		6.25	0.30	**4.82**	8.27	0.10	**1.17**	14.52	0.40	**2.72**
2-Aminophenol	91	0.00	0.00		0.00	0.00		1.42	1.27	**89.14**	1.42	1.27	**89.14**
	96	0.00	0.00		0.00	0.00		1.09	1.71	**156.82**	1.09	1.71	**156.82**
	101	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
Anthracene	91	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
	95	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
	99	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
Butyrolactone	88	4.98	0.01	**0.12**	0.00	0.00		7.89	0.48	**6.04**	12.87	0.47	**3.69**
	95	4.94	0.04	**0.82**	0.00	0.00		7.84	0.23	**2.97**	12.78	0.20	**1.58**
	100	4.72	0.34	**7.16**	4.55	0.51	**11.18**	6.67	0.78	**11.70**	15.94	1.07	**6.72**
Cyclohexanone	89	4.34	0.42	**9.61**	0.00	0.00		7.92	0.42	**5.30**	12.26	0.24	**1.94**
	98	4.64	0.47	**10.16**	6.61	0.18	**2.69**	7.59	0.68	**8.93**	18.85	1.01	**5.38**
	104	4.63	0.19	**4.11**	5.46	2.01	**36.75**	2.20	1.76	**80.22**	12.29	3.65	**29.67**
Deoxycholic acid, sodium salt	89	1.96	1.97	**100.26**	6.09	0.44	**7.21**	8.34	0.34	**4.05**	16.39	2.59	**15.78**
	97	1.27	1.32	**103.73**	5.55	0.57	**10.32**	0.00	0.00		6.82	0.75	**10.92**
	102	0.00	0.00		5.89	0.53	**8.94**	0.00	0.00		5.89	0.53	**8.94**
Diacetone alcohol	89	3.79	0.98	**25.83**	0.00	0.00		8.13	0.97	**11.88**	11.92	0.58	**4.87**
	98	4.90	0.03	**0.61**	5.57	0.29	**5.17**	6.53	0.86	**13.19**	17.00	1.02	**6.02**
	104	4.84	0.05	**1.07**	6.10	0.17	**2.74**	5.28	1.79	**33.88**	16.22	1.88	**11.57**
Dibenzoyl-L-tartaric acid	90	1.38	2.40	**173.21**	0.00	0.00		0.00	0.00		1.38	2.40	**173.21**
	93	4.83	0.03	**0.60**	0.00	0.00		0.00	0.00		4.83	0.03	**0.60**
	102	4.72	0.11	**2.25**	1.59	1.73	**108.99**	0.00	0.00		6.30	1.81	**28.65**

Substance	Test Number	Hemorrhage			Lysis			Coagulation			Overall *In Vitro* Score		
		Mean for 3 Eggs	SD[1] for 3 Eggs	%CV[2] for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs
2,4-Dichloro-5-sulfamoyl-benzoic acid	91	1.61	2.78	**173.21**	0.00	0.00		0.00	0.00		1.61	2.78	**173.21**
	93	4.82	0.04	**0.73**	0.00	0.00		1.21	1.13	**93.77**	6.03	1.15	**19.01**
	100	3.67	0.99	**27.03**	0.00	0.00		0.00	0.00		3.67	0.99	**27.03**
Dimethyl biguanidine	92	0.00	0.00		0.00	0.00		8.07	0.53	**6.61**	8.07	0.53	**6.61**
	93	0.00	0.00		4.02	1.89	**46.97**	6.76	1.83	**27.07**	10.78	2.00	**18.55**
	103	0.00	0.00		6.46	0.12	**1.80**	0.00	0.00		6.46	0.12	**1.80**
Dimethyl sulfoxide	88	0.00	0.00		6.38	0.26	**4.02**	8.49	0.22	**2.55**	14.87	0.21	**1.41**
	93	0.39	0.68	**173.21**	0.00	0.00		7.00	0.36	**5.11**	7.39	0.85	**11.49**
	101	0.00	0.00		6.15	0.38	**6.15**	5.36	0.62	**11.50**	11.51	0.43	**3.74**
Ethanol	89	0.00	0.00		0.00	0.00		8.43	0.22	**2.57**	8.43	0.22	**2.57**
	97	0.00	0.00		5.79	0.08	**1.40**	5.68	0.35	**6.08**	11.47	0.42	**3.64**
	102	0.00	0.00		6.27	0.45	**7.12**	7.80	0.29	**3.71**	14.07	0.40	**2.83**
2-Ethoxyethanol	86	0.85	1.47	**173.21**	0.42	0.73	**173.21**	8.62	0.35	**4.08**	9.89	1.85	**18.75**
	95	1.82	2.35	**128.66**	0.00	0.00		6.22	0.23	**3.62**	8.04	2.14	**26.55**
	99	0.00	0.00		5.63	0.29	**5.11**	7.81	0.40	**5.12**	13.44	0.18	**1.35**
Ethylenediaminetetra-acetic acid, dipotassium	91	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
	94	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
	99	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
Furan	88	0.00	0.00		0.43	0.74	**173.21**	4.08	3.02	**73.96**	4.51	2.28	**50.59**
	95	0.92	1.60	**173.21**	1.74	1.55	**89.39**	3.88	2.37	**61.19**	6.54	2.65	**40.51**
	100	0.00	0.00		5.06	0.48	**9.47**	0.44	0.55	**123.92**	5.50	0.48	**8.74**
Gluconolactone	91	0.00	0.00		0.00	0.00		8.17	0.48	**5.89**	8.17	0.48	**5.89**
	93	0.00	0.00		2.08	3.61	**173.21**	0.00	0.00		2.08	3.61	**173.21**
	101	0.00	0.00		3.40	2.09	**61.51**	0.00	0.00		3.40	2.09	**61.51**
DL-Glutamic acid	91	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
	95	2.03	1.78	**87.69**	0.00	0.00		0.00	0.00		2.03	1.78	**87.69**

Substance	Test Number	Hemorrhage			Lysis			Coagulation			Overall *In Vitro* Score		
		Mean for 3 Eggs	SD[1] for 3 Eggs	%CV[2] for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs
	100	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
3-Glycidopropyl-trimethoxysilane	99	3.63	0.48	**13.10**	0.00	0.00		0.00	0.00		3.63	0.48	**13.10**
	100	3.63	0.16	**4.33**	0.00	0.00		1.79	0.81	**45.01**	5.42	0.75	**13.87**
	105	3.90	0.11	**2.88**	0.00	0.00		0.00	0.00		3.90	0.11	**2.88**
Hexadecyltrimethyl-ammonium bromide	90	4.59	0.19	**4.15**	4.22	1.19	**28.26**	7.58	0.41	**5.37**	16.39	1.05	**6.43**
	97	2.81	2.44	**86.70**	4.85	1.11	**22.91**	0.00	0.00		7.66	2.03	**26.43**
	103	0.00	0.00		6.32	0.19	**2.93**	2.15	1.95	**90.78**	8.47	1.93	**22.78**
Hexane	86	1.24	0.78	**63.10**	0.00	0.00		4.62	0.19	**4.06**	5.86	0.80	**13.63**
	93	0.00	0.00		0.00	0.00		0.57	0.99	**173.21**	0.57	0.99	**173.21**
	105	0.00	0.00		2.82	2.48	**87.96**	0.00	0.00		2.82	2.48	**87.96**
Iminodibenzyl	92	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
	96	0.00	0.00		0.00	0.00		0.09	0.16	**173.21**	0.09	0.16	**173.21**
	102	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
Magnesium carbonate	92	0.00	0.00		0.00	0.00		3.53	1.33	**37.76**	3.53	1.33	**37.76**
	101	0.00	0.00		0.00	0.00		0.76	1.32	**173.21**	0.76	1.32	**173.21**
	106	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
Methyl isobutyl ketone	88	2.09	1.85	**88.54**	0.00	0.00		7.16	0.48	**6.73**	9.25	2.15	**23.26**
	96	3.79	0.77	**20.40**	2.39	0.45	**19.01**	5.98	1.76	**29.46**	12.16	1.17	**9.61**
	105	3.46	0.44	**12.77**	6.60	0.19	**2.81**	0.00	0.00		10.06	0.48	**4.78**
MYRJ 45	92	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
	97	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
	102	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
1-Nitropropane	86	0.42	0.73	**173.21**	0.00	0.00		2.64	2.32	**88.05**	3.06	2.86	**93.20**
	87	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
	95	1.32	0.88	**66.81**	1.55	2.68	**173.21**	2.51	2.41	**95.92**	5.37	0.71	**13.25**
Octanol	88	2.01	1.75	**87.26**	1.51	2.62	**173.21**	4.47	1.66	**37.08**	7.99	2.35	**29.37**

Substance	Test Number	Hemorrhage			Lysis			Coagulation			Overall *In Vitro* Score		
		Mean for 3 Eggs	SD[1] for 3 Eggs	%CV[2] for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs
	102	3.56	0.51	**14.33**	3.84	0.12	**3.02**	2.90	0.17	**5.88**	10.29	0.58	**5.67**
	106	3.37	0.15	**4.56**	5.73	0.48	**8.42**	2.14	1.50	**70.17**	11.25	1.32	**11.71**
2,4-Pentanedione	86	4.41	0.33	**7.60**	0.00	0.00		5.86	1.97	**33.57**	10.27	2.01	**19.58**
	87	4.37	0.19	**4.44**	0.00	0.00		6.39	0.90	**14.08**	10.76	1.07	**9.90**
	93	4.17	0.23	**5.62**	0.00	0.00		1.20	2.08	**173.21**	5.37	2.05	**38.06**
1-Phenyl-3-pyrazolidone	91	0.00	0.00		0.00	0.00		0.60	1.04	**173.21**	0.60	1.04	**173.21**
	96	0.00	0.00		0.00	0.00		0.79	1.05	**132.77**	0.79	1.05	**132.77**
	101	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
Polyoxythethylene 23 lauryl ether	92	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
	97	4.52	0.08	**1.68**	0.00	0.00		0.00	0.00		4.52	0.08	**1.68**
	103	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
Propyl-4-hydroxy-benzoate	92	1.11	1.92	**173.21**	0.00	0.00		0.38	0.66	**173.21**	1.49	2.58	**173.21**
	96	2.82	0.58	**20.37**	0.00	0.00		0.25	0.43	**173.21**	3.07	0.72	**23.36**
	101	1.07	0.87	**81.17**	0.00	0.00		0.00	0.00		1.07	0.87	**81.17**
Pyridine	89	2.97	2.61	**87.69**	0.00	0.00		8.68	0.23	**2.62**	11.65	2.39	**20.51**
	98	4.65	0.30	**6.55**	6.89	0.04	**0.52**	5.74	3.20	**55.83**	17.28	3.03	**17.54**
	104	4.34	0.87	**19.93**	6.74	0.28	**4.17**	7.31	0.51	**6.99**	18.39	0.44	**2.37**
Quinacrine	90	4.64	0.03	**0.75**	0.00	0.00		1.05	1.82	**173.21**	5.69	1.85	**32.57**
	93	4.82	0.05	**0.96**	0.00	0.00		0.00	0.00		4.82	0.05	**0.96**
	103	0.07	0.12	**173.21**	3.72	1.23	**33.14**	5.19	1.68	**32.35**	8.97	2.89	**32.23**
Tetraaminopyrimidine sulfate	92	1.59	2.75	**173.21**	0.00	0.00		0.00	0.00		1.59	2.75	**173.21**
	93	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
	103	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
Thiourea	90	3.88	0.09	**2.19**	6.82	0.07	**1.06**	7.48	0.53	**7.07**	18.18	0.50	**2.76**
	103	3.83	0.06	**1.68**	6.61	0.03	**0.44**	0.00	0.00		10.44	0.04	**0.35**
	107	4.02	0.13	**3.11**	6.70	0.06	**0.87**	0.00	0.00		10.72	0.13	**1.21**

Substance	Test Number	Hemorrhage			Lysis			Coagulation			Overall *In Vitro* Score		
		Mean for 3 Eggs	SD[1] for 3 Eggs	%CV[2] for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs
1,2,3-Tricholoropropane	89	0.53	0.83	**157.05**	0.00	0.00		5.50	2.43	**44.21**	6.03	2.85	**47.29**
	98	3.70	0.55	**14.76**	0.81	0.96	**118.49**	4.99	0.60	**11.94**	9.50	1.11	**11.74**
	104	3.27	0.55	**16.98**	3.84	0.48	**12.47**	0.91	0.35	**38.63**	8.02	0.31	**3.92**
1,2,4-Trimethylbenzene	88	0.37	0.55	**150.21**	0.00	0.00		4.09	2.45	**59.88**	4.46	2.92	**65.53**
	95	0.62	1.07	**173.21**	0.00	0.00		0.88	1.52	**173.21**	1.50	2.59	**173.21**
	100	0.00	0.00		4.90	1.05	**21.39**	2.42	1.55	**64.13**	7.32	1.40	**19.08**
Triton X-155	92	0.25	0.43	**173.21**	0.00	0.00		1.03	1.53	**148.70**	1.28	1.33	**103.67**
	98	2.77	1.29	**46.38**	2.98	2.59	**86.86**	0.00	0.00		5.75	3.83	**66.62**
	104	0.00	0.00		4.74	0.17	**3.48**	0.00	0.00		4.74	0.17	**3.48**
Benzethonium chloride[3]	90	4.71	0.18	**3.83**	0.00	0.00		7.71	0.47	**6.08**	12.42	0.63	**5.08**
	98	4.39	0.40	**9.12**	5.84	0.53	**9.00**	7.79	0.61	**7.79**	18.03	0.89	**4.95**
	104	0.00	0.00		6.53	0.06	**0.90**	0.37	0.33	**89.68**	6.90	0.28	**4.06**
	107	0.00	0.00		6.76	0.04	**0.60**	6.08	0.27	**4.48**	12.84	0.28	**2.18**
Ethylacetoacetate[3]	89	3.97	0.16	**4.12**	0.00	0.00		3.52	0.58	**16.56**	7.49	0.68	**9.08**
	97	3.16	0.59	**18.72**	1.45	1.95	**134.57**	0.00	0.00		4.61	1.37	**29.81**
	102	3.99	0.45	**11.23**	4.57	0.30	**6.47**	5.04	0.67	**13.26**	13.61	0.42	**3.05**
Imidazole[3]	96	4.41	0.34	**7.63**	4.31	0.87	**20.16**	8.91	0.00	**0.00**	17.63	1.20	**6.80**
	100	4.83	0.03	**0.52**	6.22	0.62	**9.93**	5.47	0.99	**18.14**	16.52	1.61	**9.72**
	105	4.90	0.03	**0.59**	6.89	0.03	**0.42**	7.29	0.53	**7.28**	19.09	0.49	**2.55**
	118	4.68	0.22	**4.76**	6.85	0.06	**0.88**	7.03	0.20	**2.84**	18.57	0.30	**1.60**
	115	4.90	0.03	**0.51**	6.56	0.25	**3.78**	8.48	0.33	**3.90**	19.94	0.11	**0.54**
	116	4.80	0.04	**0.84**	6.71	0.19	**2.82**	7.70	0.20	**2.59**	19.20	0.22	**1.16**
N-Laurylsarcosine, sodium salt[3]	92	2.68	2.37	**88.71**	6.23	0.47	**7.62**	8.71	0.06	**0.72**	17.62	2.11	**11.98**
	94	2.91	2.52	**86.74**	6.34	0.23	**3.70**	1.13	1.26	**111.58**	10.38	1.69	**16.24**
	106	0.00	0.00		6.91	0.03	**0.36**	4.06	0.23	**5.59**	10.97	0.23	**2.14**
	103	1.46	2.53	**173.21**	6.63	0.03	**0.38**	0.24	0.42	**173.21**	8.33	2.33	**27.95**

Substance	Test Number	Hemorrhage			Lysis			Coagulation			Overall *In Vitro* Score		
		Mean for 3 Eggs	SD[1] for 3 Eggs	%CV[2] for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs
Laurylsulfobetaine[3]	92	0.00	0.00		6.14	0.16	**2.55**	2.92	0.83	**28.29**	9.06	0.94	**10.40**
	94	0.22	0.39	**173.21**	5.71	1.43	**25.03**	3.75	3.12	**83.15**	9.68	4.15	**42.87**
	104	0.00	0.00		6.83	0.02	**0.25**	0.00	0.00		6.83	0.02	**0.25**
Methanol[3]	89	0.00	0.00		3.69	3.29	**89.14**	8.57	0.11	**1.33**	12.26	3.36	**27.40**
	93	0.00	0.00		0.00	0.00		7.97	0.12	**1.57**	7.97	0.12	**1.57**
	102	0.00	0.00		6.79	0.09	**1.33**	8.38	0.12	**1.49**	15.17	0.20	**1.32**
	105	0.00	0.00		6.84	0.05	**0.66**	5.81	1.59	**27.37**	12.65	1.55	**12.22**
2-Methoxyethanol[3]	88	0.00	0.00		5.94	1.14	**19.25**	8.39	0.22	**2.64**	14.33	0.93	**6.47**
	89	0.00	0.00		5.09	1.22	**24.00**	8.45	0.30	**3.59**	13.54	1.27	**9.40**
	96	0.00	0.00		5.39	0.32	**5.95**	7.96	0.05	**0.58**	13.35	0.29	**2.14**
	101	0.00	0.00		6.02	0.29	**4.84**	5.66	0.92	**16.25**	11.68	0.71	**6.11**
Promethazine hydrochloride[3]	85	0.00	0.00		6.69	0.11	**1.64**	8.37	0.71	**8.47**	15.06	0.80	**5.30**
	90	2.58	0.76	**29.32**	0.00	0.00		8.57	0.12	**1.46**	11.15	0.77	**6.91**
	102	0.00	0.00		6.71	0.07	**1.03**	8.51	0.02	**0.20**	15.22	0.05	**0.34**
	97	0.00	0.00		6.70	0.18	**2.61**	8.29	0.09	**1.04**	14.99	0.20	**1.31**
Triethanolamine[3]	89	0.00	0.00		3.23	0.50	**15.64**	7.59	0.80	**10.48**	10.82	1.28	**11.82**
	104	0.00	0.00		6.70	0.18	**2.61**	5.72	0.88	**15.35**	12.42	0.91	**7.34**
	107	0.00	0.00		6.36	0.35	**5.52**	6.75	0.89	**13.13**	13.11	0.78	**5.94**
Mean (SD) for All Substances[4]		**1.64 (1.93)**			**2.68 (2.88)**			**3.59 (3.44)**			**7.92 (5.84)**		
Range for All Substances		**0.12-173.21**			**0.25-173.21**			**0.00-173.21**			**0.25-173.21**		
%CV for Substances[5]		**117.56**			**107.52**			**95.69**			**73.74**		
Number of Experiments		**146**			**146**			**146**			**146**		
Mean (SD) Excluding Nine Substances[4]		**1.63 (1.90)**			**1.87 (2.57)**			**2.83 (3.25)**			**6.33 (5.43)**		
Range Excluding Nine Substances		**0.12-173.21**			**0.25-173.21**			**0.00-173.21**			**0.35-173.21**		
%CV Excluding Nine Substances[5]		**116.13**			**137.49**			**115.07**			**85.84**		

Substance	Test Number	Hemorrhage			Lysis			Coagulation			Overall *In Vitro* Score		
		Mean for 3 Eggs	SD[1] for 3 Eggs	%CV[2] for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs
Number of Experiments		**111**			**111**			**111**			**111**		
Mean Overall *In Vitro* Score %CV for All Substances		**32.52**											
Median Overall *In Vitro* Score %CV for all Substances		**11.49**											
Mean Overall *In Vitro* Score %CV Excluding Nine Substances		**41.48**											
Median Overall *In Vitro* Score %CV Excluding Nine Substances		**17.54**											

[1]SD=standard deviation.
[2]%CV=percent coefficient of variation.
[3]Data not originally presented in Gilleron et al. (1996).
[4]Mean was calculated using the values from the "Mean for 3 Eggs" column for each endpoint and the Overall *In Vitro* Score. The standard deviation (SD) was calculated based on the values in these individual columns.
[5]To avoid eliminating data for which the %CV (coefficient of variation) value could not be calculated (i.e., where the mean and SD both equaled 0), the %CV values were calculated using the mean and standard deviation calculated as described in footnote 4 of this table.

vitro IS(B) scores for the entire data set (last column in **Table IV-11**), including the data for the nine substances previously noted and excluding studies where such values could not be calculated, were 32.25 and 11.49, respectively. When the data for the nine substances noted were removed, the mean and median replicate egg repeatability %CV values for the overall IS(B) scores were 41.58 and 17.54, respectively.

3.2.2 Gilleron et al. (1997)

Individual egg results for 60 substances evaluated by the HET-CAM IS(B) analysis method and reported on by Gilleron et al. (1997) were provided by the authors to NICEATM. Among the data, the test results for four of the 60 substances included in the 1997 publication (Maneb, 1-napthalene acetic acid, Tween 20, and 1-napthalene acetic acid, sodium salt) were no longer available. Since alternative HET-CAM test data were available for these substances, these data were provided to NICEATM. The overall replicate egg mean and median %CV values were evaluated with and without the inclusion of these data.

For each test substance, three different eggs were used in each of at least three replicate experiments. For this evaluation, the %CV values were determined for each endpoint evaluated (hemorrhage, lysis, coagulation) and for the overall *in vitro* IS(B) score. For each of the endpoints, there were a number of experiments where the test substance did not induce any effects (i.e., the average score of the three replicate eggs and thus the SD of the scores were both zero) (see **Table IV-12**). For the hemorrhage endpoint, 91 of 184 experiments (49%) resulted in an average score and SD of zero for the three replicate eggs; for the lysis endpoint, 22 of 184 experiments (12%) resulted in an average score and SD of zero for the three replicate eggs; while, for the coagulation endpoint, 16 of 184 experiments (9%) resulted in an average score and SD of zero for the three replicate eggs. For the overall *in vitro* IS(B) score, 6 of 184 experiments (3%) resulted in an average score and SD of zero for the three replicate eggs. Only one test substance (Maneb) produced no response in any of the three endpoints evaluated in the three replicate eggs in each of three replicate experiments. The replicate egg repeatability %CV values for individual experiments, excluding studies where such values could not be calculated, ranged from 0.23 to 173.21 for hemorrhage, from 0.00 to 173.21 for lysis, from 0.37 to 173.21 for coagulation, and from 0.13 to 173.21 for the overall *in vitro* IS(B) score.

The mean and median replicate egg repeatability %CV values for the overall *in vitro* IS(B) scores for the entire data set (last column in **Table IV-12**), including the data for the four substances previously noted and excluding studies where such values could not be calculated, were 7.61 and 2.24, respectively. When the data for the four substances noted were removed the mean and median replicate egg repeatability %CV values for the overall IS(B) scores were 6.99 and 2.04, respectively.

3269 **Table IV-12. Intralaboratory Repeatability Results for HET-CAM IS(B) Data of Gilleron et al. (1997)**
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Substance	Test #	Hemorrhage			Lysis			Coagulation			Overall *In Vitro* Score		
		Mean for 3 Eggs	SD[1] for 3 Eggs	%CV[2] for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs
Acetone	131	0.00	0.00		6.94	0.02	**0.33**	8.74	0.06	**0.71**	15.68	0.09	**0.54**
	137	0.00	0.00		6.98	0.00	**0.00**	8.07	0.10	**1.29**	15.05	0.10	**0.69**
	144	0.00	0.00		6.89	0.07	**1.05**	8.33	0.38	**4.56**	15.22	0.40	**2.60**
Ammonium nitrate	117	1.04	0.91	**87.03**	6.76	0.04	**0.53**	6.28	1.11	**17.61**	14.08	0.22	**1.53**
	122	0.38	0.23	**59.62**	6.87	0.05	**0.75**	8.13	0.13	**1.61**	15.38	0.22	**1.43**
	126	1.67	0.26	**15.47**	6.86	0.02	**0.29**	8.02	0.07	**0.86**	16.55	0.29	**1.75**
L-Aspartic Acid	206	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
	214	0.00	0.00		1.29	2.23	**173.21**	1.07	1.85	**173.21**	2.36	4.09	**173.21**
	220	0.00	0.00		0.00	0.00		0.81	1.40	**173.21**	0.81	1.40	**173.21**
Benzalkonium chloride (1%)	130	0.00	0.00		6.87	0.01	**0.17**	8.50	0.05	**0.54**	15.37	0.04	**0.23**
	136	0.00	0.00		6.94	0.05	**0.74**	8.23	0.03	**0.42**	15.17	0.06	**0.36**
	144	0.00	0.00		6.91	0.04	**0.51**	8.00	0.11	**1.42**	14.91	0.12	**0.81**
Benzalkonium chloride (10%)	129	0.00	0.00		6.92	0.01	**0.17**	8.21	0.15	**1.88**	15.13	0.15	**0.96**
	134	0.00	0.00		6.89	0.10	**1.51**	8.38	0.27	**3.25**	15.27	0.38	**2.46**
	143	0.00	0.00		6.91	0.00	**0.00**	7.83	0.05	**0.66**	14.74	0.05	**0.35**
Benzalkonium chloride (5%)	129	0.00	0.00		6.92	0.01	**0.17**	8.08	0.26	**3.16**	15.00	0.27	**1.77**
	135	0.00	0.00		6.94	0.05	**0.74**	8.27	0.15	**1.79**	15.21	0.11	**0.73**
	143	0.00	0.00		6.93	0.02	**0.29**	7.28	0.57	**7.80**	14.21	0.59	**4.13**
n-Butyl acetate	207	4.74	0.04	**0.85**	2.58	2.39	**92.52**	7.77	0.22	**2.78**	15.09	2.60	**17.24**
	211	4.79	0.06	**1.27**	6.02	0.30	**5.00**	7.35	0.20	**2.68**	18.16	0.55	**3.00**
	217	4.24	0.11	**2.59**	6.26	0.13	**2.09**	7.87	0.14	**1.80**	18.37	0.38	**2.04**
Gamma-butyrolactone	131	4.94	0.01	**0.23**	6.94	0.01	**0.17**	7.68	0.18	**2.34**	19.55	0.18	**0.93**
	137	4.92	0.04	**0.73**	6.96	0.04	**0.58**	8.25	0.20	**2.38**	20.13	0.27	**1.34**
	145	4.92	0.02	**0.35**	6.95	0.03	**0.42**	6.62	0.52	**7.88**	18.49	0.48	**2.61**
Captan 90 concentrate	115	0.00	0.00		6.86	0.04	**0.59**	8.18	0.26	**3.12**	15.04	0.24	**1.63**
	118	0.00	0.00		6.84	0.06	**0.84**	7.98	0.25	**3.08**	14.82	0.19	**1.29**
	124	0.00	0.00		6.80	0.07	**1.04**	8.56	0.08	**0.88**	15.36	0.15	**0.95**
4-Carboxybenzalde-hyde	206	3.79	0.09	**2.28**	0.00	0.00		5.34	0.39	**7.35**	9.13	0.48	**5.22**
	214	2.71	2.35	**86.62**	0.00	0.00		0.00	0.00		2.71	2.35	**86.62**
	220	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	

Substance	Test #	Hemorrhage			Lysis			Coagulation			Overall *In Vitro* Score		
		Mean for 3 Eggs	SD[1] for 3 Eggs	%CV[2] for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs
Cetylpyridinium-bromide (0.1%)	210	0.00	0.00		5.96	0.07	**1.24**	7.26	0.13	**1.80**	13.22	0.19	**1.45**
	216	0.00	0.00		6.33	0.03	**0.40**	7.52	0.11	**1.40**	13.84	0.13	**0.94**
	219	0.00	0.00		5.86	0.04	**0.60**	5.10	1.26	**24.71**	10.96	1.24	**11.31**
Cetylpyridinium-bromide (6%)	129	0.00	0.00		6.81	0.03	**0.37**	7.68	0.27	**3.47**	14.49	0.26	**1.79**
	135	0.00	0.00		6.88	0.03	**0.37**	8.20	0.14	**1.65**	15.08	0.15	**0.97**
	143	0.00	0.00		6.82	0.10	**1.41**	7.42	0.14	**1.82**	14.24	0.14	**0.98**
Cetylpyridinium bromide (10%)	129	0.00	0.00		6.90	0.04	**0.52**	7.76	0.20	**2.52**	14.66	0.22	**1.52**
	135	0.00	0.00		6.89	0.05	**0.69**	8.29	0.32	**3.87**	15.18	0.37	**2.42**
	143	0.00	0.00		6.88	0.04	**0.59**	3.87	0.76	**19.66**	10.75	0.80	**7.45**
Chlorhexidine	115	4.50	0.14	**3.04**	6.05	0.20	**3.34**	0.00	0.00		10.55	0.28	**2.63**
	118	4.62	0.07	**1.42**	5.67	0.10	**1.84**	7.30	0.35	**4.75**	17.59	0.32	**1.79**
	124	4.32	0.26	**6.10**	5.71	0.31	**5.39**	6.43	0.89	**13.84**	16.46	1.45	**8.81**
Cyclohexanol	131	4.19	0.09	**2.04**	6.82	0.06	**0.82**	7.85	0.24	**3.11**	18.86	0.37	**1.95**
	137	4.06	0.10	**2.42**	6.87	0.01	**0.17**	8.13	0.25	**3.02**	19.06	0.19	**1.01**
	144	4.63	0.10	**2.18**	6.87	0.07	**1.03**	7.46	0.70	**9.43**	18.96	0.79	**4.15**
Dibenzoyl-L-tartaric acid	206	4.21	0.10	**2.33**	0.00	0.00		4.39	0.19	**4.39**	8.60	0.15	**1.76**
	214	4.65	0.20	**4.31**	4.95	0.20	**3.99**	5.07	0.46	**9.11**	14.67	0.50	**3.40**
	220	4.76	0.05	**1.09**	5.10	0.01	**0.23**	6.90	0.05	**0.75**	16.76	0.04	**0.24**
Dibenzyl phosphate	116	0.00	0.00		6.97	0.02	**0.25**	8.71	0.07	**0.80**	15.68	0.08	**0.51**
	119	0.00	0.00		6.89	0.03	**0.42**	8.15	0.56	**6.83**	15.04	0.56	**3.72**
	124	0.00	0.00		6.81	0.05	**0.66**	7.96	0.28	**3.50**	14.77	0.32	**2.18**
2,6-Dichlorobenzoyl chloride	128	0.00	0.00		5.01	0.72	**14.30**	4.94	0.25	**5.09**	9.95	0.69	**6.96**
	133	0.00	0.00		6.60	0.03	**0.38**	6.13	0.56	**9.11**	12.73	0.55	**4.29**
	141	0.00	0.00		6.30	0.24	**3.79**	3.23	4.17	**129.01**	9.53	4.21	**44.19**
2,2-Dimethylbutanoic acid	127	0.00	0.00		6.71	0.10	**1.47**	8.34	0.19	**2.25**	15.05	0.28	**1.85**
	133	0.00	0.00		6.95	0.03	**0.36**	8.39	0.15	**1.76**	15.34	0.15	**0.98**
	141	0.00	0.00		6.91	0.04	**0.51**	8.62	0.02	**0.20**	15.53	0.04	**0.24**
2,5-Dimethyl-hexandiol	150	4.39	0.17	**3.85**	6.81	0.10	**1.39**	4.56	0.26	**5.62**	15.77	0.47	**2.95**
	122	4.08	0.32	**7.80**	6.27	0.15	**2.32**	4.68	1.05	**22.45**	15.03	1.26	**8.36**
	126	4.07	0.07	**1.60**	4.58	0.49	**10.75**	6.55	0.15	**2.35**	15.20	0.64	**4.23**
Ethanol	132	0.00	0.00		6.92	0.01	**0.17**	8.01	0.03	**0.37**	14.93	0.03	**0.22**
	140	0.00	0.00		6.85	0.12	**1.69**	8.01	0.17	**2.09**	14.86	0.08	**0.54**

Substance	Test #	Hemorrhage			Lysis			Coagulation			Overall *In Vitro* Score		
		Mean for 3 Eggs	SD[1] for 3 Eggs	%CV[2] for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs
	145	0.00	0.00		6.88	0.03	**0.37**	8.01	0.37	**4.68**	14.89	0.38	**2.58**
Ethyl acetate	205	4.90	0.02	**0.41**	6.59	0.01	**0.18**	7.88	0.12	**1.54**	19.37	0.11	**0.58**
	209	4.01	0.10	**2.51**	6.82	0.06	**0.82**	8.52	0.10	**1.22**	19.35	0.23	**1.19**
	213	4.08	0.27	**6.65**	6.56	0.05	**0.72**	8.60	0.12	**1.45**	19.25	0.30	**1.57**
2-Ethyl-1-hexanol	131	4.18	0.22	**5.14**	0.00	0.00		6.36	0.56	**8.74**	10.54	0.48	**4.54**
	137	4.04	0.13	**3.10**	6.15	0.07	**1.15**	5.90	0.48	**8.22**	16.09	0.62	**3.87**
	145	3.93	0.09	**2.23**	6.03	0.26	**4.32**	1.54	0.92	**59.64**	11.49	0.73	**6.38**
Ethyl-2-methyl-acetoacetate	128	4.43	0.04	**0.79**	0.00	0.00		6.77	0.23	**3.33**	11.20	0.21	**1.84**
	134	4.48	0.15	**3.29**	6.49	0.25	**3.79**	5.36	0.86	**16.09**	16.33	0.82	**5.05**
	142	4.56	0.18	**4.02**	6.73	0.14	**2.09**	0.00	0.00		11.29	0.06	**0.49**
Ethyltrimethyl acetate	207	0.18	0.20	**115.50**	3.46	0.49	**14.11**	7.18	0.40	**5.56**	10.82	0.91	**8.38**
	211	3.06	0.34	**11.07**	3.94	0.61	**15.34**	7.51	0.47	**6.32**	14.51	1.07	**7.38**
	217	4.13	0.18	**4.47**	4.80	0.96	**20.04**	7.21	0.18	**2.44**	16.14	1.11	**6.91**
Fomesafen	117	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
	123	0.00	0.00		0.00	0.00		1.07	0.62	**58.36**	1.07	0.62	**58.36**
	150	0.00	0.00		0.00	0.00		2.56	0.66	**25.82**	2.56	0.66	**25.82**
Glycerol	209	0.00	0.00		5.44	0.16	**2.88**	8.61	0.05	**0.60**	14.05	0.11	**0.78**
	216	0.00	0.00		6.77	0.04	**0.52**	8.78	0.03	**0.39**	15.55	0.07	**0.44**
	220	0.00	0.00		6.22	0.07	**1.18**	8.63	0.03	**0.40**	14.85	0.10	**0.67**
n-Hexanol	127	3.84	0.88	**22.80**	6.56	0.09	**1.44**	7.63	0.30	**3.88**	18.03	1.12	**6.20**
	133	4.39	0.06	**1.37**	6.92	0.02	**0.33**	6.00	0.37	**6.14**	17.31	0.43	**2.47**
	141	4.12	0.21	**5.18**	6.72	0.05	**0.74**	6.51	0.57	**8.76**	17.35	0.69	**3.98**
Imidazole	116	4.79	0.02	**0.48**	6.86	0.04	**0.59**	7.39	0.26	**3.50**	19.04	0.26	**1.35**
	121	4.64	0.11	**2.28**	6.91	0.03	**0.36**	7.73	0.09	**1.12**	19.28	0.18	**0.95**
	125	4.87	0.02	**0.31**	6.93	0.00	**0.00**	8.18	0.33	**4.04**	19.98	0.32	**1.60**
Isobutanol	127	4.42	0.11	**2.50**	6.76	0.05	**0.77**	8.15	0.20	**2.45**	19.33	0.26	**1.35**
	133	4.67	0.07	**1.46**	6.89	0.07	**1.05**	7.93	0.12	**1.53**	19.49	0.12	**0.59**
	141	4.73	0.11	**2.28**	6.92	0.05	**0.74**	7.75	0.32	**4.18**	19.40	0.41	**2.11**
Isopropanol	132	0.00	0.00		6.91	0.04	**0.59**	7.87	0.42	**5.40**	14.78	0.47	**3.15**
	137	0.00	0.00		6.97	0.02	**0.25**	8.05	0.08	**0.94**	15.02	0.06	**0.40**
	152	0.00	0.00		6.88	0.03	**0.37**	7.73	0.20	**2.53**	14.61	0.22	**1.51**
Methyl acetate	131	4.68	0.05	**1.07**	6.86	0.04	**0.59**	7.92	0.23	**2.96**	19.46	0.18	**0.91**

Substance	Test #	Hemorrhage			Lysis			Coagulation			Overall *In Vitro* Score		
		Mean for 3 Eggs	SD[1] for 3 Eggs	%CV[2] for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs
	137	4.30	0.19	**4.34**	6.97	0.04	**0.52**	8.10	0.36	**4.49**	19.37	0.52	**2.68**
	146	3.62	0.29	**7.93**	6.91	0.03	**0.42**	7.59	0.06	**0.79**	18.12	0.34	**1.89**
Methyl cyanoacetate	128	4.47	0.16	**3.60**	4.54	0.84	**18.57**	7.04	0.45	**6.40**	16.05	1.42	**8.82**
	142	4.82	0.06	**1.33**	6.57	0.08	**1.22**	3.83	1.00	**26.08**	15.23	1.00	**6.59**
	161	4.67	0.21	**4.40**	6.28	0.18	**2.83**	6.70	0.70	**10.50**	17.65	1.08	**6.10**
Methyl cyclopentane	128	3.59	0.75	**20.84**	6.84	0.06	**0.86**	8.16	0.24	**2.92**	18.59	0.56	**3.01**
	134	2.40	2.08	**86.61**	6.87	0.06	**0.88**	8.17	0.03	**0.42**	17.44	2.06	**11.82**
	151	1.45	2.51	**173.21**	6.70	0.17	**2.50**	7.23	0.35	**4.79**	15.38	2.95	**19.17**
Methyl ethyl ketone	205	4.96	0.01	**0.23**	6.68	0.08	**1.13**	8.58	0.03	**0.35**	20.22	0.10	**0.47**
	209	3.87	0.03	**0.75**	6.84	0.03	**0.37**	8.64	0.03	**0.35**	19.34	0.08	**0.42**
	213	0.00	0.00		6.85	0.04	**0.53**	8.64	0.08	**0.92**	15.49	0.12	**0.74**
Methyl isobutyl ketone	207	4.79	0.04	**0.84**	3.65	1.38	**37.72**	6.91	0.68	**9.77**	15.35	2.06	**13.39**
	211	4.86	0.04	**0.83**	6.35	0.09	**1.38**	8.48	0.02	**0.20**	19.68	0.09	**0.44**
	217	3.88	0.38	**9.81**	5.93	0.14	**2.41**	8.40	0.10	**1.24**	18.22	0.53	**2.92**
n-Octanol	205	4.68	0.14	**2.97**	5.26	0.27	**5.14**	7.69	0.35	**4.56**	17.63	0.74	**4.20**
	209	4.68	0.07	**1.40**	4.33	0.21	**4.88**	7.28	0.43	**5.85**	16.29	0.37	**2.28**
	213	4.02	0.33	**8.28**	5.64	0.37	**6.65**	6.53	0.06	**0.98**	16.18	0.02	**0.13**
Parafluoroaniline	131	2.15	1.86	**86.67**	6.85	0.01	**0.17**	8.21	0.30	**3.68**	17.21	1.61	**9.36**
	137	0.00	0.00		6.92	0.01	**0.17**	8.40	0.05	**0.62**	15.32	0.06	**0.38**
	145	0.00	0.00		6.92	0.01	**0.17**	7.04	0.65	**9.18**	13.96	0.66	**4.70**
PEG 400	210	0.00	0.00		6.22	0.83	**13.27**	7.83	1.09	**13.94**	14.05	1.92	**13.64**
	216	0.00	0.00		6.70	0.06	**0.96**	8.30	0.06	**0.75**	15.00	0.13	**0.84**
	219	0.00	0.00		6.41	0.29	**4.50**	8.58	0.14	**1.60**	14.99	0.42	**2.78**
Potassium cyanate	117	0.00	0.00		6.77	0.06	**0.95**	6.19	0.27	**4.37**	12.96	0.22	**1.71**
	122	0.00	0.00		6.86	0.02	**0.29**	8.22	0.12	**1.46**	15.08	0.10	**0.66**
	150	0.00	0.00		6.66	0.08	**1.20**	8.12	0.25	**3.10**	14.78	0.27	**1.79**
Pyridine	132	3.29	2.85	**86.60**	6.94	0.01	**0.17**	8.56	0.07	**0.81**	18.79	2.79	**14.84**
	140	0.00	0.00		6.91	0.04	**0.59**	8.10	0.08	**0.98**	15.01	0.08	**0.51**
	145	4.70	0.12	**2.49**	6.88	0.03	**0.37**	7.97	0.17	**2.07**	19.55	0.24	**1.22**
Promethazine	206	0.00	0.00		0.00	0.00		4.87	0.74	**15.12**	4.87	0.74	**15.12**
	214	0.00	0.00		2.32	1.27	**54.85**	3.92	0.42	**10.72**	6.24	0.92	**14.72**
	220	0.00	0.00		1.27	1.13	**88.73**	6.42	0.57	**8.95**	7.69	1.16	**15.07**

Substance	Test #	Hemorrhage			Lysis			Coagulation			Overall *In Vitro* Score		
		Mean for 3 Eggs	SD[1] for 3 Eggs	%CV[2] for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs
Quinacrine	206	1.41	1.20	**84.83**	0.00	0.00		5.22	1.80	**34.49**	6.63	2.50	**37.71**
	214	1.46	0.23	**15.68**	0.00	0.00		5.96	0.14	**2.38**	7.42	0.35	**4.69**
	220	0.00	0.00		1.97	0.31	**15.76**	5.84	0.06	**1.07**	7.81	0.35	**4.52**
Sodium hydroxide (1%)	127	4.94	0.04	**0.73**	6.89	0.05	**0.69**	7.32	0.21	**2.87**	19.15	0.15	**0.80**
	132	4.94	0.01	**0.23**	6.94	0.01	**0.17**	7.10	0.41	**5.77**	18.99	0.40	**2.11**
	141	4.88	0.02	**0.31**	6.95	0.03	**0.42**	7.07	0.41	**5.76**	18.90	0.45	**2.36**
Sodium hydroxide (10%)	127	4.99	0.01	**0.23**	6.91	0.00	**0.00**	8.59	0.14	**1.65**	20.49	0.13	**0.64**
	132	4.99	0.01	**0.23**	7.00	0.00	**0.00**	8.65	0.09	**1.06**	20.64	0.08	**0.39**
	140	4.89	0.08	**1.54**	6.98	0.03	**0.36**	8.68	0.24	**2.79**	20.54	0.17	**0.81**
Sodium lauryl sulfate (3%)	130	0.00	0.00		6.71	0.18	**2.65**	5.77	0.82	**14.15**	12.48	0.78	**6.25**
	136	0.00	0.00		6.84	0.03	**0.42**	7.31	0.53	**7.18**	14.15	0.50	**3.54**
	143	0.00	0.00		6.81	0.11	**1.54**	3.70	1.07	**28.83**	10.51	1.17	**11.15**
Sodium lauryl sulfate (15%)	205	0.00	0.00		6.92	0.01	**0.17**	8.47	0.09	**1.08**	15.39	0.08	**0.53**
	210	0.00	0.00		6.88	0.04	**0.51**	8.01	0.32	**3.96**	14.89	0.33	**2.21**
	213	0.00	0.00		6.90	0.05	**0.69**	7.97	0.11	**1.43**	14.87	0.16	**1.08**
Sodium oxalate	116	3.87	0.24	**6.20**	6.45	0.12	**1.80**	3.07	1.07	**34.99**	13.39	1.28	**9.55**
	120	0.00	0.00		6.78	0.11	**1.62**	7.93	0.48	**6.01**	14.71	0.43	**2.92**
	125	0.00	0.00		6.77	0.04	**0.52**	7.74	0.36	**4.65**	14.51	0.34	**2.35**
Sodium perborate, $4H_2O$	117	0.00	0.00		6.62	0.08	**1.22**	4.66	0.59	**12.59**	11.28	0.61	**5.41**
	121	0.00	0.00		6.76	0.08	**1.12**	6.71	0.31	**4.59**	13.47	0.24	**1.79**
	125	0.00	0.00		6.76	0.05	**0.70**	8.05	0.19	**2.40**	14.81	0.23	**1.56**
tetra-Aminopyrimidine sulfate	116	4.40	0.59	**13.33**	0.00	0.00		0.00	0.00		4.40	0.59	**13.33**
	120	4.07	0.43	**10.50**	0.00	0.00		0.00	0.00		4.07	0.43	**10.50**
	125	4.52	0.11	**2.48**	0.00	0.00		0.00	0.00		4.52	0.11	**2.48**
Thiourea	149	4.40	0.06	**1.42**	6.84	0.08	**1.18**	4.92	1.12	**22.81**	16.16	1.10	**6.80**
	121	4.00	0.06	**1.56**	6.90	0.02	**0.25**	7.56	0.36	**4.83**	18.46	0.34	**1.85**
	125	4.15	0.10	**2.52**	6.91	0.03	**0.42**	8.00	0.23	**2.84**	19.06	0.34	**1.76**
Toluene	207	0.00	0.00		6.70	0.04	**0.52**	8.46	0.05	**0.61**	15.16	0.06	**0.40**
	211	0.00	0.00		6.83	0.10	**1.44**	8.31	0.13	**1.57**	15.14	0.23	**1.51**
	217	4.01	0.63	**15.67**	6.87	0.04	**0.52**	7.08	0.34	**4.81**	17.96	0.29	**1.61**
Trichloroacetic acid (3%)	209	0.00	0.00		6.91	0.03	**0.36**	8.67	0.08	**0.92**	15.58	0.07	**0.42**
	216	0.00	0.00		6.98	0.03	**0.36**	8.89	0.06	**0.70**	15.87	0.09	**0.55**

Substance	Test #	Hemorrhage			Lysis			Coagulation			Overall *In Vitro* Score		
		Mean for 3 Eggs	SD[1] for 3 Eggs	%CV[2] for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs
	217	0.00	0.00		6.94	0.02	**0.33**	8.78	0.05	**0.52**	15.72	0.07	**0.43**
Trichloroacetic acid (30%)	127	0.00	0.00		6.88	0.03	**0.37**	8.71	0.06	**0.72**	15.59	0.05	**0.29**
	133	0.00	0.00		6.91	0.05	**0.68**	8.89	0.06	**0.70**	15.80	0.11	**0.68**
	141	0.00	0.00		6.91	0.00	**0.00**	8.81	0.03	**0.39**	15.72	0.03	**0.22**
Triton X-100 (10%)	129	4.55	0.07	**1.50**	6.78	0.01	**0.17**	1.98	1.02	**51.31**	13.31	0.99	**7.42**
	135	3.71	0.55	**14.73**	6.90	0.02	**0.25**	3.65	1.15	**31.54**	14.26	1.26	**8.81**
	143	4.07	0.30	**7.30**	6.74	0.11	**1.59**	2.80	1.54	**54.95**	13.61	1.17	**8.62**
Triton X-100 (5%)	130	3.99	0.30	**7.53**	6.39	0.06	**1.01**	0.00	0.00		10.38	0.24	**2.31**
	143	4.27	0.13	**3.11**	6.67	0.06	**0.96**	0.91	0.80	**87.86**	11.86	0.82	**6.92**
	152	3.85	0.31	**8.00**	6.74	0.04	**0.60**	0.00	0.00		10.59	0.35	**3.27**
Maneb[3]	117	0.00	0.00		5.09	0.29	**5.72**	0.00	0.00		5.09	0.29	**5.72**
	123	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
	126	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
	150	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
1-Napthalene acetic acid[3]	115	1.85	1.34	**72.38**	0.00	0.00		0.92	1.29	**140.68**	2.77	2.52	**90.92**
	118	2.19	0.38	**17.19**	4.00	0.44	**11.11**	3.90	1.04	**26.55**	10.09	1.41	**14.02**
	124	0.67	1.15	**173.21**	3.12	1.12	**35.78**	3.69	0.65	**17.64**	7.48	1.99	**26.62**
	149	2.84	0.60	**21.03**	0.00	0.00		0.00	0.00		2.84	0.60	**21.03**
1-Napthalene acetic acid, sodium salt[3]	115	0.00	0.00		6.73	0.07	**1.10**	7.65	0.45	**5.92**	14.38	0.51	**3.51**
	124	0.00	0.00		6.92	0.02	**0.33**	8.44	0.14	**1.68**	15.36	0.15	**0.98**
	149	0.76	1.31	**173.21**	6.84	0.03	**0.37**	7.93	0.38	**4.76**	15.52	1.43	**9.20**
Tween 20[3]	130	0.00	0.00		6.42	0.16	**2.54**	7.05	0.89	**12.69**	13.47	1.04	**7.73**
	136	0.00	0.00		6.15	0.62	**10.03**	6.75	1.16	**17.17**	12.90	1.77	**13.75**
	144	0.00	0.00		6.88	0.04	**0.51**	8.89	0.06	**0.70**	15.77	0.10	**0.62**
	210	0.00	0.00		6.51	0.34	**5.23**	7.83	0.29	**3.69**	14.34	0.61	**4.26**
	219	1.97	0.33	**16.78**	5.95	0.63	**10.54**	8.33	0.12	**1.46**	16.25	0.46	**2.83**
Mean (SD) for All[4]		**1.94 (2.12)**			**5.60 (2.31)**			**6.42 (2.68)**			**13.96 (4.89)**		
Range for All		**0.23-173.21**			**0.00-073.21**			**0.37-173.21**			**0.13-173.21**		
%CV for All[5]		**109.10**			**41.24**			**41.78**			**34.99**		
Number of Experiments		**184**			**184**			**184**			**184**		
Mean (SD) Excluding Four Substances[4]		**2.07 (2.16)**			**5.75 (2.19)**			**6.60 (2.49)**			**14.42 (4.48)**		

Substance	Test #	Hemorrhage			Lysis			Coagulation			Overall *In Vitro* Score		
		Mean for 3 Eggs	SD[1] for 3 Eggs	%CV[2] for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs	Mean for 3 Eggs	SD for 3 Eggs	%CV for 3 Eggs
Range Excluding Four Substances		**0.23-173.21**			**0.00-073.21**			**0.37-173.21**			**0.13-173.21**		
%CV Excluding Four Substances[5]		**104.43**			**38.04**			**37.78**			**31.05**		
Number of Experiments		**168**			**168**			**168**			**168**		
Mean Overall *In Vitro* Score %CV for All Substances		**7.61**											
Median Overall *In Vitro* Score %CV for All Substances		**2.24**											
Mean Overall *In Vitro* Score %CV Excluding Four Substances		**6.99**											
Median Overall *In Vitro* Score %CV Excluding Four Substances		**2.04**											

[1]SD = standard deviation.
[2]%CV = percent coefficient of variation.
[3]Data not originally presented in Gilleron et al. (1997).
[4]Mean was calculated using the values from the "Mean for 3 Eggs" column for each endpoint and the Overall *In Vitro* Score. The standard deviation was calculated based on the values in these individual columns.
[5]To avoid eliminating data for which the %CV value could not be calculated (i.e., where the mean and SD both equaled 0), the %CV values were calculated using the mean and standard deviation calculated as described in footnote 4 of this table.

3.3 Reanalysis of HET-CAM Test Method Intralaboratory Reproducibility

The authors of two articles provided HET-CAM IS(B) data that could be used to evaluate intralaboratory reproducibility (Gilleron et al. [1996, 1997]). For both sets of studies, quantitative endpoint HET-CAM test method data were available for studies repeated three to five times in a single laboratory.

3.3.1 Gilleron et al. (1996)

Individual experimental results for 46 substances evaluated by the HET-CAM IS(B) analysis method and reported on by Gilleron et al. (1996) were received from Dr. P. Vanparys and Dr. F. Van Goethem in response to a request from NICEATM. In the data provided to NICEATM, the test results for nine of the 46 substances included in the 1996 publication (laurylsulfobetaine, deoxycholic acid, ethylacetoacetate, methyl isobutyl ketone, methanol, N-laurylsarcosine, promethazine hydrochloride, 2-methoxyethanol, benzethonium chloride, and imidazole) were no longer available. Since alternative HET-CAM test data generated by this laboratory were available for these substances, these data were provided to NICEATM. The overall replicate experiment mean and median %CV values were evaluated with and without the inclusion of these data.

In these studies, three different eggs were used for each experiment, with three experiments conducted for each test substance, except for the nine substances that were not part of the original data set used for the 1996 publication. For these nine substances, data for three to five experiments were provided.

For each of the endpoints, there were a number of experiments where the test substance did not induce any effects (i.e., the average score of the repeated experiments and SD of the scores were both 0) (see **Table IV-13**). For the hemorrhage endpoint, 12 of 46 (26%) substances resulted in an average and SD of zero for the repeated experiments, the lysis endpoint 14 of 46 (30%) substances resulted in an average and SD of zero for the repeated experiments, and for the coagulation endpoint, 6 of the 46 (13%) substances resulted in an average and SD of zero for the repeated experiments. For the overall *in vitro* IS(B) score, three of 46 experiments (7%) resulted in an average score and SD of zero for the repeated experiments. One test substance (EDTA) produced no response in any of the three endpoint evaluated in the three replicate eggs in each of replicate experiments. The reproducibility %CV values for individual substances, excluding studies where such values could not be calculated, ranged from 2.59 to 173.21 for hemorrhage, from 1.55 to 173.21 for lysis, from 1.52 to 173.21 for coagulation, and from 6.66 to 173.21 for the overall *in vitro* IS(B) score.

The mean and median reproducibility %CV values for the overall *in vitro* IS(B) scores for the entire data set (last column in **Table IV-13**), including the data for the nine substances previously noted and excluding studies where such values could not be calculated, were 52.73 and 33.70, respectively. When the data for the nine substances noted were removed, the mean and median reproducibility %CV values for the overall IS(B) scores were 60.66 and 39.15, respectively.

3322 **Table IV-13. Intralaboratory Reproducibility Results for HET-CAM IS(B) Data of Gilleron et al. (1996)**
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Chemical	Hemorrhage			Lysis			Coagulation			Overall *In Vitro* Score		
	Mean of Exp.[1]	SD[2] of Exp.	%CV[3] of Exp.	Mean of Exp.	SD of Exp.	%CV of Exp.	Mean of Exp.	SD of Exp.	%CV of Exp.	Mean of Exp.	SD of Exp.	%CV of Exp.
1,2,3-Tricholorpropane	2.50	1.72	68.87	1.55	2.03	130.62	3.80	2.52	66.20	7.85	1.74	22.19
1,2,4-Trimethylbenzene	0.33	0.31	94.63	1.63	2.83	173.21	2.46	1.61	65.17	4.42	2.91	65.81
1-Nitropropane	0.58	0.67	115.89	0.52	0.89	173.21	1.72	1.49	86.69	2.81	2.70	95.85
1-Phenyl-3-pyrazolidone	0.00	0.00		0.00	0.00		0.46	0.41	89.00	0.46	0.41	89.00
2,4-Dicholor-5-sulfamolyl-benzoic acid	3.37	1.63	48.34	0.00	0.00		0.40	0.70	173.21	3.77	2.21	58.68
2,4-Pentanedione	4.32	0.13	2.92	0.00	0.00		4.48	2.86	63.70	8.80	2.98	33.85
2-Aminophenol	0.00	0.00		0.00	0.00		0.84	0.74	88.82	0.84	0.74	88.82
2-Ethoxyethanol	0.89	0.91	102.38	2.02	3.14	155.52	7.55	1.22	16.17	10.46	2.74	26.23
3-Glycidopropyl trimethoxysilane	3.72	0.15	4.17	0.00	0.00		0.60	1.03	173.21	4.31	0.96	22.34
Allyl alcohol	0.21	0.36	173.21	3.85	2.44	63.34	8.37	0.41	4.84	12.42	2.26	18.21
Anthracene	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
Butyrolactone	4.88	0.14	2.86	1.52	2.63	173.21	7.47	0.69	9.25	13.86	1.80	12.98
Cyclohexanone	4.54	0.17	3.84	4.02	3.53	87.78	5.90	3.21	54.40	14.47	3.79	26.23
Deooxycholic acid, sodium salt	1.08	0.99	92.34	5.84	0.27	4.64	2.78	4.82	173.21	9.70	5.81	59.92
Diacetone alcohol	4.51	0.62	13.84	3.89	3.38	86.87	6.65	1.43	21.49	15.05	2.74	18.18
Dibenzoyl-L-tartaric acid	3.64	1.96	53.75	0.53	0.92	173.21	0.00	0.00		4.17	2.53	60.52
Dimethyl biguanidine	0.00	0.00		3.49	3.26	93.37	4.94	4.33	87.61	8.44	2.18	25.90
Dimethyl sulfoxide	0.13	0.23	173.21	4.18	3.62	86.65	6.95	1.57	22.53	11.26	3.74	33.27
DL-Glutamic acid	0.68	1.17	173.21	0.00	0.00		0.00	0.00		0.68	1.17	173.21
Ethanol	0.00	0.00		4.02	3.49	86.81	7.30	1.44	19.73	11.32	2.82	24.92
Ethylenediaminetetraacetic acid dipotassium	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
Furan	0.31	0.53	173.21	2.41	2.39	99.17	2.80	2.05	73.08	5.51	1.02	18.44
Gluconolactone	0.00	0.00		1.83	1.72	93.82	2.72	4.72	173.21	4.55	3.20	70.34
Hexadecyltrimethylammonium bromide	2.47	2.31	93.82	5.13	1.08	21.06	3.24	3.91	120.45	10.84	4.82	44.46
Hexane	0.41	0.72	173.21	0.94	1.63	173.21	1.73	2.52	145.61	3.08	2.65	86.07
Iminodibenzyl	0.00	0.00		0.00	0.00		0.03	0.05	173.21	0.03	0.05	173.21

Chemical	Hemorrhage			Lysis			Coagulation			Overall *In Vitro* Score		
	Mean of Exp.[1]	SD[2] of Exp.	%CV[3] of Exp.	Mean of Exp.	SD of Exp.	%CV of Exp.	Mean of Exp.	SD of Exp.	%CV of Exp.	Mean of Exp.	SD of Exp.	%CV of Exp.
Magnesium carobonate	0.00	0.00		0.00	0.00		1.43	1.86	129.93	1.43	1.86	129.93
Methyl isobutyl ketone	3.11	0.90	28.98	3.00	3.34	111.51	4.38	3.84	87.64	10.49	1.50	14.33
MYRJ 45	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.00	
Octanol	2.98	0.85	28.36	3.69	2.12	57.27	3.17	1.19	37.48	9.84	1.67	17.01
Polyoxythethylene 23 lauryl ether	1.51	2.61	173.21	0.00	0.00		0.00	0.00		1.51	2.61	173.21
Propyl-4-hydroxybenzoate	1.67	1.00	60.02	0.00	0.00		0.21	0.19	91.97	1.88	1.06	56.26
Pyridine	3.99	0.89	22.35	4.54	3.94	86.62	7.24	1.47	20.31	15.77	3.61	22.90
Quinacrine	3.18	2.69	84.83	1.24	2.15	173.21	2.08	2.74	131.92	6.50	2.19	33.70
Tetraaminopyrimidine sulfate	0.53	0.92	173.21	0.00	0.00		0.00	0.00		0.53	0.92	173.21
Thiourea	3.91	0.10	2.59	6.71	0.10	1.55	2.49	4.32	173.21	13.11	4.39	33.49
Triton X-155	1.01	1.53	152.23	2.57	2.39	93.09	0.34	0.59	173.21	3.92	2.34	59.77
2-Methoxyethanol[4]	0.00	0.00		5.61	0.45	7.95	7.62	1.32	17.35	13.22	1.12	8.43
Benzethonium chloride[4]	2.28	2.63	115.61	4.79	3.21	67.17	5.49	3.50	63.81	12.55	4.55	36.23
Ethylacetoacetate[4]	3.71	0.47	12.74	2.01	2.34	116.49	2.85	2.59	90.61	8.57	4.59	53.62
Imidazole[4]	4.75	0.19	3.91	6.26	0.98	15.71	7.48	1.21	16.23	18.49	1.23	6.66
Laurylsulfobetaine[4]	0.07	0.13	173.21	6.23	0.56	9.07	2.22	1.97	88.59	8.53	1.50	17.60
Methanol[4]	0.00	0.00		4.33	3.24	74.82	7.68	1.27	16.57	12.01	2.99	24.87
N-Laurylsarcosine, sodium salt[4]	1.76	1.33	75.79	6.53	0.30	4.66	3.54	3.82	107.96	11.82	4.03	34.05
Promethazine hydrochloride[4]	0.65	1.29	200.00	5.03	3.35	66.67	8.44	0.13	1.52	14.11	1.97	13.97
Triethanolamine[4]	0.00	0.00		5.43	1.92	35.28	6.69	0.94	14.01	12.12	1.18	9.71
Mean (SD) for All[5]	**1.64 (2.04)**			**2.68 (2.96)**			**3.59 (3.52)**			**7.51 (5.28)**		
Range for All	**2.59-173.21**			**1.55-173.21**			**1.52-173.21**			**6.66-173.21**		
%CV for All[6]	**124.12**			**110.41**			**97.92**			**70.35**		
Mean (SD) Excluding Nine Substances[5]	**1.63 (2.01)**			**1.87 (2.66)**			**2.83 (3.34)**			**6.33 (5.06)**		
Range Excluding Nine Substances	**2.59-173.21**			**1.55-173.21**			**4.84-173.21**			**14.33-173.21**		
%CV Excluding Nine Substances[6]	**123.08**			**142.31**			**118.37**			**79.92**		
Mean Overall *In Vitro* Score %CV for All Substances	**52.73**											
Median Overall *In Vitro* Score	**33.70**											

Chemical	Hemorrhage			Lysis			Coagulation			Overall *In Vitro* Score		
	Mean of Exp.[1]	SD[2] of Exp.	%CV[3] of Exp.	Mean of Exp.	SD of Exp.	%CV of Exp.	Mean of Exp.	SD of Exp.	%CV of Exp.	Mean of Exp.	SD of Exp.	%CV of Exp.
%CV for All Substances												
Mean Overall *In Vitro* Score %CV Excluding Nine Substances	**60.66**											
Median Overall *In Vitro* Score %CV Excluding Nine Substances	**39.15**											

[1]Exp. = experiment
[2]SD = standard deviation
[3]%CV = percent coefficient of variation
[4]Data not originally presented in Gilleron et al. (1996).
[5]Mean was calculated using the values from the "Mean for 3 Eggs" column for each endpoint and the Overall *In Vitro* Score. The standard deviation was calculated based on the values in these individual columns.
[6]To avoid eliminating data for which the %CV value could not be calculated (i.e., where the mean and SD both equaled 0), the %CV values were calculated using the mean and standard deviation calculated as described in footnote 5 of this table.

3.3.2 Gilleron et al. (1997)

Individual experimental results for 60 substances evaluated by the HET-CAM IS(B) analysis method and reported on by Gilleron et al. (1997) were provided by the authors to NICEATM. Among the data, the test results for four of the 60 substances included in the 1997 publication (Maneb, 1-napthalene acetic acid, Tween 20, and 1-napthalene acetic acid, sodium salt) were no longer available. Since alternative HET-CAM test data were available for these substances, these data were provided to NICEATM. The overall replicate egg mean and median %CV values were evaluated with and without the inclusion of these data.

In these studies, three different eggs were used for each experiment, with generally three experiments conducted for each test substance, except for the four substances that were not part of the original data set used for the publication. For these four substances, data for three to five test runs were provided. For this evaluation, the %CV values were determined for each endpoint evaluated (hemorrhage, lysis, coagulation) and for the overall *in vitro* IS(B) score. For each of the endpoints, there were a number of experiments where the test substance did not induce any effects (i.e., the average score of the three replicate eggs and thus the SD of the scores were both zero) (see **Table IV-14**). For the hemorrhage endpoint, 25 of 60 substances (42%) resulted in an average score and SD of zero for the three replicate eggs; for the lysis endpoint, 3 of 60 substances (5%) resulted in an average score and SD of zero for the three replicate eggs; while, for the coagulation endpoint, 2 of 60 substances (3%) resulted in an average score and SD of zero for the three replicate eggs. For the overall *in vitro* IS(B) score, none of substances resulted in an average score and SD of zero for the three replicate eggs. The reproducibility %CV values for individual substances, excluding studies where such values could not be calculated, ranged from 0.20 to 173.21 for hemorrhage, from 0.12 to 200.00 for lysis, from 0.00 to 173.21 for coagulation, and from 0.34 to 200.00 for the overall *in vitro* IS(B) score.

The mean and median reproducibility %CV values for the overall *in vitro* IS(B) scores for the entire data set (last column in **Table IV-14**), including the data for the nine substances previously noted and excluding studies where such values could not be calculated, were 17.48 and 6.34, respectively. When the data for the nine substances noted were removed, the mean and median reproducibility %CV values for the overall IS(B) scores were 13.49 and 5.25, respectively. Calculations of the %CV values using only substances identified as GHS Category 1 (UN [2003]) or EPA Category 1 (EPA [1996]) are similar to those described above.

3367 **Table IV-14. Intralaboratory Reproducibility Results for HET-CAM IS(B) Data of Gilleron et al. (1997)**
3368

Chemical	GHS[1] Cat.[2] 1	EPA[3] Cat. I	Hemorrhage			Lysis			Coagulation			Overall *In Vitro* Score		
			Mean of Exp.[4]	SD[5] of Exp.	%CV[6] of Exp.	Mean of Exp.	SD of Exp.	%CV of Exp.	Mean of Exp.	SD of Exp.	%CV of Exp.	Mean of Exp.	SD of Exp.	%CV of Exp.
2,2-Dimethy-butanoic acid		X	0.00	0.00		6.86	0.13	1.90	8.45	0.15	1.77	15.31	0.24	1.59
2,5-Dimethyl-hexandiol	X	X	4.18	0.19	4.45	5.89	1.17	19.79	5.26	1.12	21.20	15.33	0.39	2.52
2,6-Dichloro-benzoyl chloride			0.00	0.00		5.97	0.85	14.20	4.77	1.46	30.58	10.74	1.74	16.22
2-Ethyl-1-hexanol			4.05	0.13	3.18	4.06	3.51	86.62	4.60	2.66	57.83	12.71	2.96	23.33
4-Carboxybenz-aldehyde			2.17	1.95	90.08	0.00	0.00		1.78	3.08	173.21	3.95	4.69	118.75
Acetone			0.00	0.00		6.94	0.05	0.65	8.38	0.34	4.03	15.32	0.32	2.12
Ammonium nitrate			1.03	0.65	62.49	6.83	0.06	0.87	7.48	1.04	13.88	15.34	1.24	8.07
Benzalkonium chloride (1%)	X	X	0.00	0.00		6.91	0.03	0.46	8.24	0.25	3.04	15.15	0.23	1.52
Benzalkonium chloride (10%)	X	X	0.00	0.00		6.91	0.02	0.24	8.14	0.28	3.46	15.05	0.28	1.83
Benzalkonium chloride (5%)	X	X	0.00	0.00		6.93	0.01	0.15	7.88	0.53	6.67	14.80	0.53	3.55
Captan 90 concentrate	X	X	0.00	0.00		6.83	0.03	0.41	8.24	0.29	3.58	15.07	0.27	1.80
Cetylpyridinium bromide (0.1%)			0.00	0.00		6.05	0.25	4.05	6.63	1.33	20.03	12.67	1.51	11.95
Cetylpyridinium bromide (10%)	X	X	0.00	0.00		6.89	0.01	0.12	6.64	2.41	36.35	13.53	2.42	17.89
Cetylpyridinium bromide (6%)	X		0.00	0.00		6.84	0.04	0.55	7.77	0.40	5.11	14.61	0.43	2.95
Chlorhexidine	X		4.48	0.15	3.41	5.81	0.21	3.59	4.58	3.99	87.12	14.86	3.78	25.44
Cyclohexanol	X	X	4.29	0.30	7.03	6.85	0.03	0.42	7.81	0.34	4.31	18.96	0.10	0.53
Dibenzoyl-L-tartaric acid	X		4.54	0.29	6.36	3.35	2.90	86.63	5.45	1.30	23.80	13.34	4.24	31.74
Dibenzyl phosphate			0.00	0.00		6.89	0.08	1.14	8.27	0.39	4.71	15.17	0.47	3.07

Chemical	GHS[1] Cat.[2] 1	EPA[3] Cat. I	Hemorrhage			Lysis			Coagulation			Overall *In Vitro* Score		
			Mean of Exp.[4]	SD[5] of Exp.	%CV[6] of Exp.	Mean of Exp.	SD of Exp.	%CV of Exp.	Mean of Exp.	SD of Exp.	%CV of Exp.	Mean of Exp.	SD of Exp.	%CV of Exp.
Ethanol			0.00	0.00		6.89	0.04	0.51	8.01	0.00	0.00	14.90	0.04	0.24
Ethyl acetate			4.33	0.49	11.38	6.66	0.14	2.13	8.33	0.39	4.74	19.32	0.07	0.34
Ethyl-2-methyl-acetoacetate			4.49	0.07	1.46	4.40	3.82	86.65	4.04	3.57	88.34	12.94	2.94	22.68
Ethytrimethyl acetate			2.45	2.04	83.27	4.07	0.68	16.68	7.30	0.18	2.50	13.82	2.73	19.72
Fomesafen			0.00	0.00		0.00	0.00		1.21	1.29	106.26	1.21	1.29	106.26
Gamma-butyro-lactone			4.93	0.01	0.20	6.95	0.01	0.14	7.52	0.83	11.00	19.39	0.83	4.29
Glycerol			0.00	0.00		6.14	0.67	10.93	8.67	0.09	1.07	14.82	0.75	5.09
Imidazole			4.77	0.12	2.43	6.90	0.04	0.54	7.77	0.40	5.10	19.43	0.49	2.51
Isobutanol	X	X	4.61	0.17	3.60	6.86	0.09	1.26	7.94	0.20	2.52	19.41	0.08	0.43
Isopropanol			0.00	0.00		6.92	0.04	0.65	7.88	0.16	2.03	14.80	0.20	1.38
L-Aspartic Acid			0.00	0.00		0.43	0.74	173.21	0.63	0.56	89.05	1.06	1.20	113.49
Methyl acetate			4.20	0.54	12.83	6.91	0.06	0.82	7.87	0.26	3.29	18.98	0.75	3.94
Methyl cyanoacetate			4.65	0.18	3.84	5.80	1.10	18.97	5.86	1.76	30.11	16.31	1.23	7.56
Methyl cyclopentane			2.48	1.07	43.31	6.80	0.09	1.31	7.85	0.54	6.87	17.14	1.62	9.48
Methyl ethyl ketone			2.94	2.60	88.56	6.79	0.09	1.36	8.62	0.03	0.40	18.35	2.52	13.71
Methyl isobutyl ketone			4.51	0.54	12.07	5.31	1.45	27.39	7.93	0.88	11.15	17.75	2.20	12.42
n-Butyl acetate			4.59	0.30	6.57	4.95	2.06	41.57	7.66	0.28	3.60	17.21	1.84	10.69
n-Hexanol			4.12	0.27	6.64	6.74	0.18	2.68	6.71	0.83	12.42	17.57	0.41	2.31
n-Octanol			4.46	0.38	8.61	5.08	0.67	13.19	7.17	0.59	8.25	16.70	0.81	4.83
Parafluoroaniline			0.72	1.24	173.21	6.90	0.04	0.64	7.88	0.74	9.34	15.50	1.63	10.51
PEG 400			0.00	0.00		6.44	0.24	3.70	8.24	0.38	4.60	14.68	0.54	3.70
Potassium cyanate			0.00	0.00		6.76	0.10	1.51	7.51	1.14	15.24	14.27	1.15	8.05
Promethazine	X	X	0.00	0.00		1.20	1.16	97.13	5.07	1.26	24.89	6.27	1.41	22.50
Pyridine	X	X	2.66	2.41	90.56	6.91	0.03	0.44	8.21	0.31	3.78	17.78	2.43	13.69
Quinacrine	X	X	0.96	0.83	86.65	0.66	1.14	173.21	5.67	0.40	7.00	7.29	0.60	8.24
Sodium hydroxide			4.92	0.03	0.69	6.93	0.03	0.43	7.16	0.14	1.91	19.01	0.13	0.68

Chemical	GHS[1] Cat.[2] 1	EPA[3] Cat. I	Hemorrhage			Lysis			Coagulation			Overall *In Vitro* Score		
			Mean of Exp.[4]	SD[5] of Exp.	%CV[6] of Exp.	Mean of Exp.	SD of Exp.	%CV of Exp.	Mean of Exp.	SD of Exp.	%CV of Exp.	Mean of Exp.	SD of Exp.	%CV of Exp.
(1%)														
Sodium hydroxide (10%)	X	X	4.95	0.06	1.17	6.96	0.05	0.67	8.64	0.05	0.53	20.56	0.08	0.37
Sodium lauryl sulfate (15%)	X	X	0.00	0.00		6.90	0.02	0.29	8.15	0.28	3.41	15.05	0.29	1.96
Sodium lauryl sulfate (3%)			0.00	0.00		6.79	0.07	0.99	5.59	1.81	32.39	12.38	1.83	14.74
Sodium oxalate	X	X	1.29	2.24	173.21	6.67	0.19	2.84	6.25	2.75	44.07	14.20	0.71	5.01
Sodium perborate, $4H_2O$	X	X	0.00	0.00		6.71	0.08	1.15	6.47	1.71	26.38	13.19	1.78	13.49
Tetraamino-pyrimidine sulfate			4.33	0.23	5.40	0.00	0.00		0.00	0.00		4.33	0.23	5.40
Thiourea			4.18	0.20	4.83	6.88	0.04	0.60	6.83	1.67	24.40	17.89	1.53	8.57
Toluene			1.34	2.31	173.21	6.80	0.09	1.28	7.95	0.76	9.52	16.09	1.62	10.07
Trichloroacetic acid (3%)			0.00	0.00		6.94	0.04	0.51	8.78	0.11	1.25	15.72	0.15	0.92
Trichloroacetic acid (30%)	X	X	0.00	0.00		6.90	0.02	0.24	8.80	0.09	1.02	15.71	0.11	0.67
Triton X-100 (10%)	X		4.11	0.42	10.26	6.81	0.08	1.20	2.81	0.84	29.72	13.73	0.48	3.52
Triton X-100 (5%)			4.04	0.22	5.34	6.60	0.19	2.80	0.30	0.53	173.21	10.94	0.80	7.28
1-Napthalene acetic acid[7]	X	X	1.89	0.91	48.25	1.78	2.09	117.21	2.13	1.96	92.30	5.79	3.61	62.36
1-Napthalene acetic acid, sodium salt[7]	X	X	0.25	0.44	173.21	6.83	0.10	1.44	8.01	0.40	5.00	15.09	0.62	4.12
Maneb[7]			0.00	0.00		1.27	2.54	200.00	0.00	0.00		1.27	2.54	200.00
Tween 20[7]			0.39	0.88	223.61	6.38	0.35	5.53	7.77	0.88	11.39	14.55	1.44	9.91
Mean (SD) for All[8]			**1.94 (2.12)**			**5.60 (2.31)**			**6.42 (2.68)**			**13.96 (4.89)**		
Range for All			**0.20-173.20**			**0.12-200.00**			**0.00-173.21**			**0.34-200.00**		
%CV for All[9]			**109.10**			**41.24**			**41.78**			**35.00**		
Mean (SD) Excluding Four Substances[8]			**2.07 (2.16)**			**5.75 (2.18)**			**6.60 (2.50)**			**14.42 (4.48)**		

Chemical	GHS[1] Cat.[2] 1	EPA[3] Cat. I	Hemorrhage			Lysis			Coagulation			Overall *In Vitro* Score		
			Mean of Exp.[4]	SD[5] of Exp.	%CV[6] of Exp.	Mean of Exp.	SD of Exp.	%CV of Exp.	Mean of Exp.	SD of Exp.	%CV of Exp.	Mean of Exp.	SD of Exp.	%CV of Exp.
Range Excluding Four Substances			**0.20-173.21**			**0.12-173.21**			**0.00-173.21**			**0.34-118.75**		
%CV Excluding Four Substances[9]			**104.43**			**38.04**			**37.78**			**31.05**		
Mean Overall *In Vitro* Score %CV for All Substances			**17.48**											
Median Overall *In Vitro* Score %CV for All Substances			**6.34**											
Mean Overall *In Vitro* Score %CV Excluding Nine Substances			**13.49**											
Median Overall *In Vitro* Score %CV Excluding Nine Substances			**5.25**											

[1]GHS = Globally Harmonized System
[2]Cat. = category
[3]EPA = U.S. Environmental Protection Agency
[4]Exp. = experiment
[5]SD = standard deviation
[6]%CV = percent coefficient of variation
[7]Data not originally presented in Gilleron et al. (1997).
[8]Mean was calculated using the values from the "Mean for 3 Eggs" column for each endpoint and the Overall *In Vitro* Score. The standard deviation was calculated based on the values in these individual columns.
[9]To avoid eliminating data for which the %CV value could not be calculated (i.e., where the mean and SD both equaled 0), the %CV values were calculated using the mean and standard deviation calculated as described in footnote 8 of this table.

3.4 Reanalysis of HET-CAM Test Method Interlaboratory Reproducibility

Generally, an analysis of interlaboratory variability has included such approaches as:

- the extent of concordance among laboratories in assigning the same regulatory classification for a particular substance (e.g., Holzhütter et al. [1996])
- a CV analysis, which is a statistical measure of the deviation of a variable from its mean (e.g., Holzhütter et al. [1996])
- ANOVA (e.g., Holzhütter et al. [1996]; ASTM [1999]), which can be used to determine if the test results obtained for an individual laboratory is significantly different from those obtained from the other laboratories
- bivariant scatter diagrams/correlation analyses for pairs of laboratories to assess the extent of divergence (e.g., Holzhütter et al. [1996])

Several of the studies included interlaboratory data for at least a subset of the substances evaluated. Using this data, the ability of the HET-CAM test method to reproducibly identify ocular corrosives and severe irritants versus nonsevere irritants (i.e., moderate and slight irritant) and nonirritants was evaluated using two approaches.

In the first approach, a qualitative assessment of reproducibility was conducted. In this evaluation, the individual laboratory *in vitro* ocular irritation classification for each substance was used to evaluate the extent of agreement among the participating laboratories in their ability to identify ocular corrosives/severe irritants versus nonsevere irritants/nonirritants. The reliability of HET-CAM was assessed separately for each study (i.e., publication) with multiple laboratory data (see CEC [1991]; Balls et al. [1995]; Spielmann et al. [1996]; Hagino et al. [1999]). In an alternative approach, the reliability of HET-CAM was assessed after pooling data across comparative studies that used the same data analysis method (e.g., IS(B)).

Substances classified, based on HET-CAM test data, as corrosive/severe irritants or nonsevere irritants/nonirritants were further classified by their *in vivo* rabbit eye test results, as determined within the GHS (UN [2003]), EPA (1996), and EU (2001) classification systems.

Because the focus of this reliability assessment is on the interlaboratory reproducibility of HET-CAM test method in identifying corrosives/severe irritants versus nonsevere irritants/nonirritants, considerable variability could exist among laboratories in their classification of substances as nonsevere irritants or nonirritants. For example, three laboratories could classify a chemical as a nonirritant and one laboratory could classify the same chemical as a moderate irritant. Within this analysis, where a nonirritant and moderate irritant classification would be placed together, this distribution of classification calls would be considered as 100% agreement between laboratories.

In the second approach, a quantitative assessment of reproducibility was determined. %CVs for test substances, where laboratory scores were available, for substances tested were reported or determined. The reproducibility of HET-CAM was assessed for studies (i.e.,

publication) where individual testing laboratory data was available (see CEC [1991]; Balls et al. [1995]; Spielmann et al. [1996]; Hagino et al. [1999]).

As discussed in Section 2.0 of the draft HET-CAM BRD, there is no standardized data collection method for HET-CAM studies and several different analysis methods have been developed (i.e., IS, Q-Score, S-Score). Therefore, the reliability assessments conducted in this section were evaluated according to each of the analysis methods described.

3.4.1 Qualitative Reanalysis of tInterlaboratory Reproducibility

3.4.1.1 *GHS Ocular Hazard Classification System*

Interlaboratory reproducibility for the HET-CAM test method was evaluated for the following reports: Balls et al. (1995), Spielmann et al. (1996) and Hagino et al. (1999). The agreement of classification calls among participating laboratories and its relationship to the GHS *in vivo* classification (UN [2003]) for the substances tested in each report is provided in **Table IV-15**.

The participating laboratories were in 100% agreement in regard to the GHS ocular irritancy classification for 21 (45%) of the 47 substances tested when using the Q-Score (Balls et al. 1995). The extent of agreement between testing laboratories was greatest for substances identified from *in vivo* rabbit eye data as GHS corrosives or severe irritants when compared to any other combination of *in vivo* and *in vitro* results (60% [9/15] accurately identified severe substances were shown to have 100% classification agreement among testing laboratories). Comparatively, greater disparity between individual substance classifications was observed for substances that were identified as false positives (i.e., positive *in vitro* but negative *in vivo*) and those substances accurately classified as nonsevere irritants. For instance, 56% (9/16) of the false positives and 58% (7/12) of the correctly identified nonsevere irritants exhibited less than 100% agreement in the GHS irritancy classifications among laboratories.

In addition to the Q-Score, Balls et al. (1995) evaluated irritancy potential for some substances by using an S-Score. The participating laboratories were in 100% agreement in regard to the GHS ocular irritancy classification (corrosive/severe irritant or nonsevere irritant/nonirritant) for 13 (68%) of the 19 tested substances. Substances that were classified as false negatives (i.e., negative *in vitro* but positive not *in vivo*) and false positives were shown to exhibit the most discordant results, with 29% (2/7) of the false negatives and 100% (2/2) of the false positives exhibiting less than 100% classification agreement between testing laboratories. There was 100% agreement among testing laboratories for substances classified as severe irritants or nonsevere/nonirritants, based on the GHS classification system (UN 2003).

3464 **Table IV-15. Evaluation of the Reliability of the HET-CAM Test Method In Predicting Ocular Corrosives and Severe**
3465 **Irritants as Defined by the GHS[1] Classification System, by Study**
3466

Report	Anal[2]	Classification (*In Vivo*/*In Vitro*)[3]	# of Labs	N[4]	Substances with 100% Agreement among Labs	Substances with 80% Agreement among Labs	Substances with 75% Agreement among Labs	Substances with 66% Agreement among Labs	Substances with 60% Agreement among Labs	Substances with ≤50% Agreement among Labs
Balls et al. (1995)	Q	+/+	2 4	4 11	3 (75%)[5] 6 (55%)	-	- 4 (36%)	-	-	1 (25%) 1 (9%)
		+/-	-	-	-	-	-	-	-	-
		-/+	4	16	4 (25%)	-	9 (56%)	-	-	3 (19%)
		-/-	2 4	1 11	1 (100%) 4 (36%)	-	- 7 (64%)	-	-	-
		?/-	2	1	1 (100%)	-	-	-	-	-
		?/+	3 4	1 2	1 (100%) 1 (50%)	-	- 1 (50%)	-	-	-
		Total	2-4	47	21 (45%)	-	21 (45%)	-	-	5 (10%)
Balls et al. (1995)	S	+/+	2	4	4 (100%)	-	-	-	-	-
		+/-	2 3 4	1 4 2	1 (100%) 2 (50%) 2 (100%)	-	-	- 2 (50%) -	-	-
		-/+	2 4	1 1	-	-	-	-	-	1 (100%) 1 (100%)
		-/-	3 4	1 2	1 (100%) 2 (100%)	-	-	-	-	-
		?/-	3	1	-	-	-	1 (100%)	-	-
		?/+	2	2	1 (50%)	-	-	-	-	1 (50%)
		Total	2-4	19	13 (68%)	-	-	3 (16%)	-	3 (16%)
Spielmann et al. (1996)	IS(B)-10	+/+	2 3	18 1	16 (89%) -	- -	- -	- 1 (100%)	- -	2 (11%) -
		+/-	2 3	4 1	4 (100%) -	- -	- -	- 1 (100%)	- -	- -
		-/+	2 3	16 2	7 (44%) 1 (50%)	- -	- -	- -	- -	9 (56%) 1 (50%)
		-/-	2 3	31 2	30 (97%) 1 (50%)	- -	- -	- 1 (50%)	- -	1 (3%) -

Report	Anal[2]	Classification (*In Vivo*/*In Vitro*)[3]	# of Labs	N[4]	Substances with 100% Agreement among Labs	Substances with 80% Agreement among Labs	Substances with 75% Agreement among Labs	Substances with 66% Agreement among Labs	Substances with 60% Agreement among Labs	Substances with ≤50% Agreement among Labs
		?/-	2 3	10 2	10 (100%) 1 (50%)	- -	- -	- 1 (50%)	- -	- -
		?/+	2 3	16 4	14 (88%) 1 (25%)	- -	- -	- 2 (50%)	- -	2 (11%) 1 (25%)
		Total		107	85 (79%)			5 (5%)		16 (15%)
Spielmann et al. (1996)	IS(B) -100	+/+	2 3	17 2	16 (94%) 1 (50%)	- -	- -	- 1 (50%)	- -	1 (6%) -
		+/-	2	2	2 (100%)	-	-	-	-	-
		-/+	2 3	27 4	20 (74%) 1 (25%)	- -	- -	- 3 (75%)	- -	7 (26%) -
		-/-	2	17	16 (94%)	-	-	-	-	1 (6%)
		?/-	2 3	6 2	6 (100%) 2 (100%)	- -	- -	- -	- -	- -
		?/+	2 3	18 4	15 (83%) 2 (50%)	- -	- -	- 2 (50%)	- -	3 (17%) -
		Total		99	81 (82%)			6 (6%)		12 (12%)
Hagino et al. (1999)	IS(A)	+/+	5	8	5 (63%)	2 (25%)	-	-	1 (12%)	-
		+/-	-	-			-	-	-	-
		-/+	5	3	3 (100%)		-	-	-	-
		-/-	5	4	1 (25%)	1 (25%)	-	-	2 (50%)	-
		?/-	-	-			-	-	-	-
		?/+	5	2	2 (100%)		-	-	-	-
		Total	2-4	17	11 (64%)	3 (18%)	-	-	3 (18%)	-

[1]GHS = Globally Harmonized System (UN [2003]).

[2]Anal = analysis method used to transform the sample data into HET-CAM scores. IS(A) = method described in Luepke (1985); Q = Q-Score, method described in Balls et al. (1995); S = S-Score, method described in Balls et al. (1995).

[3]A "+" indicates that the substance was assigned an overall classification of corrosive or a severe irritant (Category 1); a "-" indicates that the substance was assigned an overall classification of nonsevere irritant (Category 2A or 2B) or nonirritant; a "?" indicates that, due to the lack of appropriate *in vivo* data (e.g., studies were terminated too early to assess reversibility of effects; insufficient dose volume), a GHS classification could not be made. See Section 6.1 of the Draft HET-CAM BRD for a description of the rules followed to classify the ocular irritancy of test substances tested multiple times *in vitro*.

[4]N indicates number of substances.

[5]Number in parentheses indicates percentage of tested chemicals.

The participating laboratories were in 100% agreement in regard to the GHS ocular irritancy classification for 85 (79%) of the 107 substances tested when using the IS(B)-10 analysis method (Spielmann et al. [1996]). The extent of agreement between testing laboratories was greatest for substances correctly identified as GHS nonsevere irritants or nonirritants by HET-CAM (94% [31/33]. Substances listed as "-/-" were shown to have 100% classification agreement among testing laboratories. Comparatively, greater disparity between individual substance classifications was observed for substances that were identified as false positives (56% [10/18] false positive had less than 100% concordance between testing laboratories).

For the IS(B)-100 analysis method (Spielmann et al. 1996), the participating laboratories were in 100% agreement in regard to the GHS ocular irritancy classification for 81 (82%) of the 99 substances tested. As with the IS(B)-10 analysis method, the extent of agreement between testing laboratories was greatest for substances correctly identified as GHS nonsevere irritants or nonirritants by HET-CAM (94% [16/17]). Substances listed as "-/-" were shown to have 100% classification agreement among testing laboratories. Greater disparity between individual substance classifications was observed for substances that were identified as false positives (32% [10/31] false positive had less than 100% concordance between testing laboratories).

For the report by Hagino et al. (1999), the analysis was not affected by the information received subsequent to the release of the draft BRD on November 1, 2004. All the information presented here are the same as previously described in the draft HET-CAM BRD.

The overall reliability statistics, arranged by HET-CAM data analysis method, for the S-Score, Q-Score, and IS(A) methods are similar to what was described previously in the draft HET-CAM BRD.

3.4.1.2 *EPA Ocular Hazard Classification System*

Reliability analyses for the HET-CAM test method were evaluated for the following two reports: Balls et al. (1995), Spielmann et al. (1996), and Hagino et al. (1999). The agreement of classification calls among participating laboratories and its relationship to the EPA (1996) *in vivo* classification for the substances tested in each report is provided in **Table IV-16**.

The participating laboratories were in 100% agreement in regard to the EPA ocular irritancy classification for 21 (45%) of the 47 substances tested when using the Q-Score. The agreement concordance among laboratories was greatest for accurately identified corrosives/severe irritants when compared to any other combination of *in vivo* and *in vitro* results (70% [7/10] of the accurately identified corrosives/severe irritants exhibited 100% classification agreement among laboratories). Comparatively, greater disparity between individual laboratory substance classifications was observed for substances that were identified as false positives and those substances accurately classified as nonsevere irritants/nonirritants. For instance, 76% (13/17) of the false positives and 58% (7/12) of the correctly identified EPA nonsevere irritants/nonirritants exhibited less than 100% agreement in irritancy classifications among laboratories.

3521 **Table IV-16. Evaluation of the Reliability of the HET-CAM Test Method In Predicting Ocular Corrosives and Severe**
3522 **Irritants as Defined by the EPA[1] Classification System, by Study**
3523

Report	Anal[2]	Classification (*In Vivo*/*In Vitro*)[3]	# of Labs	N[4]	Substances with 100% Agreement among Labs	Substances with 80% Agreement among Labs	Substances with 75% Agreement among Labs	Substances with 66% Agreement among Labs	Substances with 60% Agreement among Labs	Substances with 50% or Less Agreement among Labs
Balls et al. (1995)	Q	+/+	2 4	4 10	3 (75%)[5] 7 (70%)	-	- 3 (30%)	-	-	1 (25%)
		+/-	-	-	-	-	-	-	-	-
		-/+	4	17	4 (24%)	-	9 (52%)	-	-	4 (24%)
		-/-	2 4	1 11	1 (100%) 4 (36%)	-	- 7 (64%)	-	-	-
		?/-	2	1	1 (100%)	-		-	-	-
		?/+	3 4	1 2	1 (100%)	-	- 2 (50%)	-	-	-
		Total	2-4	47	21 (45%)	-	21 (45%)	-	-	5 (10%)
Balls et al. (1995)	S	+/+	2	3	3 (100%)	-	-	-	-	-
		+/-	3 4	3 2	2 (66%) 2 (100%)	-	-	1 (33%) -	-	-
		-/+	2 4	1 1	-	-	-	-	-	1 (100%) 1 (100%)
		-/-	3 4	1 2	1 (100%) 2 (100%)	-	-	-	-	-
		?/-	2 3	1 2	1 (100%)	-	-	- 2 (100%)	-	-
		?/+	2	2	1 (50%)	-	-	-	-	1 (50%)
		Total	2-4	18	12 (66%)	-	-	3 (17%)	-	3 (17%)
Spielmann et al. (1996)	IS(B)-10	+/+	2 3	9 1	8 (89%) -	- -	- -	- 1 (100%)	- -	1 (11%) -
		+/-	2	3	3 (100%)	-	-	-	-	-
		-/+	2 3	18 3	9 (50%) 1 (33%)	- -	- -	- 1 (33%)	- -	9 (50%) 1 (33%)
		-/-	2 3	31 2	31 (100%) 1 (50%)	- -	- -	- 1 (50%)	- -	- -

Report	Anal[2]	Classification (*In Vivo*/*In Vitro*)[3]	# of Labs	N[4]	Substances with 100% Agreement among Labs	Substances with 80% Agreement among Labs	Substances with 75% Agreement among Labs	Substances with 66% Agreement among Labs	Substances with 60% Agreement among Labs	Substances with 50% or Less Agreement among Labs
		?/-	2 3	10 3	10 (100%) 1 (33%)	- -	- -	- 2 (66%)	- -	- -
		?/+	2 3	21 3	19 (90%) 1 (33%)	- -	- -	- 1 (33%)	- -	2 (10%) 1 (33%)
		Total	2-3	104	84 (81%)			6 (6%)		14 (13%)
Spielmann et al. (1996)	IS(B)-100	+/+	2 3	10 1	9 (90%) 1 (100%)	- -	- -	- -	- -	1 (10%) -
		+/-	2	1	1 (100%)	-	-	-	-	-
		-/+	2 3	29 4	22 (76%) 1 (25%)	- -	- -	- 3 (75%)	- -	7 (24%) -
		-/-	2 3	17 1	16 (94%) 1 (100%)	-	-	-	-	1 (6%) -
		?/-	2 3	7 1	7 (100%) 1 (100%)	- -	- -	- -	- -	- -
		?/+	2 3	21 5	19 (90%) 2 (40%)	- -	- -	- 3 (60%)	- -	2 (10%) -
		Total	2-3	97	80 (82%)			6 (6%)		11 (11%)
Hagino et al. (1999)	IS(A)	+/+	5	7	5 (71%)	2 (29%)	-	-	-	-
		+/-	-	-	-	-	-	-	-	-
		-/+	5	4	4 (100%)	-	-	-	-	-
		-/-	5	3	1 (33%)	-	-	-	2 (66%)	-
		?/-	-	-	-	-	-	-	-	-
		?/+	5	2	1 (50%)	-	-	-	1 (50%)	-
		Total	-	16	11 (69%)	3 (27%)	-	-	3 (27%)	-

[1]EPA = U.S. Environmental Protection Agency (EPA [1996]).

[2]Anal = analysis method used to transform the sample data into HET-CAM scores. IS(A) = method described in Luepke (1985); Q = Q-Score, method described in Balls et al. (1995); S = S-Score, method described in Balls et al. (1995).

[3]A "+" indicates that the substance was assigned an overall classification of corrosive or a severe irritant (Category I); a "-" indicates that the substance was assigned an overall classification of nonsevere irritant (Category II, III, or IV); a "?" indicates that, due to the lack of appropriate *in vivo* data (e.g., studies were terminated too early to assess reversibility of effects; insufficient dose volume), an EPA classification could not be made. See Section 6.1 of the Draft HET-CAM BRD for a description of the rules followed to classify the ocular irritancy of test substances tested multiple times *in vitro*.

[4]N indicates number of substances.
[5]Number in parentheses indicates percentage of tested chemicals.

In addition to the Q-Score, Balls et al. (1995) evaluated irritancy potential for some substances by using an S-Score. The participating laboratories were in 100% agreement in regard to the EPA ocular irritancy classification for 12 (66%) of the 18 tested substances. Substances that were classified as false negatives and false positives exhibited the most discordant results, with 20% (1/5) of false negatives and 100% (2/2) of false positives exhibiting less than 100% agreement among laboratories. Complete agreement was observed for all the substances that were classified as EPA corrosives/severe irritants (3/3) or as EPA nonsevere irritants/nonirritants (3/3).

The participating laboratories were in 100% agreement in regard to the EPA ocular irritancy classification 84 of the 104 (81%) substances tested when using the IS(B)-10 analysis method (Spielmann et al. 1996). The extent of agreement between testing laboratories was greatest for substances correctly identified as GHS nonsevere irritants or nonirritants by HET-CAM (100% [31/31]. Substances listed as "-/-" were shown to have 100% classification agreement among testing laboratories. Comparatively, greater disparity between individual substance classifications was observed for substances that were identified as false positives (52% [11/21] false positive had less than 100% concordance between testing laboratories). For the IS(B)-100 analysis method (Spielmann et al. [1996]), the participating laboratories were in 100% agreement in regard to the GHS ocular irritancy classification for 80 (82%) of the 97 substances tested. As with the IS(B)-10 analysis method, the extent of agreement between testing laboratories was greatest for substances correctly identified as GHS nonsevere irritants or nonirritants by HET-CAM (94% [17/18]). Substances listed as "-/-" were shown to have 100% classification agreement among testing laboratories. Greater disparity between individual substance classifications was observed for substances that were identified as false positives (33% [10/33] false positive had less than 100% concordance between testing laboratories).

For the report by Hagino et al. (1999), there was 100% agreement in regard to the EPA ocular irritancy classification for 11 (69%) of the 16 substances. Significant discordance in the classification results was observed for substances that were correctly identified as EPA nonsevere irritants/nonirritants. Of the three correctly identified EPA nonsevere irritants/nonirritants, two substances had less than 100% classification agreement among the laboratories. For EPA severe irritants, there was 100% laboratory agreement for 71% (5/7) of the tested substances.

The overall reliability statistics, arranged by HET-CAM data analysis method, for the S-Score, Q-Score, and IS(A) methods are similar to what was described previously in the draft HET-CAM BRD.

3.4.1.3 *EU Ocular Hazard Classification System*

Reliability analyses for the HET-CAM test method were evaluated for the following two reports: CEC (1991), Balls et al. (1995), Spielmann et al. (1996), and Hagino et al. (1999). The agreement of classification calls among participating laboratories and its relationship to the EU (2001) *in vivo* classification for the substances tested in each report is provided in **Table IV-17**.

3578 **Table IV-17. Evaluation of the Reliability of the HET-CAM Test Method In Predicting Ocular Corrosives and Severe**
3579 **Irritants (as Defined by the EU[1] Classification System), by Study**
3580

Report	Anal[2]	Classification (*In Vivo*/*In Vitro*)[3]	# of Labs	N[4]	Substances with 100% Agreement among Labs	Substances with 75-99% Agreement among Labs	Substances with 50-74% Agreement among Labs	Substances with 25-49% Agreement among Labs
Balls et al. (1995)	Q	+/+	2 4	4 9	3 (75%)[5] 6 (67%)	- 3 (37%)	1 (25%)	-
		+/-	-	-	-	-	-	-
		-/+	4	14	4 (28%)	7 (50%)	3 (21%)	-
		-/-	2 4	1 11	1 (100%) 4 (36%)	- 7 (63%)	-	-
		?/-	2	1	1 (100%)	-	-	-
		?/+	3 4	1 6	1 (100%) 1 (17%)	- 4 (67%)	- 1 (17%)	-
		Total	2-4	47	21 (47%)	21 (47%)	5 (6%)	-
Balls et al. (1995)	S	+/+	2	3	3 (100%)	-	-	
		+/-	2 3 4	1 3 2	1 (100%) 2 (66%) 2 (100%)	-	- 1 (33%)	
		-/+	2 4	1 1	-	-	1 (100%) 1 (100%)	
		-/-	3 4	1 2	1 (100%) 2 (100%)	-	-	
		?/-	3	2	-	-	2 (100%)	
		?/+	2	2	1 (50%)	-	1 (50%)	
		Total	2-4	18	12 (66%)	-	6 (34%)	
CEC (1991)	IS(B)	+/+	3 5 6	3 1 2	3 (100%) - -	- - 1 (50%)	- 1 (100%) 1 (50%)	- - -
		+/-	7	1	-	1 (100%)	-	-
		-/+	3 7	3 6	- -	- 1 (17%)	1 (33%) 2 (34%)	2 (66%) 3 (51%)
		-/-	3 7	6 4	3 (50%) -	- 2 (50%)	2 (33%) 2 (50%)	1 (17%) -
		?/-	-	-	-	-	-	-

Report	Anal[2]	Classification (*In Vivo*/*In Vitro*)[3]	# of Labs	N[4]	Substances with 100% Agreement among Labs	Substances with 75-99% Agreement among Labs	Substances with 50-74% Agreement among Labs	Substances with 25-49% Agreement among Labs
		?/+	-	-	-	-	-	-
		Total	3-7	26	6 (23%)	5 (19%)	9 (35%)	6 (23%)
Spielmann et al. (1996)	IS(B)-10	+/+	2 3	12 1	11 (92%) -	- -	1 (8%) 1 (100%)	- -
		+/-	2	3	3 (100%)	-	-	-
		-/+	2 3	17 2	7 (41%) 1 (50%)	- -	- 1 (50%)	10 (59%) -
		-/-	2 3	31 2	30 (97%) 1 (50%)	- -	1 (3%) 1 (50%)	- -
		?/-	2 3	11 3	11 (100%) 1 (33%)	- -	- 2 (66%)	- -
		?/+	2 3	20 4	18 (90%) 1 (25%)	-	2 (10%) 2 (50%)	- 1 (25%)
		Total	2-3	106	84 (79%)		11 (10%)	11 (10%)
Spielmann et al. (1996)	IS(B)-100	+/+	2 3	12 1	11 (92%) 1 (100%)	- -	1 (8%) -	- -
		+/-	2	1	1 (100%)	-	-	-
		-/+	2 3	28 4	21 (75%) 1 (25%)	- -	- 3 (75%)	7 (25%) -
		-/-	2	17	16 (94%)	-	-	1 (6%)
		?/-	2 3	7 2	7 (100%) 2 (100%)	- -	- -	- -
		?/+	2 3	21 2	18 (86%) 2 (100%)	- -	- -	3 (24%) -
		Total	2-3	95	80 (84%)		4 (4%)	11 (11%)
Hagino et al. (1999)	IS(A)	+/+	5	7	6 (86%)	2 (14%)	-	-
		+/-	-	-	-	-	-	-
		-/+	5	5	3 (60%)	1 (20%)	1 (20%)	-
		-/-	5	3	-	1 (25%)	2 (50%)	-
		?/-	-	-	-	-	-	-
		?/+	5	2	2 (100%)	-	-	-
		Total	2-4	17	11 (64%)	4 (24%)	3 (18%)	-

3581

[1]EU = European Union (EU [2001]).
[2]Anal = analysis method used to transform the sample data into HET-CAM scores. IS(A) = method described in Luepke (1985); Q = Q-Score, method described in Balls et al. (1995); S = S-Score, method described in Balls et al. (1995).
[3]A "+" indicates that the substance was assigned an overall classification of corrosive or severe irritant (Category R41); a "-" indicates that the substance was assigned an overall classification of nonsevere irritant (Category R36) or nonirritant; a "?" indicates that, due to the lack of appropriate *in vivo* data (i.e., insufficient dose volume), an EU classification could not be made. See Section 6.1 of the Draft HET-CAM BRD for a description of the rules followed to classify the ocular irritancy of test substances tested multiple times *in vitro*.
[4]N indicates number of substances.
[5]Number in parentheses indicates percentage of tested chemicals.

The participating laboratories were in 100% agreement in regard to the EU ocular irritancy classification for 21 (45%) of the 47 substances tested when using the Q-Score. The extent of agreement among laboratories was greatest for accurately identified EU corrosives/severe irritants when compared to any other combination of *in vivo* and *in vitro* results (69% [9/13] of the identified EU corrosives/severe irritants exhibited 100% classification agreement among laboratories). Comparatively, greater disparity between individual substance classifications was observed for substances that were identified as false positives and those substances accurately classified as EU nonsevere irritants/nonirritants. For instance, 71% (10/14) of the false positives and 58% (7/12) of the correctly identified EU nonsevere irritants/nonirritants exhibited less than 100% agreement among laboratories in irritancy classifications.

In addition to the Q-Score, Balls et al. (1995) evaluated irritancy potential for some substances by using an S-Score. The participating laboratories were in 100% agreement in regard to the EU ocular irritancy classification for 12 (66%) of the 18 tested substances. Substances that were classified as false positives exhibited the most discordant results, with 100% (2/2) of false positives exhibiting less than 100% classification agreement among laboratories.

For the CEC evaluation, the participating laboratories were in 100% agreement in regard to the EU ocular irritancy classification for 6 (23%) of the 26 substances tested when using the IS(B) analysis method. The extent of agreement among laboratories was greatest for accurately identified EU corrosives/severe irritants when compared to any other combination of *in vivo* and *in vitro* results (50% [3/6] of the identified EU corrosives/severe irritants exhibited 100% classification agreement among laboratories). Comparatively, greater disparity between individual substance classifications was observed for substances that were identified as false positives and those substances accurately classified as EU nonsevere irritants/nonirritants. For instance, 100% (9/9) of the false positives and 70% (7/10) of the correctly identified EU nonsevere irritants/nonirritants exhibited less than 100% agreement among laboratories in irritancy classifications.

The participating laboratories were in 100% agreement in regard to the EPA ocular irritancy classification 84 of the 106 (79%) substances tested when using the IS(B)-10 analysis method (Spielmann et al. [1996]). The extent of agreement between testing laboratories was greatest for substances correctly identified as GHS nonsevere irritants or nonirritants by HET-CAM (93% [31/33]). Substances listed as "-/-" were shown to have 100% classification agreement among testing laboratories. Comparatively, greater disparity between individual substance classifications was observed for substances that were identified as false positives (58% [11/19] false positive had less than 100% concordance between testing laboratories).

For the IS(B)-100 analysis method (Spielmann et al. [1996]), the participating laboratories were in 100% agreement in regard to the GHS ocular irritancy classification for 80 (84%) of the 95 substances tested. As with the IS(B)-10 analysis method, the extent of agreement between testing laboratories was greatest for substances correctly identified as GHS nonsevere irritants or nonirritants by HET-CAM (94% [16/17]). Substances listed as "-/-"

were shown to have 100% classification agreement among testing laboratories. Greater disparity between individual substance classifications was observed for substances that were identified as false positives (33% [10/33] false positive had less than 100% concordance between testing laboratories).

For the report by Hagino et al. (1999), there was 100% agreement in regard to the EU ocular irritancy classification for 11 (64%) of the 17 substances. Significant discordance in the classification results was observed for substances that were correctly identified as EU nonsevere irritants/nonirritants. Of the three correctly identified EU nonsevere irritants/nonirritants, all substances exhibited less than 100% classification agreement among laboratories. Of the seven correctly identified EU corrosives/severe irritants, six substances (86%) produced the same classification in all five laboratories. Another group of substances that showed a high degree of agreement among laboratories were false positive substances (60% [3/5]).

The overall reliability statistics, arranged by HET-CAM data analysis method, for the S-Score, Q-Score, and IS(A) methods are similar to what was described previously in the draft HET-CAM BRD.

3.4.2 Quantitative Reanalysis of Interlaboratory Reproducibility

3.4.2.1 *CEC (1991)*

Between three and five laboratories evaluated each substance tested in this report. For this evaluation, only substances tested by five laboratories were assessed. CEC (1991) used the IS(B) analysis method. The average and median %CV values for these substances were altered based on removal of some substances, whose *in vivo* classification were not based on *in vivo* rabbit data. The reanalysis is shown in **Table IV-18**.

3.4.2.2 *Balls et al. (1995)*

Individual laboratory results for tested substances were obtained from ECVAM. Balls et al. (1995) used two different analysis methods; the S-Score and Q-Score. The average and median %CV values for all the substances evaluated with the Q-Score and S-Score were not affected by the information received subsequent to the release of the draft BRD on November 1, 2004 (**Table IV-19** and **Table IV-20**).

Table IV-18. %CV[1] Values for Substances Evaluated Using the IS(B) Analysis Method (from CEC [1991])

Substance[2]	Conc.[3]	IS(B) Value	SD[4]	%CV Values
2-Butoxyethyl acetate	100%	4.76	0.31	6.6
Butanol	100%	11.44	1.0	8.7
Triacetin	100%	4.18	0.91	21.8
Glycerol	100%	9.32	2.62	28.1
Tributyltin chloride	100%	8.94	2.88	32.2
Dimethyl sulfoxide	100%	9.88	3.24	32.8
Sodium dodecyl sulfate	100%	10.02	3.33	33.3
Triethanolamine	100%	8.52	2.94	34.6
Toluene	100%	11.04	4.31	39.1
2-Methoxyethanol	100%	9.14	3.72	40.7
n-Hexane	100%	5.04	3.16	62.8
Brij 35	100%	5.58	4.18	74.9
Mean	**-**	**-**	**-**	**34.6**
Median	**-**	**-**	**-**	**33.1**
Range	**-**	**-**	**-**	**6.6-74.9**

[1]%CV = percent coefficient of variation.
[2]Substances organized by increasing %CV values.
[3]Conc. = concentration tested.
[4]SD = standard deviation.

The average and median %CV values for GHS Category 1 substances (UN 2003), based on *in vivo* results, were 36.26 and 38.93 for the Q-Score. The average and median %CV values for EPA Category I substances (EPA [1996]), based on *in vivo* results, were 33.59 and 34.81 for the Q-Score. The average and median %CV values for GHS Category 1 and EPA Category I substances evaluated using the S-Score were not affected by the information received subsequent to the release of the draft BRD (**Table IV-19** and **Table IV-20**).

3.4.2.3 *Spielmann et al. (1996)*

Individual laboratory results on tested substances were provided by Drs. Spielmann and Liebsch in response to a request by NICEATM. The data provided were for test substances, evaluated using the IS(B) analysis method and published in Spielmann et al. (1996). In the evaluation, substances were evaluated at a 10% and 100% concentration in at least two different testing laboratories. Therefore, evaluation of the reliability of the test method was conducted for each concentration tested. Additionally, in order to resolve discrepancies in results between testing laboratories, some substances were tested in one additional testing laboratory (substances are italicized in **Table IV-21**). In order to determine if the substance tested in three laboratories affected the overall %CV values, an evaluation of the overall %CV values was conducted with these substances removed.

The average and median %CV values for substances tested at 10% concentration were 60.17 and 42.65, respectively. For substances tested at 100% concentration, the average and

3700 **Table IV-19. %CV[1] Values for Substances Evaluated Using the Q-Score Analysis**
3701 **Method (from Balls et al. [1995])**
3702

Substance[2]	Conc.[3]	GHS[4] Category 1	EPA[5] Category I	Mean Q-Score	SD[6]	%CV Values
2,2-Dimethylbutanoic acid	-	-	X	12.78	1.93	15.09
Trichloroacetic acid	30%	X	X	12.32	1.89	15.35
Benzalkonium chloride	1%	X	X	4.18	0.68	16.29
Sodium hydroxide	1%	-	-	5.42	0.99	18.20
Butyl acetate	-	-	-	1.63	0.31	18.95
Methyl cyanoacetate	-	-	-	1.38	0.34	24.84
Sodium lauryl sulfate	-	-	-	2.12	0.53	25.25
Triton X-100	5%	-	-	2.25	0.61	27.14
Octanol	-	-	-	1.67	0.47	28.15
Cyclohexanol	-	X	X	4.91	1.42	29.01
Benzalkonium chloride	10%	X	X	5.59	1.72	30.68
Ethyl-2-methylacetoacetate	-	-	-	2.09	0.66	31.74
Methyl isobutyl ketone	-	-	-	1.67	0.53	31.76
Cetylpyridinium bromide	6%	X	-	2.29	0.75	32.56
Triton X-100	10%	-	-	2.32	0.82	35.62
Hexanol	-	-	-	3.88	1.45	37.40
Methyl ethyl ketone	-	-	-	4.60	1.72	37.45
Toluene	-	-	-	3.73	1.41	37.98
Sodium lauryl sulfate	15%	X	X	2.84	1.11	38.93
Cetylpyridinium bromide	10%	X	X	2.98	1.21	40.60
Parafluoraniline	-	-	-	3.55	1.57	44.31
Polyethylene glycol 400	-	-	-	1.03	0.46	44.41
Pyridine	-	X	**X**	8.74	3.88	44.42
Tween 20	-	**X**	-	0.58	0.27	45.98
Sodium hydroxide	10%	X	X	13.44	6.74	50.12
Isobutanol	-	-	-	3.82	1.98	51.99
Trichloroacetic acid	3%	-	-	10.79	5.68	52.67
Benzalkonium chloride	5%	X	X	4.76	2.61	54.87
Ethyl acetate	-	-	-	2.52	1.39	55.11
Methyl acetate	-	-	-	3.03	1.70	56.12
Ethanol	-	-	-	6.13	3.75	61.16
Acetone	-	-	-	10.75	7.41	68.95
Glycerol	-	-	-	0.79	0.56	70.83
Isopropanol	-	-	-	5.96	4.23	71.93
2,6-Dichlorobenzoyl chloride	-	-	-	5.85	4.23	72.44
2-Ethyl-1-hexanol	-	-	-	1.49	1.12	74.75
Ethyl trimethyl acetate	-	-	-	0.40	0.41	103.70
Gamma-butyrolactone	-	-	-	8.67	9.12	105.19
Cetylpyridinium bromide	0.1%	-	-	0.86	1.15	134.05
Methylcyclopentane	-	-	-	2.42	3.81	157.25
Mean for All Substances (n=40)	-	-	-	-	-	**49.83**

Substance[2]	Conc.[3]	GHS[4] Category 1	EPA[5] Category I	Mean Q-Score	SD[6]	%CV Values
Median for All Substances	-	-	-	-	-	**42.50**
Range for All Substances	-	-	-	-	-	**15.09-157.25**
Mean for Severe Irritants (GHS) (n=11)	-	-	-	-	-	**36.26**
Median for Severe Irritants	-	-	-	-	-	**38.93**
Range for Severe Irritants	-	-	-	-	-	**15.35-54.87**
Mean for Severe Irritants (EPA) (n=8)	-	-	-	-	-	**33.54**
Median for Severe Irritants	-	-	-	-	-	**34.81**
Range for Severe Irritants	-	-	-	-	-	**15.35-54.87**

[1]%CV = percent coefficient of variation.
[2]Substances organized by increasing %CV values.
[3]Conc. = concentration tested.
[4]GHS = Globally Harmonized System (UN [2003]).
[5]EPA = U.S. Environmental Protection Agency (EPA [1996]).
[6]SD = standard deviation.

Table IV-20. %CV[1] Values for Substances Evaluated Using the S-Score Analysis Method (from Balls et al. [1995])

Substance[2]	GHS[3] Category 1	EPA[4] Category I	Mean S-Score	Standard Deviation	%CV
4-Carboxybenzaldehyde	-	-	4	2.83	70.71
Fomasafen	-	-	5.25	3.77	71.90
1-Napthalene acetic acid	X	X	5.75	5.44	94.59
Sodium oxalate	X	X	8	5.48	68.47
Dibenzyl phosphate	-	-	8.25	9.60	116.42
Mean for All Substances (n=5)	-	-	-	-	**84.42**
Median for All Substances	-	-	-	-	**71.90**
Range for All Substances	-	-	-	-	**68.47-116.4**
Mean for Severe Irritants (GHS) (n=2)	-	-	-	-	**81.53**
Median for Severe Irritants	-	-	-	-	**81.5**
Range for Severe Irritants	-	-	-	-	**68.47-94.59**
Mean for Severe Irritants (EPA) (n=2)	-	-	-	-	**81.53**
Median for Severe Irritants	-	-	-	-	**81.5**
Range for Severe Irritants	-	-	-	-	**68.47-94.59**

[1]%CV = percent coefficient of variation.
[2]Substances organized by increasing %CV values.
[3]GHS = Globally Harmonized System (UN [2003]).
[4]EPA = U.S. Environmental Protection Agency (EPA [1996]).

3718 **Table IV-21. %CV[1] Values for Substances Evaluated Using IS(B) Analysis Method**
3719 **(from Spielmann et al. [1996])**
3720

Substance Name[2]	CASRN[3]	IS(B)-10 Mean	IS(B)-10 SD	%CV for IS(B)-10	IS(B)-100 Mean	IS(B)-100 SD	%CV for IS(B)-100
7-Acetoxyheptanal		1.55	2.19	141.42	10.95	8.56	78.14
n-Acetyl-Methionine	1115-47-5	9.85	5.30	53.84	-	-	-
Ambuphylline	5634-34-4	13.25	3.61	27.22	14.85	2.90	19.52
4-Amino-5-methoxy-2-methylbenzenesulfonic acid	6471-78-9	9.80	4.34	44.29	12.17	3.20	26.31
Anisole	100-66-3	3.65	5.16	141.42	18.80	0.42	2.26
B 25		0.00	0.00	-	0.00	0.00	-
n-Butanal	123-72-8	3.95	3.89	98.46	19.20	1.56	8.10
n-Butanol	71-36-3	13.95	6.15	44.10	16.60	5.09	30.67
Butyl carbamate	592-35-8	6.80	5.93	87.21	12.67	1.93	15.27
Caffeine sodium benzoate	8000-95-1	6.37	1.66	26.11	13.10	5.31	40.52
Caffeine sodium salicylate	8002-85-5	8.60	1.70	19.73	17.40	1.98	11.38
Camphen	79-92-5	6.00	5.66	94.28	-	-	-
Cerium-2-ethylhexanoate	24593-34-8	7.40	0.71	9.56	17.18	2.93	17.09
1-Chloroctane-8-ol		5.55	1.77	31.85	16.50	3.11	18.86
3-Cyclohexene-1-methanol	1679-51-2	10.95	1.20	10.98	18.95	0.07	0.37
DC 8		0.00	0.00	-	2.50	3.54	141.42
1,4-Dibutoxybenzene	104-36-9	2.10	2.97	141.42	-	-	-
Diepoxid 126	2386-87-0	5.50	3.38	61.42	10.53	4.82	45.78
2,5-Dimethylhexanediol	110-03-2	6.65	3.61	54.23	13.85	3.89	28.08
3,6-Dimethyloctanol		0.15	0.21	141.42	4.30	0.00	0.00
4,4-Dimethyl-3-oxo-pentanenitrile	59997-51-2	4.95	0.92	18.57	6.20	0.71	11.40
1-(2,6-dimethylphenoxy)-2-propanone	53012-41-2	7.42	9.99	134.67	11.80	7.60	64.42
Diphocars		14.70	5.09	34.63	15.10	3.96	26.22
1,2-Dodecanediol	1119-87-5	5.48	5.75	104.84	3.20	1.27	39.77
DTPA Pentasodium salt	140-01-2	15.58	0.11	0.73	19.65	0.35	1.80
Ede 140		1.70	2.40	141.42	2.30	3.25	141.42
1,2-Epoxydodecane	2855-19-8	2.05	2.90	141.42	4.95	5.02	101.42
Ethiosan		1.90	2.69	141.42	-	-	-
Ethyl butanal	97-96-1	1.80	2.55	141.42	18.05	0.92	5.09

Substance Name[2]	CASRN[3]	IS(B)-10 Mean	IS(B)-10 SD	%CV for IS(B)-10	IS(B)-100 Mean	IS(B)-100 SD	%CV for IS(B)-100
Gadopentetic acid dimeglumine salt	86050-77-3	4.70	2.40	51.15	5.70	3.54	62.03
Genomoll	115-96-8	9.30	0.14	1.52	10.75	1.20	11.18
C12/C14-Glucoside		9.57	1.01	10.57	16.50	0.20	1.21
L-Glutamic acid hydrochloride	138-15-8	12.95	1.77	13.65	13.45	2.47	18.40
Glycediol		0.90	1.27	141.42	2.04	2.06	101.21
Granuform	30525-89-4	1.45	2.05	141.42	0.00	0.00	#DIV/0!
Hexahydrofarnesyl-acetone	502-69-2	1.75	0.78	44.45	6.10	2.69	44.05
Hexamethylenetetramine	100-97-0	5.05	1.06	21.00	11.15	0.07	0.63
1,2,6-Hexanetriol	106-69-4	7.90	5.09	64.45	17.05	2.47	14.52
Hnol		0.40	0.57	141.42	4.05	2.76	68.09
Hoe MBF		0.00	0.00	-	0.18	0.25	141.42
Hydo 98		11.65	1.77	15.17	-	-	-
2-Hydroxyethyl imino disodium acetate	135-37-5	11.15	3.18	28.54	13.25	3.18	24.01
2-Hydroxyisobutyric acid	594-61-6	12.85	2.90	22.56	13.45	3.04	22.61
Hypo 20		3.60	5.09	141.42	6.51	3.38	51.92
Hypo 36		4.10	0.14	3.45	12.95	4.17	32.22
Hypo 45		5.17	5.15	99.62	8.33	3.76	45.16
Hypo 54		4.15	0.21	5.11	4.15	0.07	1.70
Hyton		15.25	2.47	16.23	18.40	0.28	1.54
Iminodiacetic acid	142-73-4	8.25	7.43	90.01	6.85	5.98	87.23
Isobornyl acetate	125-12-2	2.90	1.70	58.52	6.35	2.47	38.97
Isobutanal	78-84-2	1.05	1.48	141.42	19.70	0.42	2.15
Isodecylglucoside		13.55	5.16	38.10	14.35	5.16	35.97
Isononylaldehyde	35127-50-5	0.00	0.00	-	7.25	3.89	53.64
alpha-Ketoglutaric acid	328-50-7	18.95	0.21	1.12	19.75	0.07	0.36
alpha-Lactid	4511-42-6	8.60	6.08	70.66	3.90	2.75	70.55
L-Lysine Monohydrate	39665-12-8	9.13	1.24	13.56	13.65	4.60	33.67
3-Mercapto-1,2,4-triazole	3179-31-5	11.30	9.90	87.61	-	-	-
m-Methoxybenzaldehyde	591-31-1	3.15	1.34	42.65	12.65	1.48	11.74
Methyl acetate	79-20-9	4.35	0.07	1.63	17.95	2.62	14.58
Methylpentynol	77-75-8	13.85	2.19	15.83	16.50	5.09	30.86
N-(2-methylphenyl)-Imidodi-carbonimidic diamide	93-69-6	17.40	0.42	2.44	-	-	-

Substance Name[2]	CASRN[3]	IS(B)-10 Mean	IS(B)-10 SD	%CV for IS(B)-10	IS(B)-100 Mean	IS(B)-100 SD	%CV for IS(B)-100
2-Methyl-1-propanol	78-83-1	17.80	0.14	0.79	19.80	0.85	4.29
Methyltriglycol	112-35-6	4.50	0.57	12.57	14.75	3.18	21.57
Methyltriglycol	112-35-6	7.00	5.66	80.81	16.60	5.37	32.37
Napt		3.10	1.70	54.74	8.00	3.25	40.66
Nitro-bis-octylamide		0.85	1.20	141.42	4.05	3.46	85.55
Olak		17.50	1.98	11.31	18.25	1.77	9.69
Ölesulf		16.85	0.07	0.42	19.25	0.49	2.57
Phenylephrine hydrochloride	61-76-7	9.85	1.77	17.95	19.10	1.13	5.92
Phenylthiourea	103-85-5	2.00	2.83	141.42	1.55	2.19	141.42
Phosphonat A		6.70	0.14	2.11	6.80	4.67	68.63
Acefyllin piperazinate	18833-13-1	7.13	9.95	139.49	12.97	3.45	26.63
PO 2		2.15	3.04	141.42	0.15	0.21	141.42
Polyethylene glycol butyl ether	9004-77-7	13.30	3.39	25.52	19.25	0.07	0.37
Polyethylene glycol dimethyl ether	24991-55-7	2.05	2.90	141.42	13.70	8.63	62.97
Polyethylene glycol	25322-68-3	0.50	0.71	141.42	7.15	0.78	10.88
Polyhexamethylene guanidine		10.10	1.27	12.60	15.05	0.64	4.23
Polysolvan	7397-62-8	16.15	0.49	3.06	17.65	2.47	14.02
Potassium cyanate	590-28-3	17.30	2.12	12.26	17.65	2.47	14.02
Potassium hexacyanoferrate II	14459-95-1	16.50	1.84	11.14	11.75	7.71	65.60
Potassium hexacyanoferrate III	13756-66-2	5.23	1.45	27.74	6.08	0.53	8.73
2-Pseudojonon		5.75	4.17	72.56	5.70	2.26	39.70
RK Blau		2.00	2.83	141.42	-	-	-
Sacyclo		1.70	2.40	141.42	3.85	0.78	20.20
Sept		7.00	4.24	60.61	17.85	2.76	15.45
Trimethoxypropylsilane	1067-25-0	3.80	0.14	3.72	9.10	6.51	71.49
Trimethoxyoctylsilane	3069-40-7	5.00	4.10	82.02	9.20	1.13	12.30
Silan 165	29055-11-6	0.35	0.49	141.42	5.65	2.19	38.80
Silan 167	41453-78-5	1.40	1.84	131.32	3.50	1.70	48.49
Silan 253	18784-74-2	3.00	0.00	0.00	12.30	3.39	27.59
Sodium bisulfite	7631-90-5	13.30	0.85	6.38	18.40	2.26	12.30
Sodium sulfite	7757-83-7	12.25	1.34	10.97	14.20	2.69	18.92
Sodium cyanate	917-61-3	12.65	3.04	24.04	9.45	1.77	18.71

Substance Name[2]	CASRN[3]	IS(B)-10 Mean	IS(B)-10 SD	%CV for IS(B)-10	IS(B)-100 Mean	IS(B)-100 SD	%CV for IS(B)-100
Sodium disilicate	13870-28-5	20.20	0.71	3.50	17.40	1.13	6.50
Sodium hydrogen sulfate	7681-38-1	17.75	1.48	8.37	18.65	0.78	4.17
Sodium lauryl ether sulfate	3088-31-1	14.10	5.09	36.11	18.45	0.78	4.22
Sodium monochloroacetate	3926-62-3	3.75	5.30	141.42	13.45	3.75	27.86
Sodiumpyrosulfite	7681-57-4	14.87	2.41	16.22	14.60	3.05	20.90
4-((2-Sulfatoethyl)sulfonyl)-aniline	2494-89-5	19.05	1.48	7.79	-	-	-
TA 01946 Alkylsilan		8.80	1.70	19.28	13.10	4.38	33.47
Theophylline sodium acetate	8002-89-9	9.40	5.66	60.18	-	-	-
Tocla		16.30	4.81	29.50	16.95	4.88	28.78
Triisooctylamine	25549-16-0	0.40	0.57	141.42	9.05	7.14	78.91
2,2,3-Trimethyl-3-Cyclo-pentene-1-acetaldehyde	4501-58-0	2.60	0.42	16.32	12.20	3.54	28.98
Trioxane	110-88-3	11.33	2.93	25.91	17.90	0.14	0.79
Wessalith Slurry		6.57	4.86	74.00	9.90	8.20	82.85
Xanthinol nicotinate	437-74-1	7.65	5.16	67.48	13.20	5.94	45.00
Mean %CV Value				**60.17**			**35.21**
Median %CV Value				**42.65**			**26.22**
Range %CVs				**0-141.42**			**0-141.42**
Mean %CV Value (Minus Substances Tested in 3 Laboratories)				**58.07**			**34.62**
Median %CV Value (Minus Substances Tested in 3 Laboratories)				**31.85**			**21.57**
Range %CVs (Minus Substances Tested in 3 Laboratories)				**0-141.42**			**0-141.42**

[1]CV = coefficient of variation.
[3]CASRN = Chemical Abstract Service Registry Number.
[2]Italicized substances represent chemicals that were tested in three testing laboratories. Data for these substances were removed to determine their impact on the calculated %CV values for this data set.

median %CV values were lower: 35.21 and 26.22, respectively. When substances that were tested in three different testing laboratories were removed from the assessment, little change was seen in the mean and median %CV values for both concentrations tested (**Table IV-21**).

3.4.2.4 *Hagino et al. (1999) and Ohno et al. (1999)*

The Japanese Ministry of Health and Welfare evaluated the HET-CAM test method in five different laboratories as part of a validation effort to assess alternative ocular irritation test method. Nine, 15, and 14 cosmetic ingredients were evaluated in the first, second, and third steps of the validation study, respectively. These studies used the IS(A) analysis method to assess potential irritancy classifications. Average individual laboratory results and standard

deviations for tested substances were reported in Hagino et al. (1999). Additional information on this evaluation can be obtained from the draft HET-CAM BRD.

The average and median %CV for substances classified as GHS Category 1 (UN [2003]) for the substances described in Hagino et al. (1999)[1], which described the third validation phase, were not affected by information received subsequent to release of the draft HET-CAM BRD. The average and median %CV for substances classified as EPA Category I (EPA [1996]) were 23.86 and 26.0, respectively (see **Table IV-22**).

Table IV-22. %CV[1] Values for Substances Evaluated Using the IS(A) Analysis Method (from Hagino et al. 1999)

Substance[2]	Conc.[3]	GHS[4] Category 1	EPA[5] Category I	%CV
Acetic acid	10%	X	X	8
Potassium laurate	10%	X	X	12
Stearyltrimethylammonium chloride	10%	X	X	22
Domiphen bromide	10%	X	X	26
Butanol	10%	X		28
Di(2-ethylhexyl) sodium sulfosuccinate	10%	X	X	28
Cetyltrimethylammonium bromide	10%	X	X	32
Lactic acid	100%	X	X	39
Mean for Severe Irritants (GHS) (n=8)				**24.4**
Median for Severe Irritants				**27.0**
Range for Severe Irritants				**8-39**
Mean for Severe Irritants (EPA) (n=6)				**23.86**
Median for Severe Irritants				**26.0**
Range for Severe Irritants				**8-39**

[1]%CV = percent coefficient of variation.
[2]Substances organized by increasing %CV values.
[3]Conc. = concentration tested.
[4]GHS = Globally Harmonized System (UN [2003]).
[5]EPA = U.S. Environmental Protection Agency (EPA [1996]).

[1] Percent CV values were not determined for the other phases because average data were not provided in literature references.

3.4.3 Additional Reanalyses of Interlaboratory Reproducibility

No additional analyses of interlaboratory reproducibility were received or reviewed subsequent to the release of the draft HET-CAM BRD.

3.5 HET-CAM Test Method Historical Positive and Negative Control Data - Reanalysis

3.5.1 Data Provided by Dr. Philippe Vanparys

HET-CAM studies using 0.9% NaCl as a negative control were provided by Dr. P. Vanparys in response to a request from NICEATM. Studies were conducted with and without the use of a Test Substance Applicator (TSA). The use of a TSA, described in Gilleron et al. (1996, 1997) is a device used to contain solids and/or liquids to a specific location on the CAM.

Over 90 tests with 0.9% sodium chloride (NaCl) using the TSA and three tests with 0.9% NaCl without using TSA were provided. As shown in **Table IV-23**, time to development of endpoints and the overall irritation scores calculated were consistent and classified as nonirritants for all tests. HET-CAM studies using dimethyl formamide (DMF) and imidazole as positive controls were provided by Dr. P. Vanparys in response to a request from NICEATM. Studies were conducted with and without the use of a TSA.

Table IV-23. Comparison of Means and Standard Deviations of 0.9% NaCl[1] With and Without Use of the Test Substance Applicator

0.9% NaCl	N[2]	Hemorrhage[3] (mean ± SD[5])	Lysis[3] (mean ± SD)	Coagulation[3] (mean ± SD)	*In Vitro* Score[4] (mean ± SD)
With TSA[6]	92	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Without TSA	3	0 ± 0	0 ± 0	0 ± 0	0 ± 0

[1]NaCl = sodium chloride.
[2]N = number of tests
[3]Mean values of time until development of identified endpoint.
[4]*In Vitro* irritation score calculated as IS(B).
[5]SD = standard deviation.
[6]TSA = test substance applicator.

With the DMF studies that were conducted with the TSA, the hemorrhage endpoint was evaluated inside the TSA and outside the TSA. Of note, the time of development of the hemorrhage endpoint inside the TSA was significantly lower than the time to development of the hemorrhage endpoint outside the TSA (**Table IV-24**). The reason for the difference is not clear. Two proposed reasons for the difference in time to development, according to Dr. Vanparys, are (1) the vessels outside the TSA may open more easily than those under the TSA or (2) once the liquid is applied it the liquid accumulates around the edge of the TSA rather than between the TSA and CAM.

Table IV-24. Comparison of Means and Standard Deviations for Positive Controls Tested With and Without Test Substance Applicator

Positive Control	N[1]	Hemorrhage[2] (mean ± SD[4])	Lysis[2] (mean ± SD)	Coagulation[2] (mean ± SD)	*In Vitro* Score[3] (mean ± SD)
DMF[5]: With TSA[6]	69	0.02 ± 0.17[7]	6.93 ± 0.03	8.82 ± 15.77	15.77 ± 0.19
DMF: With TSA[3]	10	3.36 ± 0.32	6.54 ± 0.19	8.81 ± 0.04	18.71 ± 0.38
DMF: Without TSA	2	4.00 ± 0.13	6.84 ± 0.05	8.76 ± 0.08	19.60 ± 0.15
Imidazole: Without TSA	15	4.50 ± 0.39	6.84 ± 0.08	8.66 ± 0.17	20.00 ± 0.45

[1]N = number of tests.
[2]Mean values of time until development of identified endpoint.
[3]*In Vitro* irritation score calculated as IS(B).
[4] SD = standard deviation.
[5]DMF = dimethylformamide
[6]TSA = test substance applicator.
[7]Hemorrhage endpoint in studies described in the first row were evaluated inside the TSA while hemorrhage endpoint in studies described in the second row were evaluated outside the TSA.

Using the data provided by Dr. P. Vanparys, the intralaboratory reproducibility of the positive controls was evaluated. For the positive control imidazole, the %CV values were calculated for each endpoint as well as for the overall IS(B) score. The range of %CV values was 0.12-18.97 for the hemorrhage endpoint, 0.34-1.20 for the lysis endpoint, and 0.20-2.11 for the coagulation endpoint. The range of %CV values for the overall IS(B) score was 0.12-1.58. The average and median %CV values for the overall IS(B) score (last column in **Table IV-25**) were 0.97 and 0.5, respectively.

For the positive control DMF, the data where hemorrhages develop inside the TSA was evaluated. The range of %CV values was 0.00-1.27 for the lysis endpoint and 0.00-1.76 for the coagulation endpoint. For the hemorrhage endpoint, a single test produced a result other than zero for the mean and the tested eggs and the standard deviation; the %CV value for the single test was 173.94. The range of %CV values for the overall IS(B) score was 0.04-14.07. The average and median %CV values for the overall IS(B) score (last column in **Table IV-26**) were 0.59 and 0.29, respectively.

Table IV-25. Intralaboratory %CV[1] Evaluation for Imidazole

Experiment	Hemorrhage		%CV of Exp.	Lysis		%CV of Exp.	Coagulation		%CV of Exp.	Total Score		%CV of Exp.
	Mean of Exp.[2]	SD[3] of Exp.		Mean of Exp.	SD of Exp.		Mean of Exp.	SD of Exp.		Mean of Exp.	SD of Exp.	
186	4.35	0.83	18.97	6.82	0.03	0.42	8.40	0.08	0.94	19.58	0.89	4.54
190	4.91	0.02	0.47	6.91	0.03	0.42	8.74	0.05	0.52	20.56	0.09	0.45
194	4.27	0.22	5.04	6.78	0.07	1.09	8.86	0.02	0.20	19.91	0.29	1.45
214	3.95	0.08	1.90	6.89	0.02	0.25	8.76	0.03	0.34	19.60	0.10	0.50
220	4.34	0.12	2.79	6.87	0.08	1.17	8.71	0.11	1.30	19.93	0.10	0.50
269	3.84	0.32	8.35	6.92	0.02	0.33	8.73	0.03	0.34	19.49	0.31	1.58
270	4.00	0.13	3.12	6.73	0.07	1.05	8.31	0.13	1.57	19.05	0.23	1.18
274	4.25	0.10	2.46	6.83	0.05	0.76	8.54	0.03	0.41	19.62	0.17	0.88
278	4.60	0.13	2.83	6.91	0.03	0.42	8.79	0.03	0.34	20.30	0.10	0.49
281	4.56	0.01	0.25	6.92	0.01	0.17	8.75	0.02	0.20	20.24	0.03	0.12
5A	4.88	0.03	0.52	6.66	0.08	1.20	8.88	0.03	0.34	20.41	0.14	0.66
7A-9A	4.94	0.01	0.23	6.87	0.02	0.34	8.49	0.06	0.71	20.30	0.03	0.17
12A	4.93	0.01	0.12	6.81	0.03	0.37	8.54	0.08	0.88	20.28	0.09	0.43
13	4.93	0.02	0.35	6.85	0.05	0.75	8.57	0.18	2.11	20.35	0.24	1.17
14	4.76	0.03	0.56	6.87	0.02	0.34	8.81	0.07	0.79	20.44	0.09	0.43
Mean (SD)	**4.5 (0.39)**			**6.84 (0.08)**			**8.66 (0.17)**			**20.00 (0.45)**		
Range of %CV	**0.12 – 18.97**			**0.34-1.20**			**0.20-2.11**			**0.12-1.58**		
Overall %CV	**8.6**			**1.10**			**1.99**			**2.23**		
Mean Total Score %CV	**0.97**											
Median Total Score %CV	**0.50**											

[1]CV = coefficient of variation.
[2]Exp. = experiment.
[3]SD = standard deviation.

3828 **Table IV-26. Intralaboratory Analyses %CV[1] Evaluation for Dimethylformamide**
3829

Experiment	Hemorrhage		%CV of Exp.	Lysis		%CV of Exp.	Coagulation		%CV of Exp.	Total Score		%CV of Exp.
	Mean of Exp.[1]	SD[2] of Exp.		Mean of Exp.	SD of Exp.		Mean of Exp.	SD of Exp.		Mean of Exp.	SD of Exp.	
183	0.00	0.00		6.83	0.08	1.11	8.83	0.03	0.39	15.66	0.11	0.70
185	0.00	0.00		6.87	0.04	0.52	8.61	0.03	0.35	15.48	0.04	0.26
186	0.00	0.00		6.85	0.10	1.44	8.52	0.15	1.76	15.37	0.20	1.30
188	0.00	0.00		6.90	0.04	0.59	8.36	0.12	1.45	15.26	0.16	1.04
189	0.00	0.00		6.88	0.05	0.69	8.62	0.10	1.12	15.50	0.14	0.91
190	0.00	0.00		6.92	0.01	0.17	8.78	0.02	0.20	15.70	0.03	0.16
191	0.00	0.00		6.93	0.04	0.58	8.82	0.00	0.00	15.75	0.04	0.26
192	0.00	0.00		6.95	0.03	0.36	8.79	0.05	0.59	15.74	0.08	0.48
193	0.00	0.00		6.91	0.05	0.68	8.91	0.03	0.34	15.82	0.08	0.48
194	0.00	0.00		6.82	0.04	0.59	8.90	0.03	0.39	15.72	0.07	0.41
196	0.00	0.00		6.93	0.02	0.29	8.74	0.06	0.71	15.67	0.07	0.45
198	0.00	0.00		6.91	0.03	0.36	8.72	0.05	0.53	15.63	0.07	0.43
201	0.00	0.00		6.91	0.05	0.68	8.65	0.06	0.72	15.56	0.11	0.70
202	0.00	0.00		6.95	0.03	0.42	8.79	0.06	0.68	15.74	0.09	0.55
203	0.00	0.00		6.92	0.01	0.17	8.77	0.02	0.20	15.69	0.03	0.16
205	0.00	0.00		6.95	0.03	0.36	8.87	0.02	0.20	15.82	0.04	0.26
207	0.00	0.00		6.94	0.02	0.33	8.83	0.06	0.71	15.77	0.09	0.54
208	1.42	2.47	173.94	6.92	0.01	0.17	8.68	0.08	0.87	17.02	2.39	14.07
209	0.00	0.00		6.94	0.01	0.17	8.79	0.03	0.34	15.73	0.04	0.26
211	0.00	0.00		6.94	0.01	0.17	8.84	0.05	0.52	15.78	0.06	0.36
212	0.00	0.00		6.95	0.03	0.42	8.85	0.00	0.00	15.80	0.03	0.18
213	0.00	0.00		6.92	0.01	0.17	8.78	0.05	0.52	15.70	0.05	0.29
215	0.00	0.00		6.83	0.05	0.69	8.71	0.05	0.53	15.54	0.09	0.60
217	0.00	0.00		6.91	0.04	0.51	8.80	0.02	0.20	15.71	0.05	0.33
230	0.00	0.00		6.91	0.03	0.36	8.92	0.02	0.19	15.83	0.04	0.26
231	0.00	0.00		6.98	0.00	0.00	8.87	0.02	0.20	15.85	0.02	0.11
232	0.00	0.00		6.96	0.02	0.25	8.86	0.02	0.20	15.82	0.03	0.22
233	0.00	0.00		6.96	0.03	0.41	8.84	0.03	0.39	15.80	0.06	0.35
234	0.00	0.00		6.94	0.01	0.17	8.84	0.02	0.20	15.80	0.02	0.10
235	0.00	0.00		6.96	0.02	0.25	8.86	0.02	0.20	15.82	0.03	0.22
236	0.00	0.00		6.97	0.02	0.25	8.89	0.02	0.19	15.86	0.03	0.19
237	0.00	0.00		6.97	0.02	0.25	8.77	0.09	1.05	15.74	0.08	0.50

Experiment	Hemorrhage		%CV of Exp.	Lysis		%CV of Exp.	Coagulation		%CV of Exp.	Total Score		%CV of Exp.
	Mean of Exp.[1]	SD[2] of Exp.		Mean of Exp.	SD of Exp.		Mean of Exp.	SD of Exp.		Mean of Exp.	SD of Exp.	
238	0.00	0.00		6.94	0.01	0.17	8.86	0.02	0.20	15.80	0.03	0.16
240	0.00	0.00		6.97	0.02	0.25	8.87	0.02	0.20	15.84	0.03	0.22
241	0.00	0.00		6.97	0.02	0.25	8.89	0.03	0.39	15.86	0.05	0.33
242	0.00	0.00		6.94	0.01	0.17	8.87	0.02	0.20	15.81	0.03	0.18
243	0.00	0.00		6.96	0.02	0.25	8.90	0.02	0.19	15.86	0.03	0.19
244	0.00	0.00		6.95	0.03	0.36	8.90	0.03	0.39	15.85	0.06	0.37
245	0.00	0.00		6.96	0.02	0.25	8.89	0.02	0.19	15.85	0.03	0.22
251	0.00	0.00		6.93	0.06	0.90	8.81	0.07	0.79	15.74	0.13	0.83
252	0.00	0.00		6.94	0.01	0.17	8.86	0.02	0.20	15.80	0.03	0.16
253	0.00	0.00		6.95	0.03	0.36	8.84	0.08	0.85	15.79	0.09	0.57
254	0.00	0.00		6.91	0.04	0.51	8.81	0.08	0.86	15.72	0.11	0.70
255	0.00	0.00		6.93	0.00	0.00	8.81	0.05	0.52	15.74	0.05	0.29
256	0.00	0.00		6.94	0.01	0.17	8.86	0.02	0.20	15.80	0.03	0.16
257	0.00	0.00		6.93	0.02	0.29	8.84	0.02	0.20	15.77	0.04	0.23
258	0.00	0.00		6.96	0.02	0.25	8.85	0.03	0.34	15.81	0.05	0.29
259	0.00	0.00		6.93	0.04	0.58	8.85	0.08	0.90	15.78	0.12	0.76
260	0.00	0.00		6.94	0.01	0.17	8.85	0.03	0.34	15.79	0.04	0.26
261	0.00	0.00		6.95	0.03	0.36	8.86	0.05	0.52	15.81	0.07	0.45
262	0.00	0.00		6.94	0.01	0.17	8.87	0.02	0.20	15.81	0.02	0.10
263	0.00	0.00		6.94	0.02	0.33	8.86	0.02	0.20	15.80	0.04	0.22
264	0.00	0.00		6.97	0.02	0.25	8.87	0.02	0.20	15.84	0.02	0.11
265	0.00	0.00		6.96	0.02	0.25	8.88	0.03	0.34	15.84	0.05	0.29
266	0.00	0.00		6.89	0.09	1.27	8.76	0.13	1.49	15.65	0.22	1.39
267	0.00	0.00		6.94	0.01	0.17	8.84	0.02	0.20	15.78	0.02	0.10
268	0.00	0.00		6.95	0.00	0.00	8.89	0.02	0.19	15.84	0.02	0.11
269	0.00	0.00		6.95	0.00	0.00	8.89	0.02	0.19	15.84	0.02	0.11
270	0.00	0.00		6.94	0.01	0.17	8.88	0.03	0.34	15.82	0.04	0.26
271	0.00	0.00		6.94	0.01	0.17	8.84	0.02	0.20	15.78	0.01	0.04
272	0.00	0.00		6.95	0.04	0.51	8.81	0.07	0.79	15.76	0.10	0.65
273	0.00	0.00		6.95	0.03	0.42	8.85	0.03	0.34	15.80	0.06	0.36
274	0.00	0.00		6.94	0.02	0.33	8.86	0.06	0.70	15.80	0.09	0.54
275	0.00	0.00		6.96	0.02	0.25	8.89	0.02	0.19	15.85	0.02	0.11
277	0.00	0.00		6.90	0.04	0.52	8.80	0.06	0.71	15.70	0.10	0.63
278	0.00	0.00		6.94	0.02	0.33	8.82	0.03	0.34	15.76	0.05	0.33

Experiment	Hemorrhage		%CV of Exp.	Lysis		%CV of Exp.	Coagulation		%CV of Exp.	Total Score		%CV of Exp.
	Mean of Exp.[1]	SD[2] of Exp.		Mean of Exp.	SD of Exp.		Mean of Exp.	SD of Exp.		Mean of Exp.	SD of Exp.	
279	0.00	0.00		6.93	0.00	0.00	8.83	0.03	0.39	15.76	0.03	0.22
280	0.00	0.00		6.90	0.08	1.10	8.81	0.10	1.09	15.71	0.17	1.10
282	0.00	0.00		6.92	0.02	0.33	8.85	0.03	0.34	15.77	0.05	0.33
Mean (SD)	**0.02 (0.17)**			**6.93 (0.03)**			**8.82 (0.09)**			**15.77 (0.19)**		
Range[4] of %CV values	**173.94**[1]			**0.00-1.27**			**0.00-1.76**			**0.04-14.07**		
Overall %CV	**850**			**0.49**			**1.05**			**1.20**		
Mean Total Score %CV	**0.59**											
Median Total Score %CV	**0.29**											

[1]CV = coefficient of variation.
[2]Exp. = experiment.
[3]SD = standard deviation.
[4]Range is representative of a single value since CV values for other experiments could not be calculated since mean and SD values were zero.

3.5.2 Data Provided by Dr. med Horst Spielmann and Dr. Manfred Liebsch

HET-CAM studies using 1% SDS and 0.1 N NaOH were provided by Dr. med H. Spielmann and Dr. M. Liebsch in response to a request from NICEATM. Using the mean values determined for these studies, the overall irritation score calculated (according to the method of Kalweit et al. [1987, 1990]) for these substances classified them as irritants (**Table IV-27**).

Table IV-27. Means and Standard Deviations of Positive Control Test Substances

Positive Control	Hemorrhage[1] (mean ± SD[2])	Lysis[1] (mean ± SD)	Coagulation[1] (mean ± SD)
1% SDS[3] (n=377)	14.69 ± 5.36	35.18 ± 17.15	---[4]
0.1 N NaOH[5] (n=336)	8.96 ± 4.96	35.60 ± 24.71	48.04 ± 34.56

[1]Mean values of time until development of identified endpoint.
[2]SD = standard deviation.
[3]SDS = sodium dodecyl sulfate.
[4]It was indicated that 1% SDS does not produce coagulation in the CAM after application. However, in the studies conducted coagulation was identified in a single study. In these evaluations, the non-existing data was calculated with an arbitrary value of "0". Therefore, the calculation of a mean value for the coagulation endpoint was not meaningful.
[5]NaOH = sodium hydroxide.

3.6 Reliability of the HET-CAM Test Method for Identifying Ocular Corrosives and Severe Irritants – Summary of Reanlysis

Previously, an evaluation of the intralaboratory repeatability and reproducibility of the HET-CAM test method could not be conducted. However, subsequent to the original reliability analysis (see draft HET-CAM BRD, November 1, 2004), replicate data received allowed for a quantitative analysis of intralaboratory repeatability and reproducibility of HET-CAM test method endpoints.

The analysis of intralaboratory repeatability was evaluated using data from two different publications (Gilleron et al. [1996, 1997]) that were provided in response to a request from NICEATM. In both studies, the hemorrhage endpoint had a high %CV value (104-117). Additionally, the %CV values for the coagulation endpoint were the lowest of the three endpoints evaluated in the HET-CAM test method. However, the actual values were quite disparate between the two studies (e.g., Gilleron et al. [1996] coagulation %CV = 95.69; Gilleron et al. [1997] coagulation %CV = 41.78). The difference in the numbers may be due to several factors including test substances evaluated and differences in the test method protocols used between the two studies. The overall IS(B) %CV values for the two studies were 41.48 (Gilleron et al. [1996]) and 6.99 (Gilleron et al. [1997]). However, the calculated variability for the endpoints and the overall test method may be exaggerated because of the relatively small values that are obtained from each of the endpoints (5 for hemorrhage, 7 for lysis, and 9 for coagulation).

Similar results were obtained from the analysis of intralaboratory reproducibility. The overall %CV values were 53 and 17.5 for the two studies evaluated. For the study by Gilleron et al. (1997), where substances could be classified according to the GHS and EPA classification systems, %CV values for severe irritants were similar to the values obtained for the overall database.

The previous analysis also included an evaluation of interlaboratory reproducibility using both qualitative and quantitative approaches. Additional data received subsequent to the draft HET-CAM BRD allowed for a more in-depth quantitative and qualitative analysis of interlaboratory reproducibility. For the qualitative evaluation of data from Spielmann et al. (1996), 100% agreement between testing laboratories was between 80% and 85% for all the test substances. Furthermore, quantitative evaluation of the interlaboratory reproducibility for the Spielmann et al. (1996) data yielded an overall %CV value of about 35.

The previous interlaboratory reproducibility analyses also were modified based on the re-classification of substances as an ocular corrosive/severe irritant or as a non-corrosive/non-severe irritant. However, the overall results obtained in the revised analysis were not different from the original analysis.

Finally, historical positive and negative control data were provided by two different sources. The negative control substance evaluated was 0.9% NaCl. The positive control substances were DMF, imidazole, 1% SDS, and 0.1 N NaOH. The studies showed that all control substances consistently produced appropriate responses (e.g., negative control consistently produced a response that would be classified as nonirritant and positive controls consistently produced a response that would be classified as severe irritant).

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APPENDIX IV-A

SUBSTANCES USED IN THE HET-CAM TEST METHOD REANALYSIS

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Substances Used in the HET-CAM Test Method Reanalysis

Substance Name	CASRN[1]	*In Vitro* Concentration Tested	*In Vivo* Concentration Tested	Chemical Class	Form Tested	pH	Property of Interest	*In Vivo* (GHS)[2] Classification[3]	GHS Category 1 Subclass[4]	*In Vivo* (EPA)[5] Classification[6]	*In Vivo* (EU)[7] Classification[8]	*In Vitro* Classification (IS(A))[9]	*In Vitro* Classification (IS(B))[10]	*In Vitro* Classification (S-Score)[11]	*In Vitro* Classification (Q-Score)[12]	*In Vitro* Classification (IS(B)-10)[13]	*In Vitro* Classification (IS(B)-100)[14]	*In Vitro* Classifcaion (IS and ET[15]	Reference
Triethanolamine	102-71-6	10%	10%	Amine, Alcohol	Solution			Nonirritant		Category IV	Nonirritant	Severe							Bagley et al. (1992)
Triton X-100	9002-93-1	1%	1%	Ether	Solution			Nonirritant		Category III	Nonirritant	Severe							Bagley et al. (1992)
Acetone	67-64-1	100%	100%	Ketone	Liquid			Category 2A		Category II	R36				Severe				Balls et al. (1995)
Ammonium nitrate	6484-52-2	100%	100%	Inorganic salt, Onium	Solid			Category 2B		Category III	R36			Severe	Moderate				Balls et al. (1995)
L-Aspartic acid	70-47-3	100%	100%	Amino acid	Solid			SCNM[16]		SCNM	SCNM			Nonirritant	Nonirritant				Balls et al. (1995)
Benzalkonium chloride	8001-54-5	1%	1%	Onium	Solution			Category 1/Category 2A	1	Category I	R36/R41				Severe				Balls et al. (1995)
Benzalkonium chloride	8001-54-5	5%	5%	Onium	Solution			Category 1	2	Category I	R41				Severe				Balls et al. (1995)
Benzalkonium chloride	8001-54-5	10%	10%	Onium	Solution			Category 1	4	Category I	R41				Severe				Balls et al. (1995)
Benzoyl-L-tartaric acid	2743-38-6	100%	100%	Carboxylic acid, Ester	Solid			Category 1	2	SCNM	R41			Nonirritant					Balls et al. (1995)
Butyl acetate	123-86-4	100%	100%	Ester	Liquid			Nonirritant		Category III	Nonirritant				Moderate				Balls et al. (1995)
gamma-Butyrolactone	96-48-0	100%	100%	Heterocycle, Lactone	Liquid			Category 2A		Category II	R36				Severe				Balls et al. (1995)
Captan 90 concentrate	133-06-2	100%	100%	Imide, Organic sulfur compound	Solid			Category 1	4	Category I	R41			Nonirritant					Balls et al. (1995)
4-Carboxybenzaldehyde	619-66-9	100%	100%	Carboxylic acid, Aldehyde	Solid			Category 2A		Category II	R36			Moderate					Balls et al. (1995)
Cetylpyridinium bromide	140-72-7	0.1%	0.1%	Heterocyclic compounds, Onium	Solution			Nonirritant		Category III	Nonirritant				Nonirritant				Balls et al. (1995)
Cetylpyridinium bromide	140-72-7	6%	6%	Heterocyclic compounds, Onium	Solution			Category 1	2	SCNM	R41				Severe				Balls et al. (1995)
Cetylpyridinium bromide	140-72-7	10%	10%	Heterocyclic compounds, Onium	Solution			Category 1	4	Category I	R41				Severe				Balls et al. (1995)
Chlorhexidine	55-56-1	100%	100%	Amidine	Solid			Category 1	4	SCNM	SCNM			Moderate					Balls et al. (1995)
Cyclohexanol	108-93-0	100%	100%	Alcohol	Liquid			Category 1	2	Category I	R41				Severe				Balls et al. (1995)
Dibenzyl phosphate	1623-08-1	100%	100%	Ester	Solid			Category 2A		Category II	R36			Severe					Balls et al. (1995)
2,6-Dichlorobenzoyl chloride	4659-45-4	100%	100%	Acyl halide	Liquid			Category 2A		Category II	SCNM				Severe				Balls et al. (1995)
2,2-Dimethylbutanoic acid	595-37-9	100%	100%	Carboxylic acid	Liquid			SCNM		Category I	SCNM				Severe				Balls et al. (1995)
2,5-Dimethylhexanediol	110-03-2	100%	100%	Alcohol	Solid			Category 1	1	Category I	R41			Severe	Severe				Balls et al. (1995)
Ethanol	64-17-5	100%	100%	Alcohol	Liquid			Category 2A		Category III	Nonirritant				Severe				Balls et al. (1995)
Ethyl acetate	141-78-6	100%	100%	Ester	Liquid			Nonirritant		Category III	Nonirritant				Severe				Balls et al. (1995)
2-Ethyl-1-hexanol	104-76-7	100%	100%	Alcohol	Liquid			Category 2A		Category II	R36				Nonirritant				Balls et al. (1995)
Ethyl-2-methylacetoacetate	609-14-3	100%	100%	Ketone, Ester	Liquid			Category 2B		Category III	Nonirritant				Severe				Balls et al. (1995)
Ethyl trimethyl acetate	3938-95-2	100%	100%	Ester	Liquid			Nonirritant		Category III	Nonirritant				Nonirritant				Balls et al. (1995)
Fomesafen	72128-02-0	100%	100%	Imide, Ether, Nitro compound	Solid			Nonirritant		Category III	Nonirritant			Moderate					Balls et al. (1995)
Glycerol	56-81-5	100%	100%	Alcohol	Liquid			Nonirritant		Category IV	Nonirritant				Nonirritant				Balls et al. (1995)
n-Hexanol	111-27-3	100%	100%	Alcohol	Liquid			Category 2A		Category II	R36				Severe				Balls et al. (1995)
Imidazole	288-32-4	100%	100%	Heterocycle	Solid			Category 1	4	Category I	R41			Severe	Severe				Balls et al. (1995)
Isobutanol	78-83-1	100%	100%	Alcohol	Liquid			Category 2A		Category II	R36				Severe				Balls et al. (1995)
Isopropanol	67-63-0	100%	100%	Alcohol	Liquid			Category 2A		Category III	SCNM				Severe				Balls et al. (1995)
Maneb	12427-38-2	100%	100%	Amine, Organic salt, Urea	Liquid			SCNM		Category III	SCNM			Nonirritant	Nonirritant				Balls et al. (1995)
Methyl acetate	79-20-9	100%	100%	Ester	Liquid			Category 2A		Category II	R36				Severe				Balls et al. (1995)
Methyl cyanoacetate	105-34-0	100%	100%	Ester, Nitrile	Liquid			Category 2A		Category II	R36				Moderate				Balls et al. (1995)
Methylcyclopentane	96-37-7	100%	100%	Cyclic hydrocarbon	Liquid			Nonirritant		Category III	Nonirritant				Nonirritant				Balls et al. (1995)
Methyl ethyl ketone	78-93-3	100%	100%	Ketone	Liquid			Category 2A		Category III	R36				Severe				Balls et al. (1995)
Methyl isobutyl ketone	108-10-1	100%	100%	Ketone	Liquid			Nonirritant		Category III	Nonirritant				Moderate				Balls et al. (1995)
1-Naphthalene acetic acid	86-87-3	100%	100%	Carboxylic acid, Polycyclic compound	Solid			Category 1	NC	Category I	SCNM			Moderate					Balls et al. (1995)
1-Naphthalene acetic acid, Na salt	61-31-4	100%	100%	Organic salt, Carboxylic acid salt, Polycyclic compound	Solid			Category 1	1	Category I	R41			Severe	Severe				Balls et al. (1995)
n-Octanol	111-87-5	100%	100%	Alcohol	Liquid			Category 2A		Category II	R36				Moderate				Balls et al. (1995)
Parafluoraniline	371-40-4	100%	100%	Amine	Liquid			SCNM		SCNM	SCNM				Severe				Balls et al. (1995)
Polyethylene glycol 400	25322-68-3	100%	100%	Alcohol, Ether	Liquid			Nonirritant		Category IV	Nonirritant				Nonirritant				Balls et al. (1995)
Potassium cyanate	590-28-3	100%	100%	Inorganic salt	Solid			SCNM		SCNM	SCNM			Severe	Severe				Balls et al. (1995)
Promethazine HCl	58-33-3	100%	100%	Amine, Heterocycle, Organic sulfur compound	Solid			Category 1	1	Category I	R41			Severe	Severe				Balls et al. (1995)
Pyridine	110-86-1	100%	100%	Heterocycle	Liquid			Category 1	4	Category I	R41				Severe				Balls et al. (1995)
Quinacrine	69-05-6	100%	100%	Amine, Heterocycle, Polycyclic compound	Solid			Category 1	3	Category I	R41			Nonirritant					Balls et al. (1995)
Sodium hydroxide	1310-73-2	1%	1%	Alkali	Solution			Category 2B		Category III	R36				Severe				Balls et al. (1995)
Sodium hydroxide	1310-73-2	10%	10%	Alkali	Solution			Category 1	4	Category I	R41				Severe				Balls et al. (1995)
Sodium lauryl sulfate	151-21-3	3%	3%	Organic salt, Carboxylic acid salt	Solution			Nonirritant		Category III	Nonirritant				Severe				Balls et al. (1995)
Sodium lauryl sulfate	151-21-3	15%	15%	Organic salt, Carboxylic acid salt	Solution			Category 1	NC	Category I	SCNM				Severe				Balls et al. (1995)

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Sodium oxalate	62-76-0	100%	100%	Organic salt, Carboxylic acid salt	Solid			Category 1	4	Category I	R41			Moderate					Balls et al. (1995)
Sodium perborate	10486-00-7	100%	100%	Inorganic salt, Boron containing compound	Solid			Category 1	4	Category I	R41			Nonirritant					Balls et al. (1995)
Tetraaminopyrimidine sulfate	5392-28-9	100%	100%	Amine, Heterocycle	Solid			Nonirritant		Category III	Nonirritant			Nonirritant					Balls et al. (1995)
Thiourea	62-56-6	100%	100%	Organic sulfur compound	Solid									Severe	Nonirritant				Balls et al. (1995)
Toluene	108-88-3	100%	100%	Polycyclic compound	Liquid			Nonirritant		Category III	Nonirritant				Severe				Balls et al. (1995)
Trichloroacetic acid	76-03-9	3%	3%	Carboxylic acid	Solution			Nonirritant		Category III	Nonirritant				Severe				Balls et al. (1995)
Trichloroacetic acid	76-03-9	30%	30%	Carboxylic acid	Solution			Category 1	4	Category I	R41				Severe				Balls et al. (1995)
Triton X-100	9002-93-1	5%	5%	Ether	Solution			Categorry 2A/Category 2B		Category III	Nonirritant/R36				Severe				Balls et al. (1995)
Triton X-100	9002-93-1	10%	10%	Ether	Solution			Category 1	4	Category II	SCNM				Severe				Balls et al. (1995)
Tween 20	9005-64-5	100%	100%	Ester, Ether	Liquid			Nonirritant		Category III	Nonirritant				Nonirritant				Balls et al. (1995)
Acetic acid	64-19-7	100%		Carboxylic acid	Liquid						R41		Severe						CEC (1991)
Acetic acid	64-19-7	10%		Carboxylic acid	Solution						R41		Severe						CEC (1991)
Benzalkonium chloride	8001-54-5	100%		Onium	Unknown		Cationic Surfactant				R41		Severe						CEC (1991)
Brij 35	9002-92-0	100%		Alcohol	Solid		Nonionic Surfactant				Nonirritant		Slight						CEC (1991)
Butanol	71-36-3	100%		Alcohol	Liquid						R36		Severe						CEC (1991)
Butanol	71-36-3	10%		Alcohol	Solution						R36		Severe						CEC (1991)
Dimethyl sulfoxide	67-68-5	100%		Organic sulfur compound	Liquid						Nonirritant		Severe						CEC (1991)
Dimethyl sulfoxide	67-68-5	10%		Organic sulfur compound	Solution						Nonirritant		Slight						CEC (1991)
Glycerol	56-81-5	100%		Alcohol	Liquid						Nonirritant		Severe						CEC (1991)
Glycerol	56-81-5	10%		Alcohol	Solution						Nonirritant		Slight						CEC (1991)
n-Hexane	110-54-3	100%		Acyclic hydrocarbon	Liquid						Nonirritant		Slight						CEC (1991)
n-Hexane	110-54-3	10%		Acyclic hydrocarbon	Solution						Nonirritant		Severe						CEC (1991)
2-Methoxyethanol	109-86-4	100%		Alcohol	Liquid						Nonirritant		Severe						CEC (1991)
2-Methoxyethanol	109-86-4	10%		Alcohol	Solution						Nonirritant		Moderate						CEC (1991)
Sodium dodecyl sulfate	151-21-3	100%		Organic salt, Carboxylic acid salt	Solid		Anionic Surfactant				R41		Severe						CEC (1991)
Sodium dodecyl sulfate	151-21-3	10%		Organic salt, Carboxylic acid salt	Solution		Anionic Surfactant				R36		Severe						CEC (1991)
Toluene	108-88-3	100%		Polycyclic compound	Liquid						Nonirritant		Severe						CEC (1991)
Triethanolamine	102-71-6	100%		Amine, Alcohol	Liquid						Nonirritant		Severe						CEC (1991)
Triethanolamine	102-71-6	10%		Amine, Alcohol	Solution						Nonirritant		Slight						CEC (1991)
Triacetin	102-76-1	100%		Ester	Liquid						Nonirritant		Slight						CEC (1991)
Triacetin	102-76-1	10%		Ester	Solution						Nonirritant		Slight						CEC (1991)
Tributyltin chloride	1461-22-9	100%		Organometallic compound	Solid						R41		Moderate						CEC (1991)
Tributyltin chloride	1461-22-9	10%		Organometallic compound	Solution						R41		Severe						CEC (1991)
2-Butoxyethyl acetate	112-07-2	100%		Ester	Liquid						Nonirritant		Slight						CEC (1991)
2-Butoxyethyl acetate	112-07-2	10%		Ester	Solution						Nonirritant		Slight						CEC (1991)
Dibutyltin chloride	683-18-1	100%		Organic salt	Solid						R41		Severe						CEC (1991)
Hydroalcoholic Formulation 1-5% Alcohol Containing Formulation (PROD-00187)		Undiluted	Undiluted	Formulation	Solution			Nonirritant		Category III	Nonirritant		Slight						Gettings et al. (1991)
Hydroalcoholic Formulation 2-10% Alcohol Containing Formulation (PROD-00183)		Undiluted	Undiluted	Formulation	Solution			Nonirritant		Category IV	Nonirritant		Moderate						Gettings et al. (1991)
Hydroalcoholic Formulation 3-15% Alcohol Containing Formulation (PROD-00186)		Undiluted	Undiluted	Formulation	Solution			Nonirritant		Category IV	Nonirritant		Moderate						Gettings et al. (1991)
Hydroalcoholic Formulation 4-20% Alcohol Containing Formulation (PROD-00185)		Undiluted	Undiluted	Formulation	Solution			Nonirritant		Category IV	Nonirritant		Moderate						Gettings et al. (1991)
Hydroalcoholic Formulation 5-33% Alcohol Containing Formulation (PROD-00184)		Undiluted	Undiluted	Formulation	Solution			Nonirritant		Category III	Nonirritant		No Data						Gettings et al. (1991)

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Hydroalcoholic Formulation 6-40% Alcohol Containing Formulation (PROD-00189)		Undiluted	Undiluted	Formulation	Solution			Category 1	1	Category I	R41		Severe						Gettings et al. (1991)
Hydroalcoholic Formulation 7-55% Alcohol Containing Formulation (PROD-00188)		Undiluted	Undiluted	Formulation	Solution			Category 1	1	Category I	R41		Severe						Gettings et al. (1991)
Hydroalcoholic Formulation 8-65% Alcohol Containing Formulation (PROD-00180)		Undiluted	Undiluted	Formulation	Solution			Category 2B		Category II	Nonirritant		Severe						Gettings et al. (1991)
Hydroalcoholic Formulation 9-83% Alcohol Containing Formulation (PROD-00181)		Undiluted	Undiluted	Formulation	Solution			Category 2A		Category II	SCNM		Severe						Gettings et al. (1991)
Hydroalcoholic Formulation 10-90% Alcohol Containing Formulation (PROD-00182)		Undiluted	Undiluted	Formulation	Solution			Category 1	1	Category I	R41		Severe						Gettings et al. (1991)
Oil/Water Emulsion-HZA		Undiluted	Undiluted	Formulation	Solution			Nonirritant		Category III	Nonirritant	Nonirritant	Slight						Gettings et al. (1994)
Oil/Water Emulsion-HZC		Undiluted	Undiluted	Formulation	Solution			Nonirritant		Category III	Nonirritant	Nonirritant	Slight						Gettings et al. (1994)
Oil/Water Emulsion-HZE		Undiluted	Undiluted	Formulation	Solution			Nonirritant		Category IV	Nonirritant	Nonirritant	Slight						Gettings et al. (1994)
Oil/Water Emulsion-HZF		Undiluted	Undiluted	Formulation	Solution			Nonirritant		Category III	Nonirritant	Moderate	Slight						Gettings et al. (1994)
Oil/Water Emulsion-HZH		Undiluted	Undiluted	Formulation	Solution			Nonirritant		Category III	Nonirritant	Severe	Severe						Gettings et al. (1994)
Oil/Water Emulsion-HZI		Undiluted	Undiluted	Formulation	Solution			Nonirritant		Category IV	Nonirritant	Slight	Nonirritant						Gettings et al. (1994)
Oil/Water Emulsion-HZJ		Undiluted	Undiluted	Formulation	Solution			Nonirritant		Category IV	Nonirritant	Nonirritant	Slight						Gettings et al. (1994)
Oil/Water Emulsion-HZL		Undiluted	Undiluted	Formulation	Solution			Nonirritant		Category III	Nonirritant	Slight	Severe						Gettings et al. (1994)
Oil/Water Emulsion-HZM		Undiluted	Undiluted	Formulation	Solution			Nonirritant		Category III	Nonirritant	Moderate	Severe						Gettings et al. (1994)
Oil/Water Emulsion-HZN		Undiluted	Undiluted	Formulation	Solution			Nonirritant		Category IV	Nonirritant	Slight	Slight						Gettings et al. (1994)
Oil/Water Emulsion-HZO		Undiluted	Undiluted	Formulation	Solution			Nonirritant		Category IV	Nonirritant	Nonirritant	Nonirritant						Gettings et al. (1994)
Oil/Water Emulsion-HZR		Undiluted	Undiluted	Formulation	Solution			Category 1	1	Category I	R41	Severe	Severe						Gettings et al. (1994)
Oil/Water Emulsion-HZS		Undiluted	Undiluted	Formulation	Solution			Nonirritant		Category IV	Nonirritant	Severe	Moderate						Gettings et al. (1994)
Oil/Water Emulsion-HZT		Undiluted	Undiluted	Formulation	Solution			Nonirritant		Category IV	Nonirritant	Slight	Slight						Gettings et al. (1994)
Oil/Water Emulsion-HZU		Undiluted	Undiluted	Formulation	Solution			Nonirritant		Category IV	Nonirritant	Nonirritant	Slight						Gettings et al. (1994)
Oil/Water Emulsion-HZV		Undiluted	Undiluted	Formulation	Solution			Nonirritant		Category III	Nonirritant	Nonirritant	Nonirritant						Gettings et al. (1994)
Oil/Water Emulsion-HZW		Undiluted	Undiluted	Formulation	Solution			Nonirritant		Category III	Nonirritant	Nonirritant	Moderate						Gettings et al. (1994)
Oil/Water Emulsion-HZY		Undiluted	Undiluted	Formulation	Solution			Nonirritant		Category IV	Nonirritant	Severe	Severe						Gettings et al. (1994)
Surfactant Based Formulation 1-HZA		10%	Undiluted	Formulation	Solution			Category 1	1	Category I	R41	Moderate	Severe						Gettings et al. (1996)
Surfactant Based Formulation 2-HZB		10%	Undiluted	Formulation	Solution			Category 1	1	Category I	R41	Slight	Moderate						Gettings et al. (1996)
Surfactant Based Formulation 3-HZC		10%	Undiluted	Formulation	Solution			Category 1	1	Category I	R41	Severe	Severe						Gettings et al. (1996)
Surfactant Based Formulation 4-HZD		10%	Undiluted	Formulation	Solution			Category 2B		Category III	Nonirritant	Moderate	Moderate						Gettings et al. (1996)
Surfactant Based Formulation 5-HZE		10%	Undiluted	Formulation	Solution			SCNM		Category I	SCNM	Slight	Severe						Gettings et al. (1996)
Surfactant Based Formulation 6-HZF		10%	Undiluted	Formulation	Solution			Category 1	1	Category I	R41	Moderate	Severe						Gettings et al. (1996)
Surfactant Based Formulation 7-HZG		10%	Undiluted	Formulation	Solution			Category 1	1	Category I	R41	Moderate	Moderate						Gettings et al. (1996)
Surfactant Based Formulation 8-HZH		10%	Undiluted	Formulation	Solution			Nonirritant		Category IV	Nonirritant	Slight	Slight						Gettings et al. (1996)

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Surfactant Based Formulation 9-HZI		10%	Undiluted	Formulation	Solution			Category 1	1	Category I	R41	Severe	Severe						Gettings et al. (1996)
Surfactant Based Formulation 10-HZJ		10%	Undiluted	Formulation	Solution			Nonirritant		Category IV	Nonirritant	Slight	Moderate						Gettings et al. (1996)
Surfactant Based Formulation 11-HZK		10%	Undiluted	Formulation	Solution			Category 1	1	Category I	R41	Moderate	Severe						Gettings et al. (1996)
Surfactant Based Formulation 12-HZL		10%	Undiluted	Formulation	Solution			Category 1	1	Category I	R41	Severe	Severe						Gettings et al. (1996)
Surfactant Based Formulation 13-HZM		10%	Undiluted	Formulation	Solution			Category 1	1	Category I	R41	Slight	Slight						Gettings et al. (1996)
Surfactant Based Formulation 14-HZN		10%	Undiluted	Formulation	Solution			Category 1	1	Category I	R41	Moderate	Moderate						Gettings et al. (1996)
Surfactant Based Formulation 15-HZP		10%	Undiluted	Formulation	Solution			Nonirritant		Category III	Nonirritant	Slight	Slight						Gettings et al. (1996)
Surfactant Based Formulation 16-HZO		10%	Undiluted	Formulation	Solution			Nonirritant		Category III	Nonirritant	Slight	Slight						Gettings et al. (1996)
Surfactant Based Formulation 17-HZR		10%	Undiluted	Formulation	Solution			Category 1	1	Category I	R41	Moderate	Moderate						Gettings et al. (1996)
Surfactant Based Formulation 18-HZS		10%	Undiluted	Formulation	Solution			Category 1	1	Category I	R41	Moderate	Severe						Gettings et al. (1996)
Surfactant Based Formulation 19-HZT		10%	Undiluted	Formulation	Solution			Nonirritant		Category IV	Nonirritant	Nonirritant	Slight						Gettings et al. (1996)
Surfactant Based Formulation 20-HZU		10%	Undiluted	Formulation	Solution			Category 2B		Category III	R36	Slight	Moderate						Gettings et al. (1996)
Surfactant Based Formulation 21-HZV		10%	Undiluted	Formulation	Solution			Category 1	1	Category I	R41	Moderate	Moderate						Gettings et al. (1996)
Surfactant Based Formulation 22-HZW		10%	Undiluted	Formulation	Solution			Category 1	1	Category I	R41	Moderate	Moderate						Gettings et al. (1996)
Surfactant Based Formulation 23-HZX		10%	Undiluted	Formulation	Solution			Category 1	1	Category I	R41	Severe	Severe						Gettings et al. (1996)
Surfactant Based Formulation 24-HZY		10%	Undiluted	Formulation	Solution			Category 1	1	Category I	R41	Moderate	Severe						Gettings et al. (1996)
Surfactant Based Formulation 25-HZZ		10%	Undiluted	Formulation	Solution			Nonirritant		Category IV	Nonirritant	Nonirritant	Slight						Gettings et al. (1996)
2-Methoxyethanol	109-86-4	100%	100%	Alcohol, Ether	Liquid						Nonirritant		Severe						Gilleron et al. (1996)
Triton X-155	9010-44-0	100%	100%	Alcohol, Ether	Liquid		Nonionic Surfactant				Nonirritant		Slight						Gilleron et al. (1996)
DL-Glutamic acid	19285-83-7	100%	100%	Amino acid	Solid						Nonirritant		Nonirritant						Gilleron et al. (1996)
Triethanolamine	102-71-6	100%	100%	Amine, Alcohol	Liquid						Nonirritant		Severe						Gilleron et al. (1996)
Allyl alcohol	107-18-6	100%	100%	Alcohol	Liquid						R36		Severe						Gilleron et al. (1996)
1-Nitropropane	108-03-2	100%	100%	Acyclic hydrocarbon, Nitro compound	Liquid						Nonirritant		Slight						Gilleron et al. (1996)
Methyl isobutyl ketone	108-10-1	100%	100%	Ketone	Liquid						Nonirritant		Severe						Gilleron et al. (1996)
Cyclohexanone	108-94-1	100%	100%	Ketone, Cyclic hydrocarbon	Liquid						Nonirritant		Severe						Gilleron et al. (1996)
1,2,4-Trichloropropane	95-63-6	100%	100%	Cyclic hydrocarbon	Liquid						Nonirritant		Slight						Gilleron et al. (1996)
Furan	110-00-9	100%	100%	Heterocycle	Liquid						Nonirritant		Moderate						Gilleron et al. (1996)
Hexane	110-54-3	100%	100%	Acyclic hydrocarbon	Liquid						Nonirritant		Slight						Gilleron et al. (1996)
2-Ethoxyethanol	110-80-5	100%	100%	Alcohol	Liquid						Nonirritant		Severe						Gilleron et al. (1996)
Pyridine	110-86-1	100%	100%	Heterocycle	Liquid						R36		Severe						Gilleron et al. (1996)
Octanol	111-87-5	100%	100%	Alcohol	Liquid						R36		Severe						Gilleron et al. (1996)
Anthracene	120-12-7	100%	100%	Polycyclic compound	Solid						Nonirritant		Nonirritant						Gilleron et al. (1996)
Benzethonium chloride	121-54-0	100%	100%	Amine, Onium	Solid		Cationic Surfactant				R41		Severe						Gilleron et al. (1996)
Diacetone alcohol	123-42-2	100%	100%	Ketone	Liquid						Nonirritant		Severe						Gilleron et al. (1996)
2,4-Pentadione	123-54-6	100%	100%	Ketone	Liquid						Nonirritant		Moderate						Gilleron et al. (1996)
Ethylacetoacetate	141-97-9	100%	100%	Carboxylic acid, Ketone	Liquid						Nonirritant		Severe						Gilleron et al. (1996)
Laurylsulfobetaine	14933-08-5	100%	100%	Amine, Onium	Unknown		Zwitterionic Surfactant				R36		Moderate						Gilleron et al. (1996)
3-Glycidopropyltrimethoxysilane	2530-83-8	100%	100%	Ether, Organosilicon compound	Liquid						Nonirritant		Slight						Gilleron et al. (1996)
2,4-Dicholor-5-sulfamolyl-benzoic acid	2736-23-4	100%	100%	Amide, Organic sulfur compound	Solid						Nonirritant		Slight						Gilleron et al. (1996)
Dibenzoyl-L-tartaric acid	2743-38-6	100%	100%	Carboxylic acid, Ester	Solid						R41		Slight						Gilleron et al. (1996)
Imidazole	288-32-4	100%	100%	Heterocycle	Solid						R36		Severe						Gilleron et al. (1996)
Iminodibenzyl	494-19-9	100%	100%	Heterocycle	Solid						Nonirritant		Nonirritant						Gilleron et al. (1996)
Tetraaminopyrimidine sulfate	5392-28-9	100%	100%	Amine, Heterocycle	Solid						Nonirritant		Nonirritant						Gilleron et al. (1996)
Magnesium carbonate	56378-72-4	100%	100%	Alcohol	Solid						Nonirritant		Slight						Gilleron et al. (1996)
Hexadecyltrimethylammonium bromide	57-09-0	100%	100%	Organic salt, Onium	Liquid		Cationic Surfactant				R36		Severe						Gilleron et al. (1996)
Promethazine HCl	58-33-3	100%	100%	Amine, Heterocycle, Organic sulfur compound	Solid						R41		Severe						Gilleron et al. (1996)

Substance Name	CASRN[1]	*In Vitro* Concentration Tested	*In Vivo* Concentration Tested	Chemical Class	Form Tested	pH	Property of Interest	*In Vivo* (GHS)[2] Classification[3]	GHS Category 1 Subclass[4]	*In Vivo* (EPA)[5] Classification[6]	*In Vivo* (EU)[7] Classification[8]	*In Vitro* Classification (IS(A))[9]	*In Vitro* Classification (IS(B))[10]	*In Vitro* Classification (S-Score)[11]	*In Vitro* Classification (Q-Score)[12]	*In Vitro* Classification (IS(B)-10)[13]	*In Vitro* Classification (IS(B)-100)[14]	*In Vitro* Classifiaion (IS and LTC)[15]	Reference
Thiourea	62-56-6	100%	100%	Organic sulfur compound	Solid						R36		Severe						Gilleron et al. (1996)
Ethanol	64-17-5	100%	100%	Alcohol	Liquid						Nonirritant		Severe						Gilleron et al. (1996)
Dimethyl biguanidine	657-24-9	100%	100%	Amidine	Solid						Nonirritant		Moderate						Gilleron et al. (1996)
Methanol	67-56-1	100%	100%	Alcohol	Liquid						Nonirritant		Severe						Gilleron et al. (1996)
Dimethyl sulfoxide	67-68-5	100%	100%	Organic sulfur compound	Liquid						Nonirritant		Severe						Gilleron et al. (1996)
Quinacrine	69-05-6	100%	100%	Amine, Heterocycle, Polycyclic compound	Solid						R36		Moderate						Gilleron et al. (1996)
Gluconolactone	90-80-2	100%	100%	Carboxylic acid, Lactone, Carbohydrate	Solid						Nonirritant		Slight						Gilleron et al. (1996)
1-Phenyl-3-pyrazolidine	92-43-3	100%	100%	Heterocycle	Solid						Nonirritant		Nonirritant						Gilleron et al. (1996)
Propyl-4-hydroxybenzoate	94-13-3	100%	100%	Carboxylic acid, Phenol	Solid						Nonirritant		Slight						Gilleron et al. (1996)
1,2,3-Trichloropropane	96-18-4	100%	100%	Acyclic hydrocarbon	Liquid						Nonirritant		Moderate						Gilleron et al. (1996)
Gamma-butyrolactone	96-48-0	100%	100%	Heterocycle, Lactone	Liquid						R36		Severe						Gilleron et al. (1996)
Polyoxyethylene 23 lauryl ether	9002-92-0	100%	100%	Alcohol	Solid		Nonionic Surfactant				Nonirritant		Slight						Gilleron et al. (1996)
EDTA dipotassium	25105-12-9	100%	100%	Amine, Carboxylic acid, Organic salt	Solid						Nonirritant		Nonirritant						Gilleron et al. (1996)
Deoxycholic acid, sodium salt	302-95-4	100%	100%	Alcohol, Carboxylic acid, Organic salt	Solid		Nonionic Surfactant				R36		Severe						Gilleron et al. (1996)
N-Lauroylsarcosine, sodium salt	7631-98-3	100%	100%	Aminde, Amine Salt	Solid		Anionic Surfactant				Nonirritant		Severe						Gilleron et al. (1996)
2-Aminophemol	95-55-6	100%	100%	Amine, Phenol	Solid						Nonirritant		Nonirritant						Gilleron et al. (1996)
MYRJ 45		100%	100%	Unknown	Solid		Nonionic Surfactant				Nonirritant		Nonirritant						Gilleron et al. (1996)
1-Naphthalene acetic acid	86-87-3	100%	100%	Carboxylic acid, Polycyclic compound	Solid			Category 1	NC	Category I	SCNM		Moderate						Gilleron et al. (1997)
1-Naphthalene acetic acid, Na salt	61-31-4	100%	100%	Organic salt, Carboxylic acid salt, Polycyclic compound	Solid			Category 1	1	Category I	R41		Severe						Gilleron et al. (1997)
2,2-Dimethylbutanoic acid	595-37-9	100%	100%	Carboxylic acid	Liquid			SCNM		Category I	SCNM		Severe						Gilleron et al. (1997)
2,5-Dimethylhexanediol	110-03-2	100%	100%	Alcohol	Solid			Category 1	1	Category I	R41		Severe						Gilleron et al. (1997)
2,6-Dichlorobenzoyl chloride	4659-45-4	100%	100%	Acyl halide	Liquid			Category 2A		Category II	SCNM		Severe						Gilleron et al. (1997)
2-Ethyl-1-hexanol	104-76-7	100%	100%	Alcohol	Liquid			Category 2A		Category II	R36		Severe						Gilleron et al. (1997)
4-Carboxybenzaldehyde	619-66-9	100%	100%	Carboxylic acid, Aldehyde	Solid			Category 2A		Category II	R36		Slight						Gilleron et al. (1997)
Acetone	67-64-1	100%	100%	Ketone	Liquid			Category 2A		Category II	R36		Severe						Gilleron et al. (1997)
Ammonium nitrate	6484-52-2	100%	100%	Inorganic salt, Onium	Solid			Category 2B		Category III	R36		Severe						Gilleron et al. (1997)
Benzalkonium chloride	8001-54-5	100%	5%	Onium	Solution		Cationic Surfactant	Category 1/Category 2A	2	Category I	R36/R41		Severe						Gilleron et al. (1997)
Benzalkonium chloride	8001-54-5	100%	10%	Onium	Solution		Cationic Surfactant	Category 1	4	Category I	R41		Severe						Gilleron et al. (1997)
Benzalkonium chloride	8001-54-5	100%	1%	Onium	Solution		Cationic Surfactant	Category 1	1	Category I	R41		Severe						Gilleron et al. (1997)
Benzoyl-L-tartaric acid	2743-38-6	100%	100%	Carboxylic acid, Ester	Solid			Category 1	2	SCNM	R41		Severe						Gilleron et al. (1997)
Butyl acetate	123-86-4	100%	100%	Ester	Liquid			Nonirritant		Category III	Nonirritant		Severe						Gilleron et al. (1997)
Captan 90 concentrate	133-06-2	100%	100%	Imide, Organic sulfur compound	Solid			Category 1	4	Category I	R41		Severe						Gilleron et al. (1997)
Cetylpyridinium bromide	140-72-7	100%	0.10%	Heterocyclic compounds, Onium	Solution		Cationic Surfactant	Nonirritant		Category III	Nonirritant		Severe						Gilleron et al. (1997)
Cetylpyridinium bromide	140-72-7	100%	10%	Heterocyclic compounds, Onium	Solution		Cationic Surfactant	Category 1	4	SCNM	R41		Severe						Gilleron et al. (1997)
Cetylpyridinium bromide	140-72-7	100%	6%	Heterocyclic compounds, Onium	Solution		Cationic Surfactant	Category 1	2	Category I	R41		Severe						Gilleron et al. (1997)
Chlorhexidine	55-56-1	100%	100%	Amidine	Solid			Category 1	4	SCNM	SCNM		Severe						Gilleron et al. (1997)
Cyclohexanol	108-93-0	100%	100%	Alcohol	Liquid			Category 1	2	Category I	R41		Severe						Gilleron et al. (1997)
Dibenzyl phosphate	1623-08-1	100%	100%	Ester	Solid			Category 2A		Category II	R36		Severe						Gilleron et al. (1997)
Ethanol	64-17-5	100%	100%	Alcohol	Liquid			Category 2A		Category III	Nonirritant		Severe						Gilleron et al. (1997)
Ethyl acetate	141-78-6	100%	100%	Ester	Liquid			Nonirritant		Category III	Nonirritant		Severe						Gilleron et al. (1997)
Ethyl trimethyl acetate	3938-95-2	100%	100%	Ester	Liquid			Nonirritant		Category III	Nonirritant		Severe						Gilleron et al. (1997)
Ethyl-2-methylacetoacetate	609-14-3	100%	100%	Ketone, Ester	Liquid			Category 2B		Category III	Nonirritant		Severe						Gilleron et al. (1997)
Fomesafen	72128-02-0	100%	100%	Imide, Ether, Nitro compound	Solid			Nonirritant		Category III	Nonirritant		Slight						Gilleron et al. (1997)
Gamma-butyrolactone	96-48-0	100%	100%	Heterocycle, Lactone	Liquid			Category 2A		Category II	R36		Severe						Gilleron et al. (1997)
Glycerol	56-81-5	100%	100%	Alcohol	Liquid			Nonirritant		Category IV	Nonirritant		Severe						Gilleron et al. (1997)
Hexanol	111-27-3	100%	100%	Alcohol	Liquid			Category 2A		Category II	R36		Severe						Gilleron et al. (1997)
Imidazole	288-32-4	100%	100%	Heterocycle	Solid			Category 1	4	Category I	R41		Severe						Gilleron et al. (1997)
Isobutanol	78-83-1	100%	100%	Alcohol	Liquid			Category 2A		Category II	R36		Severe						Gilleron et al. (1997)
Isopropanol	67-63-0	100%	100%	Alcohol	Liquid			Category 2A		Category III	SCNM		Severe						Gilleron et al. (1997)

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L-Aspartic acid	70-47-3	100%	100%	Amino acid	Solid			SCNM		SCNM	SCNM		Slight						Gilleron et al. (1997)
Maneb	12427-38-2	100%	100%	Amine, Organic salt, Urea	Solid			SCNM		Category III	SCNM		Nonirritant						Gilleron et al. (1997)
Methyl acetate	79-20-9	100%	100%	Ester	Liquid			Category 2A		Category II	R36		Severe						Gilleron et al. (1997)
Methyl cyanoacetate	105-34-0	100%	100%	Ester, Nitrile	Liquid			Category 2A		Category II	R36		Severe						Gilleron et al. (1997)
Methyl ethyl ketone	78-93-3	100%	100%	Ketone	Liquid			Category 2A		Category III	R36		Severe						Gilleron et al. (1997)
Methyl isobutyl ketone	108-10-1	100%	100%	Ketone	Liquid			Nonirritant		Category III	Nonirritant		Severe						Gilleron et al. (1997)
Methylcyclopentane	96-37-7	100%	100%	Cyclic hydrocarbon	Liquid			Nonirritant		Category III	Nonirritant		Severe						Gilleron et al. (1997)
Octanol	111-87-5	100%	100%	Alcohol	Liquid			Category 2A		Category II	R36		Severe						Gilleron et al. (1997)
Parafluoraniline	371-40-4	100%	100%	Amine	Liquid			SCNM		SCNM	SCNM		Severe						Gilleron et al. (1997)
Polyethylene glycol 400	25322-68-3	100%	100%	Alcohol, Ether	Liquid		Nonionic Surfactant	Nonirritant		Category IV	Nonirritant		Severe						Gilleron et al. (1997)
Potassium cyanate	590-28-3	100%	100%	Inorganic salt	Solid			SCNM		SCNM	SCNM		Severe						Gilleron et al. (1997)
Promethazine HCl	58-33-3	100%	100%	Amine, Heterocycle, Organic sulfur compound	Solid			Category 1	1	Category I	R41		Moderate						Gilleron et al. (1997)
Pyridine	110-86-1	100%	100%	Heterocycle	Liquid			Category 1	4	Category I	R41		Severe						Gilleron et al. (1997)
Quinacrine	69-05-6	100%	100%	Amine, Heterocycle, Polycyclic compound	Solid			Category 1	3	Category I	R41		Moderate						Gilleron et al. (1997)
Sodium hydroxide	1310-73-2	100%	1%	Alkali	Solid			Category 2B		Category III	R36		Severe						Gilleron et al. (1997)
Sodium hydroxide	1310-73-2	100%	10%	Alkali	Solid			Category 1	4	Category I	R41		Severe						Gilleron et al. (1997)
Sodium lauryl sulfate	151-21-3	100%	3%	Organic salt, Carboxylic acid salt	Solid		Anionic Surfactant	Nonirritant		Category III	Nonirritant		Severe						Gilleron et al. (1997)
Sodium lauryl sulfate	151-21-3	100%	15%	Organic salt, Carboxylic acid salt	Solid		Anionic Surfactant	Category 1	NC	Category I	SCNM		Severe						Gilleron et al. (1997)
Sodium oxalate	62-76-0	100%	100%	Organic salt, Carboxylic acid salt	Solid			Category 1	4	Category I	R41		Severe						Gilleron et al. (1997)
Sodium perborate	10486-00-7	100%	100%	Inorganic salt, Boron containing compound	Solid			Category 1	4	Category I	R41		Severe						Gilleron et al. (1997)
Tetraaminopyrimidine sulfate	5392-28-9	100%	100%	Amine, Heterocycle	Solid			Nonirritant		Category III	Nonirritant		Slight						Gilleron et al. (1997)
Thiourea	62-56-6	100%	100%	Organic sulfur compound	Solid								Severe						Gilleron et al. (1997)
Toluene	108-88-3	100%	100%	Polycyclic compound	Liquid			Nonirritant		Category III	Nonirritant		Severe						Gilleron et al. (1997)
Trichloroacetic acid	76-03-9	100%	30%	Carboxylic acid	Liquid			Nonirritant		Category III	Nonirritant		Severe						Gilleron et al. (1997)
Trichloroacetic acid	76-03-9	100%	3%	Carboxylic acid	Liquid			Category 1	4	Category I	R41		Severe						Gilleron et al. (1997)
Triton X-100	9002-93-1	Undiluted	5%	Ether	Liquid		Nonionic Surfactant	Categorry 2A/Category 2B		Category III	Nonirritant/R36		Severe						Gilleron et al. (1997)
Triton X-100	9002-93-1	Undiluted	10%	Ether	Liquid		Nonionic Surfactant	Category 1	4	Category II	SCNM		Severe						Gilleron et al. (1997)
Tween 20	9005-64-5	100%	100%	Ester, Ether	Liquid		Nonionic Surfactant	Nonirritant		Category III	Nonirritant		Severe						Gilleron et al. (1997)
Acetic acid	64-19-7	10%	10%	Carboxylic acid	Unknown			Category 1	4	Category I	R41	Severe							Hagino et al. (1999)/Submitted Y. Ohno Data
Butanol	71-36-3	10%	10%	Alcohol	Unknown			Category 1	4	SCNM	R41	Severe							Hagino et al. (1999)/Submitted Y. Ohno Data
Cetyltrimethylammonium bromide	57-09-0	10%	10%	Organic salt, Onium	Unknown			Category 1	4	Category I	R41	Severe							Hagino et al. (1999)/Submitted Y. Ohno Data
Chlorhexidine gluconate Solution (20% Solution)	18472-51-0	10%	10%	Amidine, Ester	Unknown			Category 2B		Category II	Nonirritant	Severe							Hagino et al. (1999)/Submitted Y. Ohno Data
Di(2-ethylhexyl) sodium sulfosuccinate	577-11-7	10%	10%	Organic salt, Sulfur containing compound, Ester	Unknown			Category 1	4	Category I	R36	Severe							Hagino et al. (1999)/Submitted Y. Ohno Data
Diisopropanolamine	110-97-4	10%	10%	Amine, Alcohol	Unknown			Nonirritant		Category III	Nonirritant	Moderate							Hagino et al. (1999)/Submitted Y. Ohno Data
Domiphen bromide	538-71-6	10%	10%	Organic salt, Onium, Ether	Unknown			Category 1	4	Category I	R41	Severe							Hagino et al. (1999)/Submitted Y. Ohno Data
Ethanol	64-17-5	10%	10%	Alcohol	Unknown			Nonirritant		Category IV	Nonirritant	Slight							Hagino et al. (1999)/Submitted Y. Ohno Data
Ethanol	64-17-5	100%	100%	Alcohol	Unknown			SCNM		SCNM	SCNM	Severe							Hagino et al. (1999)/Submitted Y. Ohno Data
Glycolic acid	79-14-1	10%	10%	Carboxylic acid, Alcohol	Unknown			Category 2B		Category III	Nonirritant	Severe							Hagino et al. (1999)/Submitted Y. Ohno Data
Lactic acid	50-21-5	10%	10%	Carboxylic acid, Alcohol	Unknown			SCNM		Category III	SCNM	Severe							Hagino et al. (1999)/Submitted Y. Ohno Data

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Lactic acid	50-21-5	100%	100%	Carboxylic acid, Alcohol	Unknown			Category 1	4	Category I	R41	Severe							Hagino et al. (1999)/Submitted Y. Ohno Data
Potassium laurate	10124-65-9	10%	10%	Organic salt, Carboxylic acid salt	Unknown			Category 1	4	Category I	R41	Severe							Hagino et al. (1999)/Submitted Y. Ohno Data
Stearyltrimethylammonium chloride	15461-40-2	10%	10%	Organic salt, Onium	Unknown			Category 1	4	Category I	R41	Severe							Hagino et al. (1999)/Submitted Y. Ohno Data
Triethanolamine	102-71-6	10%	10%	Amine, Alcohol	Unknown			Nonirritant		Category IV	Nonirritant	Slight							Hagino et al. (1999)/Submitted Y.
Triethanolamine	102-71-6	100%	100%	Amine, Alcohol	Unknown			Nonirritant		Category III	Nonirritant	Moderate							Hagino et al. (1999)/Submitted Y. Ohno Data
Monoethanolamine	141-43-5	10%	10%	Amine, Alcohol	Unknown			Category 2B		Category III	Nonirritant	Severe							Hagino et al. (1999)/Submitted Y. Ohno Data
Ethanol	64-17-5	10%		Alcohol	Unknown			Nonirritant		Category IV	Nonirritant	Slight							Kojima et al. (1995)
Potassium laurate	10124-65-9	10%		Organic salt, Carboxylic acid salt	Unknown			Category 1	4	Category I	R41	Severe							Kojima et al. (1995)
Sodium lauryl sulfate	151-21-3	10%		Organic salt, Carboxylic acid salt	Unknown			Category 1/Category 2A	4	Category I/Category II	R41/Nonirritant	Moderate							Kojima et al. (1995)
Stearyltrimethylammonium chloride	15461-40-2	10%		Organic salt, Onium	Unknown			Category 1	4	Category I	R41	Severe							Kojima et al. (1995)
Triton X-100	9002-93-1	10%		Ether	Unknown			Category 1		Category II	SCNM	Moderate							Kojima et al. (1995)
C12/C14-Glucoside			100%	Alcohol, Ether	Unknown	9		Category 1	1	Category I	R41					Severe	Severe		Spielmann et al. (1996)
Isodecylglucoside			100%	Alcohol, Ether	Unknown	9		SCNM		SCNM	SCNM					Severe	Severe	R41	Spielmann et al. (1996)
Nitro-bis-octylamide			100%	Alcohol, Ether	Unknown	ns		Nonirritant		Category III	Nonirritant					Slight	Moderate	Nonirritant	Spielmann et al. (1996)
7-Acetoxyheptanal			100%	Aldehyde, Ester	Unknown	ns		Category 1	1	Category I	R41					Slight	Severe	Nonirritant	Spielmann et al. (1996)
Sodium disilicate	13870-28-5		100%	Inorganic salt	Solid	11.4		Category 1	4	SCNM	SCNM					Severe	Severe	R41	Spielmann et al. (1996)
Sodium hydrogen sulfate	7681-38-1		100%	Inorganic salt	Solid	1.1		Category 1	4	SCNM	SCNM					Severe	Severe	R41	Spielmann et al. (1996)
n-Acetyl-Methionine	1115-47-5		100%	Amide, Amino acid	Solid	2.2		Category 1	4	SCNM	R41					Severe	Severe	R41	Spielmann et al. (1996)
Ambuphylline	5634-34-4		100%	Amine, Heterocycle, Alcohol	Solid	9		Nonirritant		Category IV	Nonirritant					Severe	Severe	Nonirritant	Spielmann et al. (1996)
4-Amino-5-methoxy-2-methylbenzenesulfonic acid	6471-78-9		100%	Amine, Ether, Organic sulfur compound	Unknown	1.5		Category 1	4	SCNM	SCNM					Moderate	Severe		Spielmann et al. (1996)
Ammoniumpersulfate	7727-54-0		100%	Inorganic salt	Solid	1.5		SCNM		SCNM	SCNM					Slight	Severe	Nonirritant	Spielmann et al. (1996)
Anisole	100-66-3		100%	Ether	Liquid	ns		SCNM		SCNM	SCNM					Moderate	Severe	Nonirritant	Spielmann et al. (1996)
B 25			100%	Unknown	Unknown	ns		Nonirritant		Category IV	Nonirritant					Nonirritant	Nonirritant	Nonirritant	Spielmann et al. (1996)
n-Butanal	123-72-8		100%	Aldehyde	Liquid	<7		Category 2B		Category III	Nonirritant					Moderate	Severe	Nonirritant	Spielmann et al. (1996)
n-Butanol	71-36-3		100%	Alcohol	Liquid	ns		Category 1	4	SCNM	SCNM					Severe	Severe	R36	Spielmann et al. (1996)
Butyl carbamate	592-35-8		100%	Ester	Solid	ns		SCNM		SCNM	SCNM					Severe	Severe		Spielmann et al. (1996)
Caffeine sodium benzoate	8000-95-1		100%	Heterocycle, Organic salt, Carboxylic acid salt	Solid	7		Nonirritant		Category IV	Nonirritant					Moderate	Severe		Spielmann et al. (1996)
Caffeine sodium salicylate	8002-85-5		100%	Heterocycle, Phenol, Organic salt	Solid	7		Nonirritant		Category IV	Nonirritant					Severe	Severe	Nonirritant	Spielmann et al. (1996)
Camphen	79-92-5		100%	Cyclic hydrocarbon	Solid	7		Category 2B		Category III	R36					Severe	Slight	Nonirritant	Spielmann et al. (1996)
Cerium-2-ethylhexanoate	24593-34-8		100%	Organic salt, Carboxylic acid salt	Unknown	3		Nonirritant		Category III	Nonirritant					Moderate	Severe	Nonirritant	Spielmann et al. (1996)
1-Chloroctane-8-ol			100%	Alcohol	Unknown	ns		Category 1	1	Category I	R41					Moderate	Severe	Nonirritant	Spielmann et al. (1996)
3-Cyclohexene-1-methanol	1679-51-2		100%	Alcohol	Unknown	ns		SCNM		SCNM	SCNM					Severe	Severe	R36	Spielmann et al. (1996)
DC 8			100%	Unknown	Unknown	ns		Nonirritant		Category IV	Nonirritant					Nonirritant	Moderate	Nonirritant	Spielmann et al. (1996)
1,4-Dibutoxy-benzene	104-36-9		100%	Ether	Unknown	7		Category 2B		Category III	R36					Slight	Nonirritant	Nonirritant	Spielmann et al. (1996)
Diepoxid 126	2386-87-0		100%	Heterocycle, Ester, Ether	Liquid	ns		SCNM		SCNM	SCNM					Moderate	Severe		Spielmann et al. (1996)
2,5-Dimethylhexanediol	110-03-2		100%	Alcohol	Solid	ns		Category 1	1	Category I	R36					Severe	Severe		Spielmann et al. (1996)

Substance Name	CASRN[1]	*In Vitro* Concentration Tested	*In Vivo* Concentration Tested	Chemical Class	Form Tested	pH	Property of Interest	*In Vivo* (GHS) Classification[2]	GHS Category 1 Subclass[3]	*In Vivo* (EPA) Classification[4]	*In Vivo* (EU) Classification[5]	*In Vitro* Classification (IS(A))[6]	*In Vitro* Classification (IS(B))[7]	*In Vitro* Classification (S-Score)[8]	*In Vitro* Classification (Q-Score)[9]	*In Vitro* Classification (IS(B)-10)[10]	*In Vitro* Classification (IS(B)-100)[11]	*In Vitro* Classificaion (IS and LTC)[12]	Reference
3,6-Dimethyloctanol			100%	Alcohol	Unknown	7		Category 1	1	Category I	R41					Nonirritant	Slight	Nonirritant	Spielmann et al. (1996)
4,4-Dimethyl-3-oxo-pentanenitrile	59997-51-2		100%	Ketone, Nitrile	Solid	ns		Nonirritant		Category IV	Nonirritant					Moderate	Moderate		Spielmann et al. (1996)
1-(2,6-dimethylphenoxy)-2-propanone	53012-41-2		100%	Alcohol, Ether	Liquid	5		Nonirritant		Category IV	Nonirritant					Severe	Severe		Spielmann et al. (1996)
Diphocars			100%	Unknown	Unknown	ns		Category 1	4	Category I	R41					Severe	Severe	R41	Spielmann et al. (1996)
1,2-Dodecanediol	1119-87-5		100%	Alcohol	Solid	ns		SCNM		SCNM	SCNM					Slight	Slight		Spielmann et al. (1996)
DTPA Pentasodium salt	140-01-2		100%	Organic salt, Carboxylic acid salt, Amino acid	Unknown	11.5		SCNM		SCNM	SCNM					Severe	Severe	R41	Spielmann et al. (1996)
Ede 140			100%	Unknown	Unknown	ns		Nonirritant		Category IV	Nonirritant					Slight	Slight	Nonirritant	Spielmann et al. (1996)
1,2-Epoxycyclooctane	286-62-4		100%	Ether	Solid	4.5		Nonirritant		Category III	Nonirritant					Severe	Moderate	Nonirritant	Spielmann et al. (1996)
1,2-Epoxydodecane	2855-19-8		100%	Ether	Solid	ns		SCNM		SCNM	SCNM					Slight	Moderate	Nonirritant	Spielmann et al. (1996)
Ethiosan			100%	Unknown	Unknown	8.5		SCNM		Category III	SCNM					Slight	-		Spielmann et al. (1996)
Ethyl butanal	97-96-1		100%	Aldehyde	Liquid	<7		SCNM		SCNM	SCNM					Nonirritant	Severe	Nonirritant	Spielmann et al. (1996)
Genomoll	115-96-8		100%	Ester, Organophophorous compound	Solid	6		Nonirritant		Category IV	Nonirritant					Severe	Severe	Nonirritant	Spielmann et al. (1996)
L-Glutamic acid hydrochloride	138-15-8		100%	Organic salt, Carboxylic acid salt, Amino acid	Unknown	0.9		SCNM		SCNM	SCNM					Severe	Severe	R41	Spielmann et al. (1996)
Glycediol			100%	Ether	Unknown	ns		Nonirritant		Category IV	Nonirritant					Slight	Slight	Nonirritant	Spielmann et al. (1996)
Granuform	30525-89-4		100%	Ether	Solid	4		Category 1	4	SCNM	SCNM					Slight	Nonirritant		Spielmann et al. (1996)
Hexahydrofarnesylacetone	502-69-2		100%	Ketone	Unknown	ns		Nonirritant		Category III	Nonirritant					Slight	Moderate	Nonirritant	Spielmann et al. (1996)
Hexamethylenetetramine	100-97-0		100%	Amine	Solid	8.5		Nonirritant		Category IV	Nonirritant					Moderate	Severe	Nonirritant	Spielmann et al. (1996)
1,2,6-Hexanetriol	106-69-4		100%	Alcohol	Solid	4.5		Nonirritant		Category IV	Nonirritant					Severe	Severe	Nonirritant	Spielmann et al. (1996)
Hnol			100%	Unknown	Unknown	ns		Nonirritant		Category IV	Nonirritant					Nonirritant	Moderate	Nonirritant	Spielmann et al. (1996)
Hoe MBF			100%	Unknown	Unknown	4.3		Nonirritant		Category III	Nonirritant					Nonirritant	Nonirritant		Spielmann et al. (1996)
Hydo 98			100%	Unknown	Unknown	6.5		Category 1	1	Category I	R41					Severe	Severe	R41	Spielmann et al. (1996)
2-Hydroxyethyliminodiso diumacetate	135-37-5		100%	Amine, Alcohol, Organic salt	Unknown	10.6		Nonirritant		Category IV	Nonirritant					Severe	Severe	R36	Spielmann et al. (1996)
2-Hydroxyisobutyric acid	594-61-6		100%	Carboxylic acid	Solid	1		Category 1	4	SCNM	R41					Severe	Severe	R36	Spielmann et al. (1996)
Hypo 20			100%	Unknown	Unknown	6.5		Nonirritant		Category IV	Nonirritant					Moderate	Moderate	Nonirritant	Spielmann et al. (1996)
Hypo 36			100%	Unknown	Unknown	7		Nonirritant		Category IV	Nonirritant					Severe	Severe	Nonirritant	Spielmann et al. (1996)
Hypo 45			100%	Unknown	Unknown	7		Nonirritant		Category IV	Nonirritant					Slight	Severe		Spielmann et al. (1996)
Hypo 54			100%	Unknown	Unknown	6.5		SCNM		SCNM	SCNM					Slight	Slight	Nonirritant	Spielmann et al. (1996)
Hyton			100%	Unknown	Unknown	8.5		SCNM		SCNM	SCNM					Severe	Severe	R41	Spielmann et al. (1996)
Iminodiacetic acid	142-73-4		100%	Amine, Carboxylic acid	Solid	2.3		SCNM		SCNM	SCNM					Severe	Severe		Spielmann et al. (1996)
Isobornyl acetate	125-12-2		100%	Ester	Solid	ns		Nonirritant		Category IV	Nonirritant					Slight	Moderate	Nonirritant	Spielmann et al. (1996)
Isobutanal	78-84-2		100%	Aldehyde	Liquid	<7		Category 2B		Category III	Nonirritant					Slight	Severe	Nonirritant	Spielmann et al. (1996)
Isononylaldehyde	35127-50-5		100%	Aldehyde	Liquid	<7		Nonirritant		Category III	Nonirritant					Nonirritant	Severe	Nonirritant	Spielmann et al. (1996)
alpha-Ketoglutaric acid	328-50-7		100%	Carboxylic acid	Solid	1.75		Category 1	4	SCNM	R41					Severe	Severe	R41	Spielmann et al. (1996)
Lactic acid	79-33-4		100%	Carboxylic acid, Alcohol	Unknown	2		SCNM		SCNM	SCNM					Severe	Severe	R41	Spielmann et al. (1996)
alpha-Lactid	4511-42-6		100%	Heterocycle, Lactone	Solid	3		SCNM		Category III	SCNM					Severe	Slight		Spielmann et al. (1996)
L-Lysine Monohydrate	39665-12-8		100%	Amino acid	Solid	10		SCNM		Category III	SCNM					Severe	Severe	Nonirritant	Spielmann et al. (1996)

Substance Name	CASRN[1]	*In Vitro* Concentration Tested	*In Vivo* Concentration Tested	Chemical Class	Form Tested	pH	Property of Interest	*In Vivo* (GHS) Classification[2]	GHS Category 1 Subclass[3]	*In Vivo* (EPA) Classification[4]	*In Vivo* (EU) Classification[5]	*In Vitro* Classification (IS(A))[6]	*In Vitro* Classification (IS(B))[7]	*In Vitro* Classification (S-Score)[8]	*In Vitro* Classification (Q-Score)[9]	*In Vitro* Classification (IS(B)-10)[10]	*In Vitro* Classification (IS(B)-100)[11]	*In Vitro* Classificaion (IS and LTC)[12]	Reference
Mecre			100%	Unknown	Unknown	7		Nonirritant		Category IV	Nonirritant					Severe	-		Spielmann et al. (1996)
3-Mercapto-1,2,4-triazole	3179-31-5		100%	Heterocycle, Organic sulfur compound, Alcohol	Solid	4		SCNM		SCNM	SCNM					Severe	-	R36	Spielmann et al. (1996)
m-Methoxybenzaldehyde	591-31-1		100%	Aldehyde, Ether	Solid	ns		Nonirritant		Category IV	Nonirritant					Slight	Severe	Nonirritant	Spielmann et al. (1996)
Methyl acetate	79-20-9		100%	Ester	Liquid	7		Category 2B		Category III	R36					Slight	Severe	Nonirritant	Spielmann et al. (1996)
Methylpentynol	77-75-8		100%	Alcohol	Liquid	ns		Category 1	4	Category I	R41					Severe	Severe	R36	Spielmann et al. (1996)
N-(2-methylphenyl)-Imidodi-carbonimidic diamide	93-69-6		100%	Amidine	Solid	11.5		Category 1	4	SCNM	SCNM					Severe	Slight	R41	Spielmann et al. (1996)
2-Methyl-1-propanol	78-83-1		100%	Alcohol	Liquid	3		Category 1	1	Category I	R41					Severe	Severe	R41	Spielmann et al. (1996)
Methyltriglycol	112-35-6		100%	Alcohol, Ether	Liquid	7		Nonirritant		Category III	Nonirritant					Severe	Severe	R36	Spielmann et al. (1996)
Methyltriglycol	112-35-6		100%	Alcohol, Ether	Liquid	7		Nonirritant		Category III	Nonirritant					Severe	Severe	Nonirritant	Spielmann et al. (1996)
Napt			100%	Unknown	Unknown	ns		Nonirritant		Category IV	Nonirritant					Slight	Severe	Nonirritant	Spielmann et al. (1996)
Olak			100%	Unknown	Unknown	8.3		Category 1	1	Category I	R41					Severe	Severe	R41	Spielmann et al. (1996)
Ölesulf			100%	Unknown	Unknown	8		Category 1	1	Category I	R41					Severe	Severe	R41	Spielmann et al. (1996)
Phenylephrine hydrochloride	61-76-7		100%	Phenol, Alcohol, Organic salt	Solid	7		Nonirritant		Category IV	Nonirritant					Severe	Severe	Nonirritant	Spielmann et al. (1996)
Phenylthiourea	103-85-5		100%	Organic sulfur compound, Urea	Solid	5.5		Nonirritant		Category IV	Nonirritant					Slight	Slight		Spielmann et al. (1996)
Phosphonat A			100%	Unknown	Unknown	2.1		Nonirritant		Category III	Nonirritant					Moderate	Severe	Nonirritant	Spielmann et al. (1996)
Piperazine	18833-13-1		100%	Heterocycle	Solid	5		Nonirritant		Category IV	Nonirritant					Severe	Severe		Spielmann et al. (1996)
PO 2			100%	Unknown	Unknown	ns		Nonirritant		Category IV	Nonirritant					Slight	Nonirritant		Spielmann et al. (1996)
Polyethylene glycol butyl ether	9004-77-7		100%	Ether	Liquid	6		SCNM		SCNM	SCNM					Severe	Severe	R41	Spielmann et al. (1996)
Polyethylene glycol dimethyl ether	24991-55-7		100%	Ether	Unknown	7		Nonirritant		Category IV	Nonirritant					Slight	Severe	Nonirritant	Spielmann et al. (1996)
Polyethylene glycol	25322-68-3		100%	Alcohol, Ether	Unknown	ns		SCNM		SCNM	SCNM					Slight	Moderate	Nonirritant	Spielmann et al. (1996)
Polysolvan	7397-62-8		100%	Alcohol, Ester	Liquid	7		SCNM		SCNM	SCNM					Severe	Severe	R36	Spielmann et al. (1996)
Potassium cyanate	590-28-3		100%	Inorganic salt	Solid	10		SCNM		SCNM	SCNM					Severe	Severe	R41	Spielmann et al. (1996)
Potassium hexacyanoferrate II	14459-95-1		100%	Carboxylic acid	Solid	9.5		SCNM		SCNM	SCNM					Severe	Severe	R36	Spielmann et al. (1996)
Potassium hexacyanoferrate III	13756-66-2		100%	Carboxylic acid	Solid	8		SCNM		SCNM	SCNM					Moderate	Moderate	Nonirritant	Spielmann et al. (1996)
Gadopentetic acid dimeglumine salt	86050-77-3		100%	Amine, Carboxylic acid, Organic salt	Unknown	ns		SCNM		SCNM	SCNM					Severe	Moderate	Nonirritant	Spielmann et al. (1996)
RK Blau			100%	Unknown	Unknown	2.6		Nonirritant		Category IV	Nonirritant					Slight	-		Spielmann et al. (1996)
Rubinrot Y			100%	Unknown	Unknown			SCNM		Category IV	SCNM					Slight	Moderate		Spielmann et al. (1996)
Sacyclo			100%	Unknown	Unknown	ns		Nonirritant		Category IV	Nonirritant					Slight	Slight	Nonirritant	Spielmann et al. (1996)
Sept			100%	Unknown	Unknown	3		Category 1	1	Category I	R41					Severe	Severe	Nonirritant	Spielmann et al. (1996)
Silan 103	1067-25-0		100%	Organosilicon compound	Liquid	ns		SCNM		SCNM	SCNM					Slight	Severe	Nonirritant	Spielmann et al. (1996)
Silan 108	3069-40-7		100%	Organosilicon compound	Liquid	ns		Nonirritant		Category III	Nonirritant					Moderate	Severe	Nonirritant	Spielmann et al. (1996)
Silan 165	29055-11-6		100%	Organosilicon compound	Unknown	ns		Nonirritant		Category IV	Nonirritant					Nonirritant	Moderate	Nonirritant	Spielmann et al. (1996)
Silan 167	41453-78-5		100%	Organosilicon compound, Organic sulfur compound	Unknown	ns		SCNM		SCNM	SCNM					Slight	Slight	Nonirritant	Spielmann et al. (1996)
Silan 253	18784-74-2		100%	Organosilicon compound	Unknown	<7		SCNM		SCNM	SCNM					Severe	Severe	Nonirritant	Spielmann et al. (1996)
Sodium bisulfite	7631-90-5		100%	Inorganic acid, Inorganic salt	Solid	4.5		Nonirritant		Category III	Nonirritant					Severe	Severe	R36	Spielmann et al. (1996)
Sodium sulfite	7757-83-7		100%	Inorganic salt	Solid	10		SCNM		Category III	SCNM					Severe	Severe	R36	Spielmann et al. (1996)

Substance Name	CASRN[1]	*In Vitro* Concentration Tested	*In Vivo* Concentration Tested	Chemical Class	Form Tested	pH	Property of Interest	*In Vivo* (GHS) Classification[2]	GHS Category 1 Subclass[3]	*In Vivo* (EPA)[4] Classification	*In Vivo* (EU)[5] Classification	*In Vitro* Classification (IS(A))[6]	*In Vitro* Classification (IS(B))[7]	*In Vitro* Classification (S-Score)[8]	*In Vitro* Classification (Q-Score)[9]	*In Vitro* Classification (IS(B)-10)[10]	*In Vitro* Classification (IS(B)-100)[11]	*In Vitro* Classificaion (IS and LTC)[12]	Reference
Sodium cyanate	917-61-3		100%	Inorganic salt	Solid	10		SCNM		Category III	SCNM					Severe	Severe	R41	Spielmann et al. (1996)
Polyhexamethylene guanidine			100%	Amidine	Unknown	7.1		Category 1	4	Category I	R41					Severe	Severe	R36	Spielmann et al. (1996)
2-Pseudojonon			100%	Unknown	Unknown	ns		Category 2B		Category III	Nonirritant					Moderate	Moderate	Nonirritant	Spielmann et al. (1996)
Sodium lauryl ether sulfate	3088-31-1		100%	Organic salt, Ester, Ether	Unknown	8		SCNM		SCNM	SCNM					Severe	Severe	R41	Spielmann et al. (1996)
Sodium monochloroacetate	3926-62-3		100%	Organic salt, Carboxylic acid salt	Solid	4.5		Category 2B		Category III	R36					Moderate	Severe	Nonirritant	Spielmann et al. (1996)
Sodiumpyrosulfite	7681-57-4		100%	Inorganic salt	Solid	4.6		SCNM		SCNM	SCNM					Severe	Severe		Spielmann et al. (1996)
4-((2-sulfatoethyl)sulfonyl)-aniline	2494-89-5		100%	Amine, Organic sulfur compound, Ether	Unknown	7		Category 1	4	SCNM	R41					Severe	Severe		Spielmann et al. (1996)
TA 01946 Alkylsilan			100%	Unknown	Unknown	ns		Nonirritant		Category IV	Nonirritant					Severe	Severe	Nonirritant	Spielmann et al. (1996)
Theophylline sodium acetate	8002-89-9		100%	Heterocycle, Organic salt, Carboxylic acid salt	Unknown	11		Nonirritant		Category IV	Nonirritant					Severe	Moderate	R36	Spielmann et al. (1996)
Tocla			100%	Unknown	Unknown	6		Category 1	1	Category I	R41					Severe	Severe	R41	Spielmann et al. (1996)
Triisooctylamine	25549-16-0		100%	Amine	Solid	7		Nonirritant		Category IV	Nonirritant					Nonirritant	Severe	Nonirritant	Spielmann et al. (1996)
2,2,3-Trimethyl-3-Cyclopentene-1-acetaldehyde	4501-58-0		100%	Aldehyde	Solid	2.3		SCNM		SCNM	SCNM					Slight	Severe	Nonirritant	Spielmann et al. (1996)
Trioxane	110-88-3		100%	Heterocycle, Ether	Solid	ns		Nonirritant		Category III	Nonirritant					Severe	Severe	Nonirritant	Spielmann et al. (1996)
Wessalith Slurry			100%	Unknown	Unknown	11		Category 2A		Category II	Nonirritant					Severe	Severe	Nonirritant	Spielmann et al. (1996)
Xanthinol nicotinate	437-74-1		100%	Amine, Heterocycle, Alcohol	Solid	6		Nonirritant		Category IV	Nonirritant					Severe	Severe	Nonirritant	Spielmann et al. (1996)
Sodium lauryl sulfate	151-21-3	1%	1%	Organic salt, Carboxylic acid salt	Solution		Anionic Surfactant	Nonirritant		Category IV	Nonirritant		Severe						Vinardell and Macián (1994)
Tween 20	9005-64-5	100%	100%	Ester, Ether	Liquid		Nonionic Surfactant	Nonirritant		Category III	Nonirritant		Slight						Vinardell and Macián (1994)

[1]CASRN = Chemical Abstract Service Registry Number.

[2]GHS=Globally Harmonized System (UN [2003])

[3]Eye Irritant Category 1 = irreversible effects on the eye/serious damage to the eye; Category 2A = reversible effects on the eye/irritating to the eyes; Category 2B = reversible effects on the eye/mildly irritating to the eyes; Nonirritant = not an eye irritant

[4]NICEATM-defined subgroups assigned based on the lesions that drove classification of a GHS Category 1 substance. 1: based on lesions that are persistent; 2: based on lesions that are severe (not including corneal opacity score equal to 4); 3: based on lesions that are severe (not including corneal opacity score equal to 4) and persistent; 4: corneal opacity score equal to 4 at any time; NC: No subclassification could be made based on the data.

[5]EPA=U.S. Environmental Protection Agency (EPA [1996])

[6]Toxicity Category I for the Primary Eye Irritation Study = Corrosive, or corneal involvement or irritation not reversible within 21 days; Category II = Corneal involvement or irritation clearing in 8-21 days; Category III = Corneal involvement or irritation clearing in 7 days or less; Category IV = Minimal effects clearing within 24 hr.

[7]EU=European Union (EU [2001])

[8]Risk phrase R41 = risk of serious damage to the eyes; R36 = irritating to the eyes; nonirritant = not an eye irritant.

[9]IS(A) represents irritation scores that were calculated using the method described in Leupke (1985)

[10]IS(B) represents irritation scores that were calculated using a method similar to the one described in Kalweit et al. (1987, 1990)

[11]S-Score represents irritation scores that were calculated using the method described in Balls et al. (1995)

[12]Q-Score represents irritation scores that were calculated using the method described in Balls et al. (1995)

[13]IS(B)-10 represents irritation scores that were calculated using the method described in Luepke (1985) when substances were tested at a 10% concentration in Spielmann et al. (1996)

[14]IS(B)-100 represents irritation scores that were calculated using the method described in Luepke (1985) when substances were tested at a 100% concentration in Spielmann et al. (1996)

Substance Name	CASRN[1]	*In Vitro* Concentration Tested	*In Vivo* Concentration Tested	Chemical Class	Form Tested	pH	Property of Interest	*In Vivo* (GHS)[2] Classification[3]	GHS Category 1 Subclass[4]	*In Vivo* (EPA)[5] Classification[6]	*In Vivo* (EU)[7] Classification[8]	*In Vitro* Classification (IS(A))[9]	*In Vitro* Classification (IS(B))[10]	*In Vitro* Classification (S-Score)[11]	*In Vitro* Classification (Q-Score)[12]	*In Vitro* Classification (IS(B)-10)[13]	*In Vitro* Classification (IS(B)-100)[14]	*In Vitro* Classificaion (IS and ITC)[15]	Reference

[15]IS and ITC represents irritation scores that were calculated using the method described in Luepke (1985) combined with the irritation threshold concentration as described in Spielmann et al. (1996)

[16]SCNM=Study Criteria Not Met.

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SECTION V

REVISED PROPOSED REFERENCE SUBSTANCES FOR OPTIMIZATION/VALIDATION STUDIES

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1.0 INTRODUCTION

On November 1, 2004, NICEATM released draft BRDs on the current status of four *in vitro* test methods for detecting ocular corrosives and severe irritants (BCOP, HET-CAM, IRE, ICE). Included in each BRD was a list of proposed reference substances for the optimization and/or validation of *in vitro* tests to detect ocular corrosives and severe irritants (available electronically at http://iccvam.niehs.nih.gov/methods/ocudocs/ocu_brd.htm). The proposed reference substances are intended to:

- represent the range of ocular responses (i.e., corrosive/severe irritant; nonsevere irritant/noncorrosive) that the test method is expected to be capable of predicting
- represent the range of chemical/product classes and physicochemical properties (e.g., solid, liquid) that the test method is expected to be capable of testing
- represent the range of known or anticipated mechanisms or modes of action for severe/irreversible ocular irritation or corrosion
- have been generated by high-quality *in vivo* rabbit eye test method studies following Organization for Economic Cooperation and Development (OECD) Test Guideline (TG) 405 (OECD [1987]) and preferably conducted in compliance with Good Laboratory Practices (GLP) guidelines (OECD [1998]; EPA [2004a, 2004b]; FDA [2004])
- have a well-defined chemical composition
- be tested at a defined concentration and at a defined purity[1]
- be readily available

On January 11-12, 2005, ICCVAM convened an Expert Panel to independently consider this list of proposed reference substances; the Expert Panel concluded that the list of proposed substances is fairly comprehensive in that the three major groups of products to which the eye is exposed (i.e., industrial chemicals, pharmaceuticals, cosmetics) are represented and that, in general, individual substances were appropriately chosen. In addition, the Expert Panel suggested several changes to the list of proposed reference substances (see the Expert Panel Report, *Evaluation of the Current Validation Status of In Vitro Test Methods for Identifying Ocular Corrosives and Severe Irritants;* this report can be obtained by contacting NICEATM or electronically from http://iccvam.niehs.nih.gov/methods/eyeirrit.htm). In response to their recommendations, a revised list of proposed reference substances has been developed that includes the following changes:

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[1]Information on purity and the concentration tested were not available for all substances included in the NICEATM *in vivo* rabbit eye test results database. A decision was made to exclude nonsevere irritants (i.e., GHS Category 2A or 2B irritants) or non-irritants but not corrosive/severe irritants (i.e., GHS Category 1) that lacked concentration data from consideration as proposed reference substances. GHS category 1 substances were included because testing at a potentially higher concentration would not likely alter their classification as a GHS Category 1 substance although it might alter the criteria by which they were classified as an ocular corrosive/severe irritant. Where information on purity was lacking, an assumption was made that testing would have been conducted with a relatively pure substance. For substances included because they cause severe ocular effects in humans but lacked appropriate *in vivo* rabbit eye test data, information on concentration and purity were not available.

- The number of inorganic substances has been increased. In addition to the two inorganic substances in the original list (potassium tetrafluoroborate, sodium perborate tetrahydrate), 11 additional inorganic substances (aluminum chloride, antimony oxide, lime, magnesium hydroxide, nitric acid, silver nitrate, sodium hydrogen difluoride, sodium hydrogen sulfate, sulfuric acid, zinc chloride) have been added. Also, as recommended by the Expert Panel, many of the additional inorganics are used in consumer products.
- Substances that are known human ocular corrosives or severe irritants, even in the absence of high quality Draize rabbit eye test data, have been added. Based on human data only, ten such substances were added; these are ammonia, chloroform, lime, magnesium hydroxide, nitric acid, potassium hydroxide, silver nitrate, sodium hydrogen difluoride, sulfuric acid, and zinc chloride.
- All 12 formulations in the original proposed list have been excluded.
- The number of surfactants has been reduced from 12 to seven.

In addition,

- the source of the Draize rabbit eye test data has been provided for each proposed reference substance
- where applicable and to the extent possible, within a chemical class, substances of lower, medium and higher molecular weight have been included (the molecular weight of each proposed substance is now provided)
- information is provided on whether each proposed reference substance has been tested in the proposed version of BCOP, HET-CAM, ICE, and IRE test methods

In addition to these recommendations, the Expert Panel commented that the total number of proposed reference substances (i.e., 89) was large, and suggested that an appropriate number of specific substances should be selected that would be considered optimal for optimization and validation studies. No specific guidance was provided as to how to determine the appropriate number of reference substances. The Expert Panel suggested that a two-stage study design could be employed for validation studies, where a small subset of the reference substances could be used to make an initial assessment of accuracy and/or reliability. If the test method was considered promising after this initial assessment, then a larger number of substances could be used to further characterize test method accuracy and/or reliability.

The number of substances needed to adequately evaluate the accuracy of an alternative test method will vary with the proposed use and mechanistic basis of the test method. Based purely on a statistical evaluation, several hundred substances could potentially be required to evaluate accuracy with a reasonably high level of confidence, even when any effects of differential potencies among the reference substances are assumed to be negligible[2]. Generally, the (1) greater the range of possible responses (in terms of potency) that the test

[2] A formal statistical evaluation is being conducted by NICEATM to estimate the appropriate number of substances to use in evaluating the accuracy of an *in vitro* ocular irritancy test method.

method is expected to be capable of measuring or predicting, (2) greater the diversity of known or anticipated mechanisms or modes of action that are involved in the toxic response, and (3) greater the number of chemical/product classes and physicochemical properties that the test method is expected to be capable of testing, the greater the number of reference substances that will be needed to adequately demonstrate the validity of an alternative test method. For the detection of ocular corrosives and severe irritants, the list of reference substances needs to include substances that:

- induce very severe responses within a relatively short time period, as well as those where the toxic response is delayed
- adversely affect the cornea, iris, and/or conjunctiva
- induce persistent versus non-persistent lesions (when assessed at 21 days post treatment)
- represent diverse chemical classes and physicochemical properties

To meet these needs, the total number of substances in the list was increased from 89 to 122.

Clarification regarding the rules for classification of severe irritants was obtained subsequent to the release of the four BRDs. This resulted in changes to the hazard classification of a few of the substances included in the original list of proposed reference substances. For the original analysis, reversibility of ocular effects for the EU and UN GHS hazard classification systems was considered to be achieved if, by post-exposure day 21, the endpoint scores fell below the threshold that resulted in a test substance being classified as a severe irritant (EU [2001]; UN [2003]). The new information obtained indicated that reversibility of ocular effects is achieved only when all scores reach zero by post-exposure day 21. This change resulted in a few substances previously classified as nonsevere irritants now being classified as severe irritants.

The chemical classes assigned to each reference substance were revised based on the MeSH chemical classification system, an internationally recognized standardized classification scheme (see http://www.nlm.nih.gov/mesh and **Appendix B**). This resulted in some reference substances being re-classified into other chemical classes, which impacted on the number of reference substances in the various chemical classes.

Finally, additional *in vivo* rabbit ocular irritancy test results were obtained from several sources that expanded the number of potential candidate substances and which needed to be considered. Additional *in vivo* rabbit eye test data were received from[3]:

- Mr. Menk Prinsen (TNO Nutrition and Food Institute), for the 44 substances reported on in Prinsen (1996) and for 50 additional substances tested at TNO (Prinsen [2005])
- ZEBET, for the 144 substances that were described in Spielmann et al. (1996) (Spielmann and Liebsch [2005a])

[3] The efforts of these individuals, institutions, and organizations that provided additional data and/or information are gratefully acknowledged.

- Drs. Vanparys and Van Goethem for the 101 substances reported in the Gilleron et al. (1996, 1997) studies
- EPA for 43 substances in the Toxic Substances Control Act (TSCA) database not previously considered

To be considered a candidate reference substance, sufficient individual rabbit data to classify its ocular irritancy according to the GHS classification system (2003) was required, and the substance needed to be readily available. The revised list, as well as the draft list of proposed reference substances, was developed on the basis of preset selection criteria as outlined in Section 12 of each draft BRD. As a result of this additional data, the total number of commercially available candidate reference substances increased from 197 to 210 (see **Table V-1**).

2.0 REVISED LIST OF PROPOSED REFERENCE SUBSTANCES

The complete list of candidate substances from which the revised proposed list of reference substances was selected is provided in **Appendices V-A1** and **V-A2**, along with detailed information for each substance. In **Appendix V-A1**, the list is sorted by CASRN and then by substance concentration, which results in all tests conducted with the same substance being sorted together, regardless of the resulting GHS ocular hazard classification (UN [2003]). In **Appendix V-A2**, the list is sorted first by GHS ocular hazard classification and then by substance name. Proposed reference substances are bolded. An explanation as to why a GHS Category 1, 2A, or 2B substance was excluded from the list of proposed reference substances is provided in the comment column of this appendix. Selection of the 15 nonirritants was based on their ability, to the extent possible, to represent the range of nonirritating responses reported *in vivo* for treated rabbits and to match the chemical/product classes and physicochemical properties included among the corrosive or severely irritating substances proposed as reference substances. The range of nonirritating responses was determined by inspecting the extent to which the treated rabbits exhibited a response other than one that would result in the test substance being classified as an irritant (i.e., GHS Category 2A/2B or Category 1; see **Appendix A**).

The revised list of reference substances proposed for future optimization and validation studies of alternative test methods intended to detect ocular corrosives/severe irritants is provided in **Appendix V-B**; this list is sorted first by GHS ocular hazard classification and then by substance name. In **Appendices V-C** and **V-D**, the proposed reference substances are sorted by chemical class and by product class, respectively. The revised list includes 79 GHS Category 1 substances (10 of which were classified as severe irritants based on human data only), 28 GHS Category 2 substances (14 Category 2A substances, 13 GHS Category 2B substances, and one substance [Triton X-100] that induced a GHS Category 2A response in one study and a 2B response in another study when tested at a 5% concentration), and 15 nonirritants. These 122 substances cover 34 chemical classes and 24 product classes and include 79 substances tested in liquid form and 43 tested as solids. The number of substances per chemical class range from one for lactones, quinones, boron compounds, and amino acids to 22 for alcohols. For many of these chemical classes, the number of substances may be too few to adequately demonstrate the accuracy of a test method for that

specific chemical class. These numbers, however, reflect the maximum number of available substances for those chemical classes identified in the candidate list of reference substances (**Appendix V-A**). The large number of alcohols in this list reflects the fact that ICE, BCOP, and HET-CAM all currently demonstrate a low accuracy for such substances, as indicated in **Sections 2** and **3** of this addendum, respectively. Thus, a large number of reference alcohols is deemed useful for the further development of these test methods. Due to the fact that alcohols are relatively common substances for which there is considerable *in vivo* data, it proved possible to include alcohols distributed across the full range of ocular toxicity categories (i.e., 11 GHS Category 1, 4 GHS Category 2A, 4 GHS Category 2B, 3 nonirritants).

2.1 Performance Standards and Proficiency Substances

Following completion of the proposed validation studies, reference substances from this list can be selected for inclusion in performance standards and for proficiency testing. This list of proposed reference substances is intended to represent the minimum number of substances considered critical to an evaluation of the validity of alternative *in vitro* ocular irritancy test methods proposed for evaluating substances from a broad range of chemical and product classes. Subsets of substances from this list may be considered for:

- optimization of a test method protocol
- performance standard reference substances for use in the validation of test methods that are functionally and mechanistically similar to a validated ocular irritancy test method
- proficiency testing to ensure the competency of a laboratory in performing a validated ocular irritancy test method

In situations where a listed substance is unavailable, other substances of the same class for which high quality *in vivo* reference data are available could be used. Furthermore, if desired, additional substances representing other chemical or product classes and for which high quality *in vivo* rabbit eye reference data are available can be added to the minimum list of reference substances to more comprehensively evaluate the accuracy of a test method.

The database of substances from which this list of reference substances was developed includes representatives from each of the four ocular hazard classifications according to the GHS classification system (UN [2003]) (**Table V-1**). **Table V-1** also includes information on the range of molecular weights for the proposed substances in each GHS ocular hazard classification. The GHS Category 1 substances that are included in the list cover the entire range of responses that could result in a corrosive/severe irritant classification, based on both persistence and severity of the resulting lesion (**Table V-2**).

Table V-1. Distribution of Substances in the *In Vivo* Rabbit Eye Test Database and Molecular Weight Ranges of the Proposed Reference Substances, by GHS[1] Ocular Hazard Classification

Classification (GHS)	Number of Entries in the *In Vivo* Rabbit Eye Test Database[2] with a GHS Classification Revised/Original	Number of Candidate Substances (i.e., GHS-Classified Substances[3] Determined to be Commercially Available) Revised/Original[4]	Number of Proposed Reference Substances Revised/Original	Additional Substances Identified as Causing Severe Ocular Damage in Humans	Final Number of Proposed Reference Substances Revised/Original	Molecular Weight Range for Proposed Reference Substances
Category 1	220/123	93/48	69/48	10	79/48	30.0 – 546.8
Category 2A	62/24	17/11	15/11	-[5]	15/11	58.1 – 384.4
Category 2B	51/68	23/27	13/15	-	13/15	80.0 – 265.3
Nonirritant	497/277	77/111	15/15	-	15/15	86.2 – 1227.5
Total	**830/492**	**210/197**	**112/89**	**10**	**122/89**	**30.0 – 1227.5**

[1]GHS = Globally Harmonized System (UN [2003]).

[2]The complete database includes multiple entries for some substances, as well as formulations, coded substances, and substances that could not be classified according to the GHS ocular hazard classification system.

[3]"Substances" is defined as a unique entry (i.e., a single substance tested at a single concentration). The substances identified as causing severe ocular effects in humans are substances for which individual rabbit eye test results were not located. One substance (Triton X-100), when tested at 5%, induced a GHS Category 2A response in one study and a Category 2B response in another study; for purposes of classification in this table, Triton X-100 is classified as a Category 2A substance.

[4] The number of entries decreased for some GHS classification categories due to (1) the reclassification of some substances as GHS Category 1 irritants, based on the persistence of any lesion to day 21 post-treatment; (2) a reassessment of current commercial availability; and (3) collapsing multiple studies with the same substance tested at the same concentration into a single entry.

[5]"-" = not applicable.

Table V-2. NICEATM-Defined Subcategories for the Proposed GHS[1] Category 1 Reference Substances

Subcategory	Criteria for Classification as a GHS Category 1	# of Substances Revised/Original
0[2]	Not Classifiable	12/0
1	Positive response based on a persistent lesion involving the cornea, iris, and/or conjunctiva through to day 21 in at least one of three rabbits and not on severity	9/18
2	Positive response based on mean for first 3 days (CO[3] score >3 and <4 or IR[4] score >1.5) in at least two of three rabbits but lesions do not persist through day 21	4/4
3	Positive response based on mean for first 3 days (CO score >3 and <4 or IR score >1.5) in at least two of three rabbits and a persistent (>21 days) lesion in at least one rabbit	4/2
4	CO score = 4 at any time in at least one of three rabbits	50/24
	Total	**79/48**

[1]GHS = United Nations Globally Harmonized System (UN [2003]).
[2]Included are two GHS Category 1 substances that could not be subclassified because classification was based on an extreme response shortly after treatment in the only animal tested and 10 substances classified as GHS Category 1 irritants because they induced a severe ocular response in accidentally-exposed humans, and appropriate *in vivo* rabbit ocular irritancy test data was not located for these 10 substances.
[4]IR = iritis.

Because of their limited numbers, all of the commercially available GHS Category 2 substances with concentration data have been included in the list of proposed reference substances. As indicated in **Table V-3**, the current list of proposed reference substances covers a wide range of chemical classes and includes both solids and liquids. Substances were assigned into one or more chemical classes (see **Appendix B**). **Table V-4** summarizes the proposed reference substances by product class. All substances were assigned into one or more product classes by referencing the National Library of Medicine Hazards Substances Database (HSDB; see http://www.nlm.nih.gov/pubs/factsheets/hsdbfs.html); other information was obtained from Material Safety Data Sheets (MSDS) obtained from the commercial supplier.

Table V-3. Chemical Classes and Properties of Interest Represented Among the Proposed Reference Substances, According to GHS[1] Ocular Hazard Classification Category

Chemical Class[1]	Number of Candidate Substances	Number of Proposed Reference Substances	GHS Category 1[2]		GHS Category 2A	GHS Category 2B	GHS NI[3]
			Based on Human Data	Based on Rabbit Data			
Chemical Class[4,5]							
Acid (inorganic)	**2**	**2**	2(2)	-[6]	-	-	-
Acid (organic)	**20**	**17**	-	13(14)	2(2)	1(3)	1(1)
Acyl Halide	**3**	**3**	-	2(2)	1(1)	-	-
Alcohol	**30**	**22**	-	11(17)	4(6)	4(4)	3(10)
Aldehyde	**6**	**4**	-	2(2)	1(1)	1(2)	0(1)
Alkali	**3**	**3**	2(2)	1(1)	-	-	-
Amide	**2**	**2**	-	1(1)	-	1(1)	-
Amidine	**6**	**5**	-	4(5)	-	-	1(1)
Amine	**23**	**17**	-	14(18)	-	2(2)	1(3)
Amino Acid	**1**	**1**	-	1(1)	-	-	-
Boron Compound	**1**	**1**	-	1(1)	-	-	-
Ester	**30**	**15**	-	8(9)	3(3)	2(5)	2(15)
Ether	**22**	**11**	-	8(12)[7]	1(1)[7]	2(2)[7]	3(14)[7]
Heterocyclic Compound	**13**	**13**	-	9(13)[8]	2(2)[8]	2(2)	1(3)
Hydrocarbon (acyclic)	**7**	**1**	1(1)	-	-	-	0(6)
Hydrocarbon (cyclic)	**11**	**2**	-	-	1(1)	0(1)	1(9)
Hydrocarbon, Halogenated	**13**	**2**	-	-	-	-	2(13)
Isocyanate	**2**	**2**	-	2(2)	-	-	-
Ketone	**8**	**5**	-	-	2(2)	2(4)	1(2)
Lactone	**1**	**1**	-	-	1(1)	-	-
Nitrate	**2**	**2**	1(1)	-	-	1(1)	-
Nitrile	**3**	**3**	-	1(1)	1(1)	1(1)	-
Nitro Compound	**5**	**2**	-	2(2)	-	-(2)	-(1)
Onium Compound	**6**	**6**	-	5(8)[8]	1(1)[8]	1(1)	-(1)
Organophosphorus Compound	**3**	**2**	-	1(1)	1(1)	-	0(1)
Organosilicon Compound	**5**	**4**	-	3(3)	-	1(1)	-(1)
Phenol	**6**	**6**	-	5(7)	-	-	1(1)
Polycyclic Compound	**4**	**3**	-	2(3)	1(1)	-	-
Quinone	**1**	**1**	-	1(1)	-	-	-
Salt (inorganic)	**12**	**12**	7(7)	4(4)	-	-	1(1)
Salt (organic)	**13**	**12**	-	6(7)	-	2(4)	3(3)
Sulfur Compound (inorganic)	**1**	**1**	1(1)	-	-	-	-

Chemical Class[1]	Number of Candidate Substances	Number of Proposed Reference Substances	GHS Category 1[2]		GHS Category 2A	GHS Category 2B	GHS NI[3]
			Based on Human Data	Based on Rabbit Data			
Sulfur Compound (organic)	**15**	**9**	-	7(8)	-	-	2(8)
Urea Compound	**1**	**1**	-	-	-	1(1)	-
Total[9]	**281**	**193**	14(14)	116(143)	22(24)	24(37)	23(95)
Properties of Interest							
Liquid	**163**	**79**	6(6)	40(61)	14(16)[10]	9(13)	10(67)
Solid	**53**	**43**	4(4)	29(31)	1(1)	4(8)	5(9)

[1]Chemical Class=Based on the MeSH Medical Subject Heading. Available http://www.nlm.nih.gov/mesh; substances may be assigned into one or more chemical classes (see **Appendix B**).
[2]GHS = Globally Harmonized System (UN [2003]).
[3]NI = nonirritant.
[4]Numbers in parenthesis indicate the number of candidate substances for that GHS category.
[5]Substances were assigned into one or more chemical classes (see **Appendix B**).
[6]" – " indicates that there are no substances in this category.
[7]Triton X-100 classified as GHS Category 1, 2A/2B and NI.
[8]Cetylpyridinium bromide classified as GHS Category 1 and 2A.
[9]The total number is greater than the total number of proposed reference substances because some substances were assigned to more than one chemical class.
[10]Triton X-100, when tested at 5%, induced a GHS Category 2A response in one study and a Category 2B response in another study; for purposes of classification in this table, Triton X-100 is classified as a Category 2A substance.

Table V-4. Product Classes Represented Among the Proposed Reference Substances, According to GHS[1] Ocular Hazard Classification Category

Product Class	Total[2]	GHS Category 1		GHS Category[3] 2A	GHS Category 2B	GHS NI[4]
		Based on Human Data	Based on Rabbit Data			
Adjuvant, Solubilizer, Wetting Agent	**1**	-[4]	1	-	-	-
Anesthetic	**2**	1	1	-	-	-
Anti-Fungal	**6**	1	4	1	-	-
Anti-Infective	**12**	3	7[3]	3[3]	-	-
Battery Acid	**1**	1	-	-	-	-
Building Material	**2**	1	-	-	-	1
Caustic Agent	**2**	-	2	-	-	-
Chemical Intermediate	**43**	8	23	4	3	5
Cleaner or Cleaning Agent	**15**	6	6	1	1	1
Cosmetic Ingredients, & Perfumes	**11**	-	8	-	2	1
Fertilizers	**4**	4	-	-	-	-
Flame Retardant	**3**	2	1	-	-	-
Food Additives	**9**	2	4	1	1	1
Herbicides	**5**	2	2	1	-	-
Industrial Chemicals & Dyes	**46**	11	28	2	2	3
Laboratory Chemicals	**28**	3	16[3]	3[3]	3	4
Pesticide & Pesticide Intermediates	**17**	1	11	1	1	3
Pharmaceuticals & Pharmaceutical Intermediates	**29**	5	15	1	4	4
Polish	**1**	-	1	-	-	-
Preservative	**4**	2	1	1	-	-
Refrigerant	**1**	1	-	-	-	-
Solvent	**21**	1	8	8	3	1
Surfactants:	**7**	-	5[3]	2[3]	2[3]	2[3]
Anionic	**3**	-	1	-	1	1
Cationic	**2**	-	2[3]	1[3]	-	-
Nonionic	**2**	-	2[3]	1[3]	1[3]	1[3]
Veterinary Agent	**6**	2	4	-	-	-

[1]GHS = United Nations Globally Harmonized System (UN [2003]).

[2]All substances were assigned into one or more product classes by referencing the National Library of Medicine Hazards Substances Database (HSDB), other information was obtained from Material Safety Data Sheets (MSDS) obtained from the commercial supplier; therefore, the total number is greater than the total number of proposed reference substances.

[3]Some substances, when tested at different concentrations, were assigned a different GHS ocular hazard classification. For this table, these substances (Triton X-100 and cetylpyridinium bromide) appear in more than one GHS category column; thus the total numbers in these columns do not add up to the numbers of substances in the total column.

[4]" – " indicates that there are no substances in this category.

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APPENDIX V-A

CANDIDATE SUBSTANCES FOR THE LIST OF PROPOSED REFERENCE SUBSTANCES FOR VALIDATION STUDIES OF *IN VITRO* TEST METHODS FOR THE IDENTIFICATION OF OCULAR CORROSIVES/SEVERE IRRITANTS

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APPENDIX V-A1

CANDIDATE SUBSTANCES FOR THE LIST OF PROPOSED REFERENCE SUBSTANCES FOR VALIDATION STUDIES OF *IN VITRO* TEST METHODS FOR THE IDENTIFICATION OF OCULAR CORROSIVES/SEVERE IRRITANTS (SORTED BY CASRN)

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Candidate Substances (Sorted by CASRN)

CASRN	Substance	In Vivo Data Source	Substance Source	Commercial Availability	Chemical Class	Product Class	Conc. Tested	Amount Tested[1]	Purity	MW	pH	Dermal Corrosivity	# of Animals Tested	Water Solubility	Log Kow	Color	Physical Form Tested	MMAS score
100-37-8	**Diethylethanolamine**	**TSCA**	**Union Carbide Corp.**	**Sigma-Aldrich Corp.**	**Alcohol, Amine**	**Chemical Intermediate, Pharmaceutical Intermediate**	**25%**	**0.1 mL**	**n.a.**	**117.2**	**?**	**?**	**6**	**?**	**?**	**colorless**	**liquid**	**94.7**
100-37-8	Diethylethanolamine	TSCA	Union Carbide Corp.	Sigma-Aldrich Corp.	Alcohol, Amine	Chemical Intermediate, Pharmaceutical Intermediate	50%	0.1 mL	n.a.	117.2	?	?	6	?	?	colorless	liquid	95.0
100-37-8	Diethylethanolamine	TSCA	Union Carbide Corp.	Sigma-Aldrich Corp.	Alcohol, Amine	Chemical Intermediate, Pharmaceutical Intermediate	100%	0.1 mL	n.a.	117.2	?	?	6	?	?	colorless	liquid	82.5
100-42-5	Styrene	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (cyclic)	Chemical Intermediate, Industrial Chemical	100%	0.1 mL	99%	104.2	?	?	4	insoluble	?	colorless	liquid	6.8
10124-65-9	**Potassium laurate**	**NIHS-Ohno**	**Japanese Cosmetic Industry Assn.**	**Pfaltz & Bauer, Inc.**	**Acid (organic) [carboxylic acid], Salt (organic)**	**Cosmetic Ingredient, Pesticide**	**10%**	**0.1 mL**	**n.a.**	**238.4**	**?**	**?**	**3**	**?**	**?**	**?**	**liquid**	**33.7**
101-86-0	**Hexyl cinnamic aldehyde**	**TSCA**	**Confidential**	**International Flavors and Frangrances, Inc. (Bulk)**	**Aldehyde**	**Cosmetic Ingredient, Food Additive, Perfume**	**12.5% in Alcohol**	**0.1 mL**	**n.a.**	**216.3**	**?**	**?**	**3**	**?**	**?**	**?**	**liquid**	**21.3**
102-36-3	**3,4-Dichlorophenyl isocyanate**	**TSCA**	**Mobay Corp.**	**Fisher Scientific International, Inc.**	**Isocyanate**	**Chemical Intermediate, Industrial Chemical**	**100%**	**0.1 mL**	**n.a.**	**188.0**	**?**	**?**	**3**	**?**	**?**	**?**	**liquid**	**10.3**
104-76-7	**2-Ethyl-1-hexanol**	**ECETOC**	**Fisher Scientific International, Inc.**	**Sigma-Aldrich Corp.**	**Alcohol**	**Solvent**	**100%**	**0.1 mL**	**99%**	**130.2**	**4.8**	**noncorrosive**	**4**	**slightly soluble**	**2.82**	**?**	**liquid**	**51.3**
10486-00-7	**Sodium perborate tetrahydrate**	**ECETOC**	**Dupont Corp.**	**Sigma-Aldrich Corp.**	**Boron Compound, Salt (inorganic)**	**Cleaning Agent**	**100%**	**60 mg**	**98.6%**	**153.9**	**10.0**	**noncorrosive**	**6**	**n.a.**	**n.a.**	**?**	**solid**	**30.5**
105-30-6	**2-Methyl-1-pentanol**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Alcohol**	**Solvent**	**100%**	**0.1 mL**	**99%**	**102.2**	**n.a.**	**noncorrosive**	**3**	**soluble (6 g/L)**	**1.75**	**?**	**liquid**	**13.0**
105-34-0	**Methyl cyanoacetate**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Ester, Nitrile**	**Chemical Intermediate**	**100%**	**0.1 mL**	**99%**	**99.1**	**5.7**	**noncorrosive**	**3**	**soluble (54 g/L)**	**n.a.**	**light yellow**	**liquid**	**27.7**
106-91-2	Glycidyl methacrylate	ECETOC	Elf Atochem, Inc.	Sigma-Aldrich Corp.	Ether	Chemical Intermediate, Dental Adhesive, Industrial Chemical	100%	0.1 mL	>99%	142.2	?	?	3	?	?	?	Liquid	28.0
107-83-5	2-Methylpentane	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (acyclic)	Solvent	100%	0.1 mL	>99.5%	86.2	n.a.	noncorrosive	6	14 mg/L	3.74	?	Liquid	2.3
108-10-1	Methyl iso-butyl ketone	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Ketone	Food Additive, Solvent	100%	0.1 mL	98%	100.2	?	?	4	20 mg/mL	1.31	?	liquid	4.8
108-83-8	**Di-iso-butyl ketone**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Ketone**	**Pharmaceutical Intermediate, Solvent**	**100%**	**0.1 mL**	**99%**	**142.2**	**n.a.**	**noncorrosive**	**3**	**0.05 g/ 100 mL**	**n.a.**	**?**	**liquid**	**7.3**
108-88-3	**Toluene**	**ECETOC**	**Fisher Scientific International, Inc.**	**Sigma-Aldrich Corp.**	**Hydrocarbon (cyclic)**	**Chemical Intermediate, Industrial Chemical, Laboratory Chemical**	**100%**	**0.1 mL**	**99%**	**92.1**	**?**	**?**	**4**	**?**	**?**	**colorless**	**liquid**	**9.0**
108-93-0	**Cyclohexanol**	**ECETOC**	**Fisher Scientific International, Inc.**	**Sigma-Aldrich Corp.**	**Alcohol**	**Solvent**	**100%**	**0.1 mL**	**97%**	**100.2**	**4.5**	**noncorrosive**	**4**	**soluble (3.6 mg/100 mL)**	**1.23**	**colorless**	**liquid**	**79.8**
109-64-8	1,3-Dibromopropane	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (halogenated)	Chemical Intermediate, Pesticide Intermediate, Pharmaceutical Intermediate	100%	0.1 mL	98.4%	201.9	?	?	3	1.7 g/L	?	?	liquid	8.0
109-99-9	**Tetrahydrofuran**	**TSCA**	**International Specialty Products Co.**	**Sigma-Aldrich Corp.**	**Ether, Heterocyclic Compound**	**Chemical Intermediate, Industrial Chemical, Pharmaceutical Intermediate, Solvent**	**100%**	**0.1 mL**	**n.a.**	**72.1**	**?**	**?**	**6**	**?**	**?**	**?**	**liquid**	**31.2**
110-03-2	**2,5-Dimethylhexanediol**	**ECETOC**	**BASF**	**Sigma-Aldrich Corp.**	**Alcohol**	**Chemical Intermediate**	**100%**	**40 mg**	**99.5%**	**146.2**	**5.7**	**noncorrosive**	**3**	**soluble**	**n.a.**	**?**	**solid**	**28.3**
110-52-1	1,4-Dibromobutane	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (halogenated)	Chemical Intermediate, Industrial Chemical, Laboratory Chemical	100%	0.1 mL	99.9%	215.9	?	?	3	insoluble	?	?	liquid	6.0
110-53-2	*n*-Amyl bromide	ECETOC	Elf Atochem, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (halogenated)	Chemical Intermediate, Pharmaceutical Intermediate, Solvent	100%	0.1 mL	>98.5%	151.0	?	?	3	?	?	?	liquid	4.0
110-86-1	**Pyridine**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Heterocyclic Compound**	**Pesticide Intermediate, Pharmaceutical Intermediate, Solvent**	**100%**	**0.1 mL**	**99.9+%**	**79.1**	**9.9**	**noncorrosive**	**3**	**soluble**	**0.65**	**?**	**liquid**	**48.0**
111-15-9	Cellosolve acetate	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Ester, Ether	Chemical Intermediate, Pesticide, Pharmaceutical Intermediate, Preservative, Solvent	100%	0.1 mL	99%	305.8	?	?	4	230 g/L	?	?	liquid	15.0
111-18-2	**N,N,N',N`-Tetramethylhexanediamine**	**TSCA**	**Union Carbide Corp.**	**Sigma-Aldrich Corp.**	**Amine**	**Anti-Infective, Industrial Chemical, Laboratory Chemical**	**100%**	**0.005 mL**	**n.a.**	**172.3**	**?**	**?**	**6**	**?**	**?**	**?**	**liquid**	**96.0**
111-24-0	1,5-Dibromopentane	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (halogenated)	Pharmaceutical Intermediate	100%	0.1 mL	99.5%	230.0	?	?	3	insoluble	?	?	liquid	4.7
111-25-1	*n*-Hexyl bromide	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (halogenated)	Industrial Chemical, Pharmaceutical Intermediate	100%	0.1 mL	>98.5%	165.1	?	?	3	?	?	?	liquid	1.3
111-27-3	***n*-Hexanol**	**ECETOC**	**Kodak Co.**	**Sigma-Aldrich Corp.**	**Alcohol**	**Solvent**	**100%**	**0.1 mL**	**98%**	**102.2**	**5.5**	**noncorrosive**	**4**	**soluble (5.8 g/L)**	**2.03**	**?**	**liquid**	**64.8**
111-48-8	Thiodiglycol	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Alcohol, Sulfur Compound (organic)	Industrial Chemical	100%	0.1 mL	99.8%	122.2	?	?	3	?	-0.75	?	liquid	5.3
1115-47-5	***n*-Acetyl-methionine**	**ZEBET**	**n.a.**	**Sigma-Aldrich Corp.**	**Amide, Amino Acid**	**Cosmetic Ingredient, Food Additive, Laboratory Chemical**	**n.a.**	**0.1 mL or 100 mg**	**n.a.**	**191.3**	**2.2**	**?**	**3**	**?**	**?**	**?**	**solid**	**57.3**
111-76-2	**Butyl cellosolve**	**ECETOC**	**Fisher Scientific International, Inc.**	**Sigma-Aldrich Corp.**	**Alcohol**	**Solvent**	**100%**	**0.1 mL**	**99%**	**118.2**	**n.a.**	**noncorrosive**	**3**	**soluble (5 g/L)**	**0.83**	**?**	**liquid**	**68.7**

CASRN	Substance	GHS Classification	Corneal score	Irital score	Conjunctival score	NICEATM Category 1 SubClass [2]	Tested in BCOP	Tested in HET-CAM	Tested in ICE	Tested in IRE	EPA Classification	EU Classification	FHSA Classification	Human Exposure Summary
100-37-8	**Diethylethanolamine**	**Category 1**	**n=6/6, CO=4**	**n=3/3, IR=2 D14**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**irritant**	**A human eye irritant (18, 42, 43)**
100-37-8	Diethylethanolamine	Category 1	n=6/6, CO=4	-	n=6/6, CR/CC>0 D21	4	-	-	-	-	Category I	R41	irritant	A human eye irritant (18, 42, 43)
100-37-8	Diethylethanolamine	Category 1	n=5/6, CO=4	-	-	4	-	-	-	-	Category I	R41	irritant	A human eye irritant (18, 42, 43)
100-42-5	Styrene	nonirritant	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM	?
10124-65-9	**Potassium laurate**	**Category 1**	**n=1/3, CO=4 D14**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**SCNM**	**Human data not located**
101-86-0	**Hexyl cinnamic aldehyde**	**Category 2B**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category III**	**nonirritant**	**SCNM**	**Human data not located**
102-36-3	**3,4-Dichlorophenyl isocyanate**	**Category 1**	**n=3/3, CO>0 D21**	**-**	**-**	**1**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**SCNM**	**An irritant to the human eye, causing lacrimation, and (rarely), conjunctivitis (13, 17)**
104-76-7	**2-Ethyl-1-hexanol**	**Category 2A**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**-**	**Category II**	**R36**	**SCNM**	**Irritation of eyes from vapor or liquid (8, 9)**
10486-00-7	**Sodium perborate tetrahydrate**	**Category 1**	**n=4/6, CO>1 D21**	**-**	**-**	**1**	**X**	**X**	**X**	**-**	**Category I**	**R41**	**SCNM**	**Very few cases of eye irritation were observed (26)**
105-30-6	**2-Methyl-1-pentanol**	**Category 2B**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category III**	**nonirritant**	**SCNM**	**Human data not located**
105-34-0	**Methyl cyanoacetate**	**Category 2A**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**-**	**Category II**	**R36**	**SCNM**	**Human data not located**
106-91-2	Glycidyl methacrylate	nonirritant	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM	?
107-83-5	2-Methylpentane	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant	A human eye irritant (23)
108-10-1	Methyl iso-butyl ketone	nonirritant	-	-	-	-	-	X	X	X	Category III	nonirritant	SCNM	?
108-83-8	**Di-iso-butyl ketone**	**nonirritant**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category IV**	**nonirritant**	**SCNM**	**Causes minor irritation to the eye (4, 20)**
108-88-3	**Toluene**	**nonirritant**	**-**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**Category III**	**nonirritant**	**SCNM**	**Vapors of toluene cause noticeable sensation of irritation to human eyes at 300-440 ppm in air, but even at 800 ppm, irritation is slight. Vapors irritate eyes and upper respiratory tract; liquid irritates eyes (10, 27).**
108-93-0	**Cyclohexanol**	**Category 1**	**n=3/4, CO=3**	**-**	**-**	**2**	**X**	**X**	**X**	**X**	**Category I**	**R41**	**SCNM**	**Irritation to the eyes of human subjects results at air concentrations of 100 ppm, and which occurs after 3 to 5 minutes exposure (13, 22)**
109-64-8	1,3-Dibromopropane	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	?
109-99-9	**Tetrahydrofuran**	**Category 1**	**n=2/6, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**SCNM**	**Review Data**	**irritant**	**A human eye irritant (27)**
110-03-2	**2,5-Dimethylhexanediol**	**Category 1**	**-**	**n=1/3, IR = 1 D21**	**n=1/3, CR=2 D21**	**1**	**X**	**X**	**X**	**-**	**Category I**	**R41**	**SCNM**	**Human data not located**
110-52-1	1,4-Dibromobutane	nonirritant	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM	?
110-53-2	*n*-Amyl bromide	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	?
110-86-1	**Pyridine**	**Category 1**	**n=1/3, CO=4**	**n=1/3, IR=2 D14**	**-**	**4**	**X**	**X**	**X**	**-**	**Category I**	**R41**	**SCNM**	**Causes irritation upon contact with the eyes (6, 20)**
111-15-9	Cellosolve acetate	nonirritant	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM	Human data not located
111-18-2	**N,N,N',N`-Tetramethylhexanediamine**	**Category 1**	**n=6/6, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**irritant**	**Human data not located**
111-24-0	1,5-Dibromopentane	nonirritant	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM	?
111-25-1	*n*-Hexyl bromide	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	?
111-27-3	***n*-Hexanol**	**Category 2A**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**X**	**Category II**	**R36**	**SCNM**	**Reported to cause eye burns (27)**
111-48-8	Thiodiglycol	nonirritant	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM	?
1115-47-5	***n*-Acetyl-methionine**	**Category 1**	**n=1/3, CO=4**	**-**	**-**	**4**	**-**	**X**	**-**	**-**	**SCNM**	**R41**	**SCNM**	**Human data not located**
111-76-2	**Butyl cellosolve**	**Category 1**	**-**	**-**	**n=2/3, CR>0, n=1/3, CC>0 D21**	**1**	**X**	**-**	**-**	**-**	**Category II**	**R36**	**SCNM**	**An irritant to the human eye. In several, single 8 hour exposures to concentrations of 100 to 200 ppm in air, participants reported discomfort and mild eye irritation. 7 workers exposed to aerosol concentrations of 200 to 300 ppm reported intense eye irritation, followed by recurrent ocular irritation after the initial exposure. (1, 14, 21, 24, 30)**

CASRN	Substance	Animal Exposure Summary for Category 1(H) Substances	Notes
100-37-8	**Diethylethanolamine**		
100-37-8	Diethylethanolamine		Severe response at 25% conc. in other study
100-37-8	Diethylethanolamine		Severe response at 25% conc. in other study
100-42-5	Styrene	?	
10124-65-9	**Potassium laurate**		
101-86-0	**Hexyl cinnamic aldehyde**		
102-36-3	**3,4-Dichlorophenyl isocyanate**		
104-76-7	**2-Ethyl-1-hexanol**		
10486-00-7	**Sodium perborate tetrahydrate**		
105-30-6	**2-Methyl-1-pentanol**		
105-34-0	**Methyl cyanoacetate**		
106-91-2	Glycidyl methacrylate	?	
107-83-5	2-Methylpentane		
108-10-1	Methyl iso-butyl ketone	?	
108-83-8	**Di-iso-butyl ketone**		
108-88-3	**Toluene**		
108-93-0	**Cyclohexanol**		
109-64-8	1,3-Dibromopropane	?	
109-99-9	**Tetrahydrofuran**		
110-03-2	**2,5-Dimethylhexanediol**		
110-52-1	1,4-Dibromobutane	?	
110-53-2	*n*-Amyl bromide	?	
110-86-1	**Pyridine**		
111-15-9	Cellosolve acetate		
111-18-2	**N,N,N',N`-Tetramethylhexanediamine**		
111-24-0	1,5-Dibromopentane	?	
111-25-1	*n*-Hexyl bromide	?	
111-27-3	***n*-Hexanol**		
111-48-8	Thiodiglycol	?	
1115-47-5	***n*-Acetyl-methionine**		
111-76-2	**Butyl cellosolve**		

CASRN	Substance	In Vivo Data Source	Substance Source	Commercial Availability	Chemical Class	Product Class	Conc. Tested	Amount Tested[1]	Purity	MW	pH	Dermal Corrosivity	# of Animals Tested	Water Solubility	Log Kow	Color	Physical Form Tested	MMAS score
111-83-1	*n*-Octyl bromide	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (halogenated)	Chemical Intermediate, Industrial Chemical	100%	0.1 mL	>99%	193.1	?	?	3	?	?	?	liquid	2.7
111-86-4	***n*-Octylamine**	**TSCA**	**Hoechst Celanese Corp.**	**Sigma-Aldrich Corp.**	**Amine**	**Chemical Intermediate, Laboratory Chemical**	**100%**	**0.1 mL**	**n.a.**	**129.2**	**?**	**?**	**4**	**?**	**?**	**?**	**liquid**	**79.5**
111-87-5	***n*-Octanol**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Alcohol**	**Solvent**	**100%**	**0.1 mL**	**>99%**	**130.2**	**6.1**	**noncorrosive**	**3**	**insoluble (540 mg/L)**	**3.00**	**?**	**liquid**	**41.0**
1119-62-6	**3,3-Dithiodipropionic acid**	**ECETOC**	**Fluka, Inc.**	**Sigma-Aldrich Corp.**	**Acid (organic) [carboxylic acid], Organosilicon Compound**	**Chemical Intermediate, Laboratory Chemical**	**100%**	**100 mg**	**99%**	**210.3**	**pKa 3.94**	**R34**	**3**	**Very soluble**	**1.38**	**?**	**solid**	**31.7**
112-40-3	*n*-Dodecane	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (acyclic)	Chemical Intermediate, Solvent	100%	0.1 mL	>99.5%	170.3	?	?	6	?	?	?	liquid	3.3
115-27-5	Chlorendic anhydride	TSCA	Velsicol Chemical Corp.	Sigma-Aldrich Corp.	Anhydride	Chemical Intermediate, Flame Retardant	n.a.	100 mg	98.8%	370.8	?	?	6	?	?	?	solid	21.8
116-53-0	**2-Methylbutyric acid**	**TSCA**	**Union Carbide Corp.**	**Sigma-Aldrich Corp.**	**Acid (organic) [carboxylic acid]**	**Chemical Intermediate, Cosmetic Ingredient, Solvent**	**100%**	**0.005 mL**	**97.9%**	**102.1**	**?**	**R34**	**6**	**?**	**1.18**	**?**	**liquid**	**38.3**
120-32-1	**2-Benzyl-4-chlorophenol**	**TSCA**	**Monsanto Co.**	**Sigma-Aldrich Corp.**	**Phenol**	**Anti-Fungal, Anti-Infective, Herbicide**	**100%**	**100 mg**	**95%**	**218.7**	**?**	**?**	**6**	**?**	**?**	**light brown**	**solid**	**100.0**
120-32-1	2-Benzyl-4-chlorophenol	TSCA	Monsanto Co.	Sigma-Aldrich Corp.	Phenol	Anti-Fungal, Anti-Infective, Herbicide	n.a.	0.1 mL	n.a.	218.7	?	?	6	?	?	light brown	liquid	71.5
12141-11-6	**Magnesium hydroxide**	**-**	**-**	**Sigma-Aldrich Corp.**	**Salt (inorganic)**	**Chemical Intermediate, Flame Retardant, Industrial Chemical, Pharmaceutical, Veterinary Agent**	**-**	**-**	**-**	**42.3**	**-**	**-**	**-**	**n.a.**	**n.a.**	**?**	**solid**	**-**
121-54-0	**Benzethonium chloride**	**LNS**	**n.a.**	**Sigma-Aldrich Corp.**	**Amine, Onium Compound**	**Anti-Infective, Pharmaceutical, Veterinary Chemical**	**10%**	**0.1 mL**	**n.a.**	**448.1**	**?**	**?**	**3**	**?**	**?**	**?**	**liquid**	**76.3**
123-72-8	*n*-Butanal	ZEBET	n.a.	Sigma-Aldrich Corp.	Aldehyde	Chemical Intermediate, Food Additive	n.a.	0.1 mL or 100 mg	n.a.	72.1	?	?	3	?	?	?	liquid	12.7
123-86-4	*n*-Butyl acetate	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Ester	Chemical Intermediate, Food Additive, Industrial Chemical, Pesticide, Solvent	100%	0.1 mL	99%	116.2	?	?	4	soluble in acetone, Ether, PPG	1.82	?	liquid	7.5
12427-38-2	**Maneb (solid)**	**ECETOC**	**US EPA**	**Sigma-Aldrich Corp.**	**Amine, Salt (organic), Urea**	**Pesticide**	**100%**	**100 mg**	**90% (approx)**	**265.3**	**8.4**	**noncorrosive**	**6**	**Moderately soluble**	**n.a.**	**?**	**solid**	**14.3**
126-73-8	Phosphoric acid, tributyl ester	TSCA	Mobay Corp.	Sigma-Aldrich Corp.	Acid, Ester	Industrial Chemical	100%	0.1 mL	99.8%	266.3	?	?	3	?	?	?	liquid	13.3
1305-78-8	**Lime**	**-**	**-**	**Sigma-Aldrich Corp.**	**Salt (inorganic)**	**Building Material, Chemical Intermediate, Cleaning Agent, Fertilizer, Industrial Chemical**	**-**	**-**	**-**	**56.1**	**-**	**-**	**-**	**n.a.**	**n.a.**	**white to grayish**	**solid**	**-**
1309-64-4	**Antimony oxide**	**TSCA**	**Monsanto Co.**	**Sigma-Aldrich Corp.**	**Salt (inorganic)**	**Flame Retardant, Industrial Chemical, Laboratory Chemical, Pharmaceutical Intermediate**	**100%**	**100 mg**	**83.5%**	**291.5**	**?**	**noncorrosive**	**6**	**?**	**?**	**white powder**	**solid**	**107.3**
1310-58-3	**Potassium hydroxide**	**-**	**-**	**Sigma-Aldrich Corp.**	**Alkali, Salt (inorganic)**	**Chemical Intermediate, Cleaning Agent, Fertilizer, Food Additive, Industrial Chemical, Veterinary Chemical**	**-**	**-**	**-**	**56.1**	**-**	**-**	**-**	**n.a.**	**n.a.**	**?**	**solid**	**-**
1310-73-2	**Sodium hydroxide**	**ECETOC**	**Fisher Scientific International, Inc.**	**Sigma-Aldrich Corp.**	**Alkali**	**Caustic Agent, Chemical Intermediate, Industrial Chemical, Pharmaceutical Intermediate, Veterinary Chemical**	**10%**	**0.1 mL**	**Reagent Grade**	**40.0**	**12.7**	**R35 (5%)**	**1**	**soluble (1 g/0.9 mL)**	**"virtually 0"**	**?**	**liquid**	**108.0**
1330-20-7	Xylene	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (cyclic)	Industrial Chemical, Laboratory Chemical, Pharmaceutical Intermediate, Solvent	100%	0.1 mL	99%	107.2	?	?	4	?	?	?	liquid	1.5
1330-20-7	Xylene	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (cyclic)	Industrial Chemical, Laboratory Chemical, Pharmaceutical Intermediate, Solvent	100%	0.1 mL	99%	107.2	?	?	4	?	?	?	liquid	9.0

CASRN	Substance	GHS Classification	Corneal score	Irital score	Conjunctival score	NICEATM Category 1 SubClass.[2]	Tested in BCOP	Tested in HET-CAM	Tested in ICE	Tested in IRE	EPA Classification	EU Classification	FHSA Classification	Human Exposure Summary
111-83-1	*n*-Octyl bromide	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	Human data not located
111-86-4	***n*-Octylamine**	**Category 1**	**n=4/4, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**SCNM**	**Human data not located**
111-87-5	***n*-Octanol**	**Category 2A**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**X**	**Category II**	**R36**	**SCNM**	**Has caused injury of the corneal epithelium, with recovery in 48 hours (11)**
1119-62-6	**3,3-Dithiodipropionic acid**	**Category 2B**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category II**	**nonirritant**	**SCNM**	**Human data not located**
112-40-3	*n*-Dodecane	nonirritant	-	-	-	-	-	-	-	-	Category III	nonirritant	nonirritant	?
115-27-5	Chlorendic anhydride	nonirritant	-	-	-	-	-	-	-	-	Category II	R36	irritant	?
116-53-0	**2-Methylbutyric acid**	**Category 1**	**n=2/6, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**Review Data**	**SCNM**	**Human data not located**
120-32-1	**2-Benzyl-4-chlorophenol**	**Category 1**	**n=6/6, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**irritant**	**Human data not located**
120-32-1	2-Benzyl-4-chlorophenol	Category 1	n=5/6, CO>0 D21	n=5/6, IR>0 D21	n=5/6, CR/CC>0 D21	1	-	-	-	-	Category I	R41	irritant	Human data not located
12141-11-6	**Magnesium hydroxide**	**Category 1(H)**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Human ocular exposure to magnesium hydroxide produces combined thermal and alkali injury. Reported effects of exposure to magnesium hydroxide are conjunctival necrosis, symblepharon, keratitis, corneal necrosis, corneal opacities, corneal scarring, corneal ulceration, corneal vascularization and iritis (44, 45)**
121-54-0	**Benzethonium chloride**	**Category 1**	**n=2/3, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**SCNM**	**Human data not located**
123-72-8	*n*-Butanal	Category 2B	-	-	-	-	-	X	-	-	Category III	nonirritant	SCNM	?
123-86-4	*n*-Butyl acetate	nonirritant	-	-	-	-	X	X	X	X	Category III	nonirritant	SCNM	?
12427-38-2	**Maneb (solid)**	**Category 2B**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**X**	**Category III**	**R36**	**irritant**	**Generally regarded as harmless, with no irritation, except for mild conjunctivitis (9)**
126-73-8	Phosphoric acid, tributyl ester	nonirritant	-	-	-	-	-	-	-	-	Category III	nonirritant	Insufficient Animal Data	?
1305-78-8	**Lime**	**Category 1(H)**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**The major complaints of workers exposed to lime consist of eye and skin irritation. Calcium oxide dust irritates the eyes primarily because of its alkalinity. Exposure to lime has been reported to cause conjunctival necrosis, symblepharon, keratitis, corneal necrosis, corneal opacities, corneal scarring, corneal ulceration, corneal vascularization and iritis (1,5,44)**
1309-64-4	**Antimony oxide**	**Category 1**	**n=6/6, CO=4**	**n=6/6, IR=2 D14**	**n=6/6, CR=3, n=3/6, CC=4 D14**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**irritant**	**Chronic exposure causes eye irritation (6, 53)**
1310-58-3	**Potassium hydroxide**	**Category 1(H)**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Eye contact with concentrated alkalis such as potassium hydroxide causes conjunctival edema and corneal destruction. Potassium hydroxide (caustic potash) is one of the strongest alkalies. It is extremely corrosive, and many reports have been made of devastating damage of the eye from contact with either the solid or solutions of potassium hydroxide. The type of injury is essentially the same as that produced by sodium hydroxide and other strong alkalies, and includes iritis, conjunctival necrosis, symblepharon, keratitis, corneal necrosis, opacities, scarring, ulceration and vascularization (1, 11, 27, 45, 47)**
1310-73-2	**Sodium hydroxide**	**Category 1**	**n=1/1, CO=4**	**n=1/1, IR=2 D21**	**n=1/1, CR/CC=3 D21**	**4**	**X**	**X**	**X**	**X**	**Category I**	**R41**	**SCNM**	**Contact with the eyes causes disintegration and sloughing of conjunctival and corneal epithelia, corneal opacification, marked edema, and ulceration; after 7 to 13 days either gradual recovery begins, or there is progression of ulceration and corneal opacification. Opacification may be so severe that iris markings are not discernable. Complications of severe eye burns are symblepharon, with overgrowth of the cornea by a vascularized membrane, progressive or recurrent corneal ulceration, permanent corneal opacification, necrosis of the bulbar conjunctiva, blanched and necrotic corneal cul-de-sac, and blindness. Eye contact; Levels of toxic effect: (1) Irritation. (2) Conjunctivitis, corneal burns. (3) Photophobia. (4) Disintegration and sloughing of conjunctival and corneal epithelium. (5) Corneal edema, ulceration, and opacification. (6) Symblepharon. (7) Overgrowth of the cornea by a vascularized membrane. (8) Permanent corneal opacification. (11, 18)**
1330-20-7	Xylene	nonirritant	-	-	-	-	X	-	-	-	Category IV	nonirritant	SCNM	?
1330-20-7	Xylene	nonirritant	-	-	-	-	-	-	-	-	Category II	nonirritant	SCNM	?

CASRN	Substance	Animal Exposure Summary for Category 1(H) Substances	Notes
111-83-1	*n*-Octyl bromide		
111-86-4	***n*-Octylamine**		
111-87-5	***n*-Octanol**		
1119-62-6	**3,3-Dithiodipropionic acid**		
112-40-3	*n*-Dodecane	?	
115-27-5	Chlorendic anhydride	?	
116-53-0	**2-Methylbutyric acid**		
120-32-1	**2-Benzyl-4-chlorophenol**		
120-32-1	2-Benzyl-4-chlorophenol		Tested as a solid in other study
12141-11-6	**Magnesium hydroxide**	**Milk of magnesia applied to rabbit eyes twice a day for three or four days caused damage to the corneal epithelium, demonstrable by staining with fluorescein. After the applications were discontinued, the corneas returned to normal in two or three days. (10)**	
121-54-0	**Benzethonium chloride**		
123-72-8	*n*-Butanal	?	Conc. tested unknown
123-86-4	*n*-Butyl acetate	?	
12427-38-2	**Maneb (solid)**		
126-73-8	Phosphoric acid, tributyl ester	?	
1305-78-8	**Lime**	**Animal Data Not Located**	
1309-64-4	**Antimony oxide**		
1310-58-3	**Potassium hydroxide**	**Animal Data Not Located**	
1310-73-2	**Sodium hydroxide**		
1330-20-7	Xylene	?	
1330-20-7	Xylene	?	

CASRN	Substance	In Vivo Data Source	Substance Source	Commercial Availability	Chemical Class	Product Class	Conc. Tested	Amount Tested[1]	Purity	MW	pH	Dermal Corrosivity	# of Animals Tested	Water Solubility	Log Kow	Color	Physical Form Tested	MMAS score
133-06-2	**Captan 90-concentrate (solid)**	**ECETOC**	**US EPA**	**Gustafson, LLC**	**Heterocyclic Compound, Sulfur Compound (organic)**	**Pesticide**	**100%**	**100 mg**	**90%**	**300.6**	**8.0**	**noncorrosive**	**3**	**soluble (5.1 mg/L)**	**2.35**	**white**	**solid**	**83.0**
1333-83-1	**Sodium hydrogen difluoride**	**-**	**-**	**Sigma-Aldrich Corp.**	**Salt (inorganic)**	**Anti-Infective, Cleaning Agent, Industrial Chemical, Preservative**	**-**	**-**	**-**	**62.0**	**-**	**-**	**-**	**n.a.**	**n.a.**	**?**	**liquid**	**-**
135-98-8	1-Methylpropyl benzene	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (cyclic)	Solvent	100%	0.1 mL	>99.5%	134.2	?	?	6	0.015 g/L	?	?	liquid	3.7
137-16-6	**N-Laurylsarcosine sodium salt**	**LNS**	**n.a.**	**Sigma-Aldrich Corp.**	**Amide, Amine, Salt (organic)**	**Cleaning Agent, Detergent, Laboratory Chemical, Surfactant (anionic)**	**10%**	**0.1 mL**	**n.a.**	**293.4**	**?**	**?**	**3**	**?**	**?**	**?**	**liquid**	**31.0**
140-66-9	**4-(1,1,3,3-Tetramethylbutyl)phenol**	**TSCA**	**Rohm and Haas Co.**	**Sigma-Aldrich Corp.**	**Phenol**	**Chemical Intermediate**	**100%**	**100 mg**	**n.a.**	**206.3**	**?**	**?**	**6**	**?**	**?**	**?**	**solid**	**90.0**
140-72-7	Cetylpyridinium bromide	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Onium Compound, Heterocyclic Compound	Anti-Infective; Laboratory Chemical; Surfactant (cationic)	0.10%	0.1 mL	99%	384.4	4.8	noncorrosive	4	soluble (5 g/L)	1.83 (100%)	faintly beige	liquid	2.7
140-72-7	**Cetylpyridinium bromide**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Onium Compound, Heterocyclic Compound**	**Anti-Infective; Laboratory Chemical; Surfactant (cationic)**	**1%**	**0.1 mL**	**99%**	**384.4**	**6.4**	**noncorrosive**	**6**	**soluble (5 g/L)**	**1.83 (100%)**	**faintly beige**	**liquid**	**36.0**
140-72-7	**Cetylpyridinium bromide**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Onium Compound, Heterocyclic Compound**	**Anti-Infective; Laboratory Chemical; Surfactant (cationic)**	**6%**	**0.1 mL**	**99%**	**384.4**	**6.0-8.0 (0.5%)**	**noncorrosive**	**4**	**soluble (5 g/L)**	**1.83 (100%)**	**faintly beige**	**liquid**	**85.8**
140-72-7	Cetylpyridinium bromide	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Onium Compound, Heterocyclic Compound	Anti-Infective; Laboratory Chemical; Surfactant (cationic)	10%	0.1 mL	99%	384.4	6.0-8.0 (0.5%)	noncorrosive	6	soluble (5 g/L)	1.83 (100%)	faintly beige	liquid	89.7
14075-53-7	**Potassium tetrafluoroborate**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Salt (inorganic)**	**Industrial Chemical, Pesticide**	**100%**	**100 mg**	**>99%**	**125.9**	**n.a.**	**R34**	**3**	**4.4 g/L**	**n.a.**	**n.a.**	**solid**	**0.0**
141-78-6	Ethyl acetate	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Ester	Cleaning Agent, Food Additive, Solvent	100%	0.1 mL	99%	88.1	?	?	4	80 g/L	?	colorless	liquid	15.0
143-07-7	**Lauric acid**	**ECETOC**	**Unichema International, Inc.**	**Sigma-Aldrich Corp.**	**Acid (organic) [carboxylic acid]**	**Surfactant (anionic)**	**100%**	**52 mg**	**>92%**	**200.3**	**4.2**	**noncorrosive**	**3**	**insoluble**	**4.20**	**colorless**	**solid**	**38.0**
1462-55-1	**2-(n-Dodecylthio)ethanol**	**ECETOC**	**Elf Atochem, Inc.**	**Sigma-Aldrich Corp.**	**Alcohol, Ether, Sulfur Compound (organic)**	**Chemical Intermediate**	**100%**	**100 mg**	**>99%**	**206.3**	**?**	**?**	**3**	**?**	**?**	**white**	**solid**	**0.0**
14866-33-2	**tetra-N-Octylammonium bromide**	**GSK**	**n.a.**	**Sigma-Aldrich Corp.**	**Onium Compound**	**Industrial Chemical, Laboratory Chemical**	**100%**	**0.1 mL or 100 mg**	**n.a.**	**546.8**	**?**	**?**	**1**	**?**	**?**	**?**	**solid**	**0.0**
1498-51-7	**Phosphorodicloridic acid, ethyl ester**	**TSCA**	**Rhone-Poulenc, Inc.**	**Sigma-Aldrich Corp.**	**Ester, Organophosphorus Compound**	**Chemical Intermediate, Pesticide**	**100%**	**0.1 mL**	**96%**	**162.9**	**?**	**R34**	**6**	**?**	**?**	**?**	**liquid**	**100.0**
151-21-3	**Sodium lauryl sulfate**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Acid (organic) [carboxylic acid], Salt (organic)**	**Cleaning Agent, Cosmetic Ingredient, Food Additive, Laboratory Chemical, Pesticide Intermediate, Surfactant (anionic)**	**3%**	**0.1 mL**	**98 %**	**288.4**	**8.0-10.0 (1% aq.)**	**noncorrosive**	**6**	**1 g/10 mL**	**1.60 (100%)**	**?**	**liquid**	**7.3**
1569-01-3	**Propasol Solvent P**	**TSCA**	**Union Carbide Corp.**	**Sigma-Aldrich Corp.**	**Alcohol**	**Solvent**	**100%**	**0.1 mL**	**n.a.**	**118.2**	**?**	**?**	**6**	**?**	**?**	**?**	**liquid**	**31.2**
1623-08-1	**Dibenzyl phosphate**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Ester, Organophosphorus Compound**	**Pesticide**	**100%**	**100 mg**	**99%**	**278.2**	**2.4**	**noncorrosive**	**3**	**n.a.**	**n.a.**	**?**	**solid**	**30.0**
1647-16-1	1,9-Decadiene	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Hydrocarbon (acyclic)	Chemical Intermediate	100%	0.1 mL	98%	138.3	?	?	6	?	?	?	liquid	5.7
16603-84-2	**Aluminum chloride**	**TSCA**	**Monsanto Co.**	**Fisher Scientific International, Inc.**	**Salt (inorganic)**	**Chemical Intermediate, Dye, Industrial Chemical, Laboratory Chemical, Pesticide, Preservative**	**n.a.**	**0.1 mL**	**n.a.**	**98.9**	**?**	**?**	**6**	**?**	**?**	**light yellow-green**	**liquid**	**82.7**
17831-71-9	**Tetraethylene glycol diacrylate**	**TSCA**	**Rhone-Poulenc, Inc.**	**Sigma-Aldrich Corp.**	**Ether, Nitro Compound**	**Chemical Intermediate, Industrial Chemical**	**100%**	**0.1 mL**	**n.a.**	**302.3**	**?**	**?**	**6**	**?**	**?**	**?**	**liquid**	**103.3**
2004-03-7	**6-Methyl purine**	**TSCA**	**Monsanto Co.**	**Sigma-Aldrich Corp.**	**Heterocyclic Compound**	**Laboratory Chemical, Pharmaceutical Intermediate**	**100%**	**0.1 mL**	**n.a.**	**134.1**	**-**	**-**	**6**	**?**	**?**	**?**	**liquid**	**48.7**
2365-48-2	**Methylthioglycolate**	**ECETOC**	**Elf Atochem, Inc.**	**Sigma-Aldrich Corp.**	**Ester, Sulfur Compound (organic)**	**Industrial Chemical**	**100%**	**0.1 mL**	**99.7%**	**106.1**	**pKa 8.22**	**noncorrosive**	**3**	**Soluble**	**0.65**	**?**	**liquid**	**53.0**
2370-63-0	2-Ethoxyethyl methacrylate	ECETOC	Elf Atochem, Inc.	Sigma-Aldrich Corp.	Ester, Ether	Dental Adhesive	100%	0.1 mL	99.8%	158.2	n.a.	noncorrosive	3	n.a.	n.a.	?	liquid	0.7
2469-55-8	**Bis-(3-aminopropyl) tetramethyl disiloxane**	**TSCA**	**General Electric Co.**	**Sigma-Aldrich Corp.**	**Amine, Amidine, Organosilicon Compound**	**Industrial Chemical**	**100%**	**0.1 mL**	**n.a.**	**248.5**	**n.a.**	**R34**	**2**	**n.a.**	**n.a.**	**?**	**liquid**	**109.0**
25103-09-7	**iso-Octylthioglycolate**	**ECETOC**	**Elf Atochem, Inc.**	**Sigma-Aldrich Corp.**	**Ester, Sulfur Compound (organic)**	**Industrial Chemical**	**100%**	**0.1 mL**	**99%**	**204.3**	**n.a.**	**noncorrosive**	**3**	**n.a.**	**n.a.**	**clear, water-white**	**liquid**	**4.0**
2530-87-2	(3-chloropropyl)trimethoxy-Silane	TSCA	Union Carbide Corp.	Fisher Scientific International, Inc.	Ether	Industrial Chemical	100%	0.1 mL	96.3%	198.7	?	?	6	?	?	colorless to yellow	liquid	0.3
2530-87-2	(3-chloropropyl)trimethoxy-Silane	TSCA	Union Carbide Corp.	Fisher Scientific International, Inc.	Ether	Industrial Chemical	100%	0.1 mL	99.7%	198.7	?	?	6	?	?	colorless to yellow	liquid	0.0
25791-96-2	Polyol 355 UCB	ISOPA	Dow Europe S.A.	Dow Chemical Co. (Bulk)	Ether	Industrial Chemical	100%	0.1 mL	99.98%	n.a.	?	?	3	?	?	?	liquid	0.0

CASRN	Substance	GHS Classification	Corneal score	Irital score	Conjunctival score	NICEATM Category 1 SubClass.[2]	Tested in BCOP	Tested in HET-CAM	Tested in ICE	Tested in IRE	EPA Classification	EU Classification	FHSA Classification	Human Exposure Summary
133-06-2	**Captan 90-concentrate (solid)**	**Category 1**	**n=3/3, CO=4**	**n=1/3, IR>0 D21**	**n=2/3, CR/CC>0 D21**	**4**	**X**	**X**	**X**	**-**	**Category I**	**R41**	**SCNM**	**Has been reported to cause conjunctivitis (12)**
1333-83-1	**Sodium hydrogen difluoride**	**Category 1(H)**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Exposure to concentrated sodium hydrogen difluoride has caused corneal necrosis, opacification, scarring, ulceration, vascularization (11, 23)**
135-98-8	1-Methylpropyl benzene	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant	?
137-16-6	**N-Laurylsarcosine sodium salt**	**Category 2B**	**-**	**-**	**-**	**-**	**X**	**-**	**-**	**-**	**Category III**	**nonirritant**	**SCNM**	**Human data not located**
140-66-9	**4-(1,1,3,3-Tetramethylbutyl)phenol**	**Category 1**	**n=6/6, CO=3**	**n=6/6, IR=2**	**-**	**2**	**-**	**-**	**-**	**-**	**SCNM**	**R41**	**SCNM**	**A human eye irritant (23)**
140-72-7	Cetylpyridinium bromide	nonirritant	-	-	-	-	X	X	-	-	Category I	R41	irritant	?
140-72-7	**Cetylpyridinium bromide**	**Category 2A**	**-**	**-**	**-**	**-**	**-**	**X**	**-**	**X**	**SCNM**	**R41**	**SCNM**	**Human data not located**
140-72-7	**Cetylpyridinium bromide**	**Category 1**	**-**	**n=3/4, I>1.5**	**-**	**2**	**X**	**-**	**X**	**X**	**Category II**	**R36**	**irritant**	**Human data not located**
140-72-7	Cetylpyridinium bromide	Category 1	n=3/6, CO=4	n=6/6, I>1.5	-	4	X	X	X	X	Category III	nonirritant	SCNM	Human data not located
14075-53-7	**Potassium tetrafluoroborate**	**nonirritant**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category IV**	**nonirritant**	**SCNM**	**Human data not located**
141-78-6	Ethyl acetate	nonirritant	-	-	-	-	X	X	X	X	Category III	nonirritant	SCNM	?
143-07-7	**Lauric acid**	**Category 1**	**n=3/3, CO>1 D21**	**-**	**n=3/3, CR=1 D21**	**1**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**SCNM**	**Human data not located**
1462-55-1	**2-(n-Dodecylthio)ethanol**	**nonirritant**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category IV**	**nonirritant**	**SCNM**	**Human data not located**
14866-33-2	**tetra-N-Octylammonium bromide**	**Category 1**	**-**	**-**	**-**	**0 (likely 4)**	**-**	**-**	**-**	**X**	**Category I**	**R41**	**SCNM**	**Human data not located**
1498-51-7	**Phosphorodicloridic acid, ethyl ester**	**Category 1**	**n=6/6, CO=4**	**-**	**n=6/6, CR=3, CC=4 D21**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**irritant**	**Vapor causes eye irritation; liquid causes sever burns to eye (27)**
151-21-3	**Sodium lauryl sulfate**	**nonirritant**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**X**	**Category III**	**nonirritant**	**irritant**	**Sodium lauryl sulfate is said to have been the commonest cause of eye irritation by commercial shampoos (10)**
1569-01-3	**Propasol Solvent P**	**Category 2B**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category II**	**nonirritant**	**irritant**	**Human data not located**
1623-08-1	**Dibenzyl phosphate**	**Category 2A**	**-**	**-**	**-**	**-**	**X**	**-**	**X**	**-**	**Category II**	**R36**	**SCNM**	**Human data not located**
1647-16-1	1,9-Decadiene	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant	?
16603-84-2	**Aluminum chloride**	**Category 1**	**n=5/6, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**irritant**	**Is caustic and irritating to the human eye, but in only 1 out of 55 instances of industrial corneal burns has healing been delayed beyond 2 days (10)**
17831-71-9	**Tetraethylene glycol diacrylate**	**Category 1**	**n=5/6, CO=4**	**n=6/6, IR=2 D14**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**irritant**	**Human data not located**
2004-03-7	**6-Methyl purine**	**Category 2B**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category IV**	**R36**	**irritant**	**Human data not located**
2365-48-2	**Methylthioglycolate**	**Category 1**	**n=1/3, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**Category II**	**R36**	**SCNM**	**Human data not located**
2370-63-0	2-Ethoxyethyl methacrylate	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	Human data not located
2469-55-8	**Bis-(3-aminopropyl) tetramethyl disiloxane**	**Category 1**	**n=2/2, CO=4**	**n=2/2, IR=2**	**n=2/2, CR=3, CC=4**	**4**	**-**	**-**	**-**	**-**	**Category I**	**Review Data**	**SCNM**	**Human data not located**
25103-09-7	**iso-Octylthioglycolate**	**nonirritant**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category IV**	**nonirritant**	**SCNM**	**Human data not located**
2530-87-2	(3-chloropropyl)trimethoxy-Silane	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant	?
2530-87-2	(3-chloropropyl)trimethoxy-Silane	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant	?
25791-96-2	Polyol 355 UCB	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	?

CASRN	Substance	Animal Exposure Summary for Category 1(H) Substances	Notes
133-06-2	**Captan 90-concentrate (solid)**		
1333-83-1	**Sodium hydrogen difluoride**	**This substance causes the formation of hydrofluoric acid when exposed to mucous membranes. Ocular toxicity is caused by hydrofluoric acid. In inhalation studies in rabbits and guinea pigs, a concentration of 50 MG/CU M, hydrogen fluoride induced discharge from the eyes. Experimental splash burns of hydrofluoric acid into the eyes of rabbits have shown a 20% solution to cause immediate damage with total corneal opacification with conjunctival ischemia, and with corneal stromal edema within an hour, followed by necrosis of anterior ocular structures. An 8% solution produced ischemia and corneal stromal edema persisting for 40-65 days, accompanied by corneal vascularization. Even a 2% a solution caused mild persistent stromal edema and vascularization., (6, 11)**	
135-98-8	1-Methylpropyl benzene	?	
137-16-6	**N-Laurylsarcosine sodium salt**		
140-66-9	**4-(1,1,3,3-Tetramethylbutyl)phenol**		
140-72-7	Cetylpyridinium bromide	?	
140-72-7	**Cetylpyridinium bromide**		
140-72-7	**Cetylpyridinium bromide**		
140-72-7	Cetylpyridinium bromide		Severe response at 6% in other study, severity based on irital effects
14075-53-7	**Potassium tetrafluoroborate**		
141-78-6	Ethyl acetate	?	
143-07-7	**Lauric acid**		
1462-55-1	**2-(n-Dodecylthio)ethanol**		
14866-33-2	**tetra-N-Octylammonium bromide**		
1498-51-7	**Phosphorodicloridic acid, ethyl ester**		
151-21-3	**Sodium lauryl sulfate**		
1569-01-3	**Propasol Solvent P**		
1623-08-1	**Dibenzyl phosphate**		
1647-16-1	1,9-Decadiene	?	
16603-84-2	**Aluminum chloride**		
17831-71-9	**Tetraethylene glycol diacrylate**		
2004-03-7	**6-Methyl purine**		
2365-48-2	**Methylthioglycolate**		
2370-63-0	2-Ethoxyethyl methacrylate		
2469-55-8	**Bis-(3-aminopropyl) tetramethyl disiloxane**		
25103-09-7	**iso-Octylthioglycolate**		
2530-87-2	(3-chloropropyl)trimethoxy-Silane	?	
2530-87-2	(3-chloropropyl)trimethoxy-Silane	?	
25791-96-2	Polyol 355 UCB	?	

CASRN	Substance	In Vivo Data Source	Substance Source	Commercial Availability	Chemical Class	Product Class	Conc. Tested	Amount Tested[1]	Purity	MW	pH	Dermal Corrosivity	# of Animals Tested	Water Solubility	Log Kow	Color	Physical Form Tested	MMAS score
2664-55-3	Nonyl acrylate	ECETOC	Elf Atochem, Inc.	Elf Atochem, Inc. (Bulk)	Ester	Industrial Chemical	100%	0.1 mL	99%	198.3	?	?	3	?	?	?	liquid	0.0
2743-38-6	Dibenzoyl-L-tartaric acid	LNS	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Acid (organic) [carboxylic acid], Ester	Chemical Intermediate	20%	0.1 mL	n.a.	358.3	2.4	noncorrosive	3	slightly soluble	n.a.	?	liquid	33.7
2743-38-6	**Dibenzoyl-L-tartaric acid**	**ECETOC**	**n.a.**	**Sigma-Aldrich Corp.**	**Acid (organic) [carboxylic acid], Ester**	**Chemical Intermediate**	**100%**	**100 mg**	**98%**	**358.3**	**n.a.**	**noncorrosive**	**3**	**slightly soluble**	**n.a.**	**?**	**solid**	**36.7**
288-32-4	Imidazole	LNS	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Heterocyclic Compound	Anti-Fungal	20%	0.1 mL	n.a.	68.1	10.3	R34	3	soluble (633 g/L)	n.a.	?	liquid	48.7
288-32-4	**Imidazole**	**ECETOC**	**n.a.**	**Sigma-Aldrich Corp.**	**Heterocyclic Compound**	**Anti-Fungal**	**100%**	**100 mg**	**99%**	**68.1**	**10.3**	**R34**	**3**	**soluble (633 g/L)**	**n.a.**	**?**	**solid**	**59.3**
2921-88-2	Chlorpyrifos	TSCA	Dow Chemical Co.	Sigma-Aldrich Corp.	Organophosphorus Compound	Pesticide	100%	0.1 mL	100.0%	350.6	?	?	6	?	?	white	liquid	0.0
2943-75-1	Triethyoxyoctylsilane	TSCA	Union Carbide Corp.	Fisher Scientific International, Inc.	Organosilicon Compound	Industrial Chemical	100%	0.1 mL	97.3%	276.5	?	?	6	?	?	?	liquid	2.7
29590-42-9	**iso-Octyl acrylate**	**ECETOC**	**Elf Atochem, Inc.**	**Sigma-Aldrich Corp.**	**Ester**	**Building Material**	**100%**	**0.1 mL**	**>99%**	**184.3**	**n.a.**	**noncorrosive**	**3**	**n.a.**	**n.a.**	**?**	**liquid**	**5.3**
29911-27-1	**Butyl Dipropasol Solvent**	**TSCA**	**Union Carbide Corp.**	**Sigma-Aldrich Corp.**	**Alcohol, Ether**	**Solvent**	**100%**	**0.1 mL**	**99%**	**176.3**	**?**	**?**	**6**	**?**	**?**	**?**	**liquid**	**24.7**
302-95-4	**Deoxycholic acid sodium salt**	**LNS**	**n.a.**	**Sigma-Aldrich Corp.**	**Alcohol, Acid (organic) [carboxylic acid], Polycyclic Compound, Salt (organic)**	**Anti-Infective, Laboratory Chemical, Solvent**	**10%**	**0.1 mL**	**n.a.**	**414.6**	**?**	**?**	**3**	**?**	**?**	**?**	**liquid**	**38.0**
30525-89-4	**Granuform**	**ZEBET**	**n.a.**	**Sigma-Aldrich Corp.**	**Aldehyde, Ether**	**Anti-Fungal, Anti-Infective, Industrial Chemical, Laboratory Chemical**	**n.a.**	**0.1 mL or 100 mg**	**n.a.**	**30.0**	**4.0**	**?**	**3**	**?**	**?**	**?**	**solid**	**75.3**
311-89-7	Perfluorotributylamine	TSCA	3M Corp.	Fisher Scientific International, Inc.	Amine	Industrial Chemical	100%	0.1 mL	80-90%	671.1	?	?	6	?	?	?	liquid	0.0
3121-61-7	**Methoxyethyl acrylate**	**ECETOC**	**Elf Atochem, Inc.**	**Sigma-Aldrich Corp.**	**Ester, Ether**	**Chemical Intermediate, Industrial Chemical, Laboratory Chemical**	**100%**	**0.1 mL**	**99.6%**	**130.1**	**n.a.**	**noncorrosive**	**3**	**Soluble**	**0.08**	**?**	**liquid**	**45.0**
3173-53-3	**Cyclohexyl isocyanate**	**TSCA**	**Mobay Corp.**	**Sigma-Aldrich Corp.**	**Isocyanate**	**Anesthetic, Chemical Intermediate, Cleaning Agent, Industrial Chemical, Pharmaceutical Intermediate, Solvent**	**100%**	**0.1 mL**	**Technical Grade**	**125.2**	**n.a.**	**R34**	**2**	**insoluble**	**6.11**	**?**	**liquid**	**101.0**
328-50-7	**alpha-Ketoglutaric acid alpha**	**ZEBET**	**n.a.**	**Sigma-Aldrich Corp.**	**Acid (organic) [carboxylic acid]**	**Chemical Intermediate, Laboratory Chemical, Pharmaceutical,**	**n.a.**	**0.1 mL or 100 mg**	**n.a.**	**146.1**	**?**	**?**	**3**	**?**	**?**	**?**	**solid**	**93.0**
3446-89-7	*p*-Methylthiobenzaldehye	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Aldehyde, Ether, Sulfur Compound (organic)	Chemical Intermediate	100%	0.1 mL	98.2%	152.2	?	?	3	?	?	?	liquid	1.3
355-42-0	Perfluoro-n-hexane	TSCA	3M Corp.	Fisher Scientific International, Inc.	Hydrocarbon (halogenated)	Industrial Chemical	100%	0.1 mL	>90%	338.0	?	?	3	?	?	?	liquid	0.0
355-42-0	Perfluoro-n-hexane	TSCA	3M Corp.	Fisher Scientific International, Inc.	Hydrocarbon (halogenated)	Industrial Chemical	100%	0.1 mL	90%	338.0	?	?	3	?	?	?	liquid	0.0
3926-62-3	Sodium monochloroacetate	ZEBET	n.a.	Sigma-Aldrich Corp.	Acid (organic) [carboxylic acid], Salt (organic)	Chemical Intermediate, Herbicide, Pharmaceutical Intermediate	n.a.	0.1 mL or 100 mg	n.a.	116.5	?	?	3	?	?	?	solid	15.7
392-68-7	Trifluoroethyl methacrylate	ECETOC	Elf Atochem, Inc.	Elf Atochem, Inc. (Bulk)	Ester	Industrial Chemical	100%	0.1 mL	99.9%	n.a.	?	?	3	?	?	?	liquid	2.7
3938-95-2	Ethyl trimethyl acetate	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Ester	Industrial Chemical	100%	0.1 mL	99%	130.2	?	?	6	?	?	?	liquid	3.8
3964-18-4	2,3-Dimethyl 2,3-dinitrobutane	TSCA	Dow Chemical Co.	Dow Chemical Co. (Bulk)	Nitro Compound	Industrial Chemical	100%	100 mg	>95%	176.2	?	?	6	?	?	?	solid	4.3
3970-62-5	**2,2-Dimethyl-3-pentanol**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Alcohol**	**Pharmaceutical**	**100%**	**0.1 mL**	**97%**	**116.2**	**n.a.**	**noncorrosive**	**3**	**insoluble**	**n.a.**	**colorless**	**liquid**	**8.3**
41253-21-8	**1,2,4-Triazole, sodium salt**	**ECETOC**	**Elf Atochem, Inc.**	**Sigma-Aldrich Corp.**	**Heterocyclic Compound, Salt (organic)**	**Anti-Fungal**	**100%**	**100 mg**	**99%**	**91.1**	**n.a.**	**noncorrosive**	**1**	**soluble**	**n.a.**	**brown**	**solid**	**104.0**
446-35-5	**2,4-Difluoronitrobenzene**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Hydrocarbon (halogenated)**	**Pesticide, Pharmaceutical Intermediate**	**100%**	**0.1 mL**	**99%**	**159.1**	**n.a.**	**noncorrosive**	**6**	**n.a.**	**n.a.**	**n.a.**	**solid**	**4.7**
4659-45-4	**2,6-Dichlorobenzoyl chloride**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Acyl Halide**	**Anti-Fungal, Anti-Infective**	**100%**	**0.1 mL**	**99%**	**209.5**	**2.5**	**R34**	**6**	**insoluble**	**2.57**	**slight yellow**	**liquid**	**23.8**
50-21-5	**Lactic Acid**	**NIHS-Ohno**	**Japanese Cosmetic Industry Assn.**	**Sigma-Aldrich Corp.**	**Alcohol, Acid (organic) [carboxylic acid]**	**Cosmetic Ingredient**	**100%**	**0.1 mL**	**n.a.**	**90.1**	**1.9**	**R34**	**3**	**soluble**	**-0.72**	**colorless**	**liquid**	**102.7**
52625-13-5	Polyol XZ 95435.00	ISOPA	Dow Europe GmbH	Dow Chemical Co. (Bulk)	Alcohol, Ether	Industrial Chemical	100%	0.1 mL	>99.5%	530.7	?	?	3	?	?	?	liquid	0.0
5333-48-2	Iso-myristyl alcohol	ECETOC	Elf Atochem, Inc.	Elf Atochem, Inc. (Bulk)	Alcohol	Industrial Chemical, Solvent	100%	0.1 mL	92.6%	n.a.	?	?	3	?	?	?	liquid	8.0
5351-04-2	**Diethylaminopropionitrile**	**ECETOC**	**Elf Atochem, Inc.**	**Fisher Scientific International, Inc.**	**Amine, Nitrile**	**Industrial Chemical**	**100%**	**0.1 mL**	**>98.8%**	**126.2**	**n.a.**	**noncorrosive**	**3**	**soluble**	**0.77**	**yellow**	**liquid**	**62.3**
538-71-6	**Domiphen bromide**	**NIHS-Ohno**	**Japanese Cosmetic Industry Assn.**	**Sigma-Aldrich Corp.**	**Ether, Onium Compound, Salt (organic)**	**Anti-Infective, Pharmaceutical**	**10%**	**0.1 mL**	**n.a.**	**414.5**	**6.2**	**noncorrosive**	**3**	**n.a.**	**n.a.**	**?**	**liquid**	**96.3**
5392-28-9	**tetra-Aminopyrimidine sulfate**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Amine, Heterocyclic Compound, Salt (organic)**	**Chemical Intermediate**	**100%**	**100 mg**	**97%**	**238.2**	**n.a.**	**noncorrosive**	**3**	**slightly soluble**	**n.a.**	**?**	**solid**	**10.3**
54029-45-7	**2-Nitro-4-thiocyanoaniline**	**GSK**	**n.a.**	**Sigma-Aldrich Corp.**	**Amine, Nitro Compound, Sulfur Compound (organic)**	**Industrial Chemical**	**100%**	**0.1 mL or 100 mg**	**n.a.**	**195.2**	**?**	**?**	**1**	**?**	**?**	**?**	**solid**	**63.0**
542-08-5	Isopropyl acetoacetate	ZEBET	n.a.	Sigma-Aldrich Corp.	Ester, Ketone	Chemical Intermediate	n.a.	0.1 mL or 100 mg	n.a.	144.2	?	?	3	?	?	?	?	12.0
542-76-7	**3-Chloropropionitrile**	**ECETOC**	**Fluka, Inc.**	**Sigma-Aldrich Corp.**	**Nitrile**	**Chemical Intermediate, Pharmaceutical Intermediate**	**100%**	**0.1 mL**	**99.9%**	**89.5**	**n.a.**	**noncorrosive**	**3**	**soluble (45 g/100 mL)**	**0.18**	**?**	**liquid**	**13.7**

CASRN	Substance	GHS Classification	Corneal score	Irital score	Conjunctival score	NICEATM Category 1 SubClass.[2]	Tested in BCOP	Tested in HET-CAM	Tested in ICE	Tested in IRE	EPA Classification	EU Classification	FHSA Classification	Human Exposure Summary
2664-55-3	Nonyl acrylate	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	?
2743-38-6	Dibenzoyl-L-tartaric acid	Category 1	n=2/3, CO=4	-	-	4	-	-	X	-	SCNM	R41	SCNM	Human data not located
2743-38-6	**Dibenzoyl-L-tartaric acid**	**Category 1**	**n=3/3, CO=3**	**-**	**-**	**3**	**X**	**X**	**X**	**-**	**Category I**	**R41**	**SCNM**	**Human data not located**
288-32-4	Imidazole	Category 1	n=1/3, CO=3 D14	-	-	1	-	-	-	-	Category I	R41	SCNM	Human data not located
288-32-4	**Imidazole**	**Category 1**	**n=2/3, CO=4**	**n=2/3, I>1.5**	**-**	**4**	**X**	**X**	**X**	**X**	**Category I**	**R41**	**SCNM**	**Human data not located**
2921-88-2	Chlorpyrifos	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant	?
2943-75-1	Triethyoxyoctylsilane	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant	?
29590-42-9	**iso-Octyl acrylate**	**nonirritant**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category IV**	**nonirritant**	**SCNM**	**Human data not located**
29911-27-1	**Butyl Dipropasol Solvent**	**Category 2B**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category III**	**nonirritant**	**irritant**	**Human data not located**
302-95-4	**Deoxycholic acid sodium salt**	**Category 2A**	**-**	**-**	**-**	**-**	**X**	**-**	**-**	**-**	**Category II**	**R36**	**SCNM**	**Human data not located**
30525-89-4	**Granuform**	**Category 1**	**n=1/3, CO=4**	**-**	**-**	**4**	**-**	**X**	**-**	**-**	**SCNM**	**Review Data**	**SCNM**	**A human eye irritant (27, 55)**
311-89-7	Perfluorotributylamine	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant	?
3121-61-7	**Methoxyethyl acrylate**	**Category 1**	**n=2/3, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**SCNM**	**R36**	**SCNM**	**Human data not located**
3173-53-3	**Cyclohexyl isocyanate**	**Category 1**	**n=2/2, CO=4**	**-**	**-**	**4**	**-**	**-**	**X**	**-**	**Category I**	**R41**	**SCNM**	**Human data not located**
328-50-7	**alpha-Ketoglutaric acid alpha**	**Category 1**	**n=2/3, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**SCNM**	**R41**	**SCNM**	**Human data not located**
3446-89-7	*p*-Methylthiobenzaldehye	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	?
355-42-0	Perfluoro-n-hexane	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	Insufficient Animal Data	?
355-42-0	Perfluoro-n-hexane	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	Insufficient Animal Data	?
3926-62-3	Sodium monochloroacetate	Category 2B	-	-	-	-	-	X	-	-	Category III	R36	SCNM	?
392-68-7	Trifluoroethyl methacrylate	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	?
3938-95-2	Ethyl trimethyl acetate	nonirritant	-	-	-	-	-	X	X	-	Category III	nonirritant	nonirritant	?
3964-18-4	2,3-Dimethyl 2,3-dinitrobutane	nonirritant	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM	?
3970-62-5	**2,2-Dimethyl-3-pentanol**	**nonirritant**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category III**	**nonirritant**	**SCNM**	**Human data not located**
41253-21-8	**1,2,4-Triazole, sodium salt**	**Category 1**	**n=1/1, CO=4**	**n=1/1, IR=2**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**SCNM**	**Human data not located**
446-35-5	**2,4-Difluoronitrobenzene**	**nonirritant**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category III**	**nonirritant**	**SCNM**	**Human data not located**
4659-45-4	**2,6-Dichlorobenzoyl chloride**	**Category 2A**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**-**	**Category II**	**R36**	**irritant**	**Human data not located**
50-21-5	**Lactic Acid**	**Category 1**	**n=3/3, CO=4**	**-**	**n=3/3, CR/CC=2 D14**	**4**	**-**	**X**	**-**	**-**	**Category I**	**R41**	**SCNM**	**Effect on the eye is similar to that of other acids of moderate strength, causing initial epithelial coagulation on the cornea and conjunctiva; more concentrated solutions can cause severe burns of the skin or eye (10, 20)**
52625-13-5	Polyol XZ 95435.00	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	?
5333-48-2	Iso-myristyl alcohol	nonirritant	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM	?
5351-04-2	**Diethylaminopropionitrile**	**Category 1**	**n=3/3, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**Category II**	**R41**	**SCNM**	**Human data not located**
538-71-6	**Domiphen bromide**	**Category 1**	**n=3/3, CO=4**	**-**	**-**	**4**	**-**	**X**	**-**	**-**	**Category I**	**R41**	**SCNM**	**Human data not located**
5392-28-9	**tetra-Aminopyrimidine sulfate**	**nonirritant**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**-**	**Category III**	**nonirritant**	**SCNM**	**Human data not located**
54029-45-7	**2-Nitro-4-thiocyanoaniline**	**Category 1**	**-**	**-**	**-**	**0 (likely 4)**	**-**	**-**	**-**	**X**	**Category I**	**R41**	**SCNM**	**Human data not located**
542-08-5	Isopropyl acetoacetate	Category 2B	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM	?
542-76-7	**3-Chloropropionitrile**	**Category 2B**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category III**	**nonirritant**	**SCNM**	**Human data not located**

CASRN	Substance	Animal Exposure Summary for Category 1(H) Substances	Notes
2664-55-3	Nonyl acrylate	?	
2743-38-6	Dibenzoyl-L-tartaric acid		Tested as a solid in other study
2743-38-6	**Dibenzoyl-L-tartaric acid**		
288-32-4	Imidazole		Tested as a solid in other study
288-32-4	**Imidazole**		
2921-88-2	Chlorpyrifos	?	
2943-75-1	Triethyoxyoctylsilane	?	
29590-42-9	**iso-Octyl acrylate**		
29911-27-1	**Butyl Dipropasol Solvent**		
302-95-4	**Deoxycholic acid sodium salt**		
30525-89-4	**Granuform**		
311-89-7	Perfluorotributylamine	?	
3121-61-7	**Methoxyethyl acrylate**		
3173-53-3	**Cyclohexyl isocyanate**		
328-50-7	**alpha-Ketoglutaric acid alpha**		
3446-89-7	*p*-Methylthiobenzaldehye	?	
355-42-0	Perfluoro-n-hexane	?	
355-42-0	Perfluoro-n-hexane	?	
3926-62-3	Sodium monochloroacetate	?	
392-68-7	Trifluoroethyl methacrylate	?	
3938-95-2	Ethyl trimethyl acetate	?	
3964-18-4	2,3-Dimethyl 2,3-dinitrobutane	?	
3970-62-5	**2,2-Dimethyl-3-pentanol**		
41253-21-8	**1,2,4-Triazole, sodium salt**		
446-35-5	**2,4-Difluoronitrobenzene**		
4659-45-4	**2,6-Dichlorobenzoyl chloride**		
50-21-5	**Lactic Acid**		
52625-13-5	Polyol XZ 95435.00	?	
5333-48-2	Iso-myristyl alcohol	?	
5351-04-2	**Diethylaminopropionitrile**		
538-71-6	**Domiphen bromide**		
5392-28-9	**tetra-Aminopyrimidine sulfate**		
54029-45-7	**2-Nitro-4-thiocyanoaniline**		
542-08-5	Isopropyl acetoacetate	?	
542-76-7	**3-Chloropropionitrile**		

CASRN	Substance	In Vivo Data Source	Substance Source	Commercial Availability	Chemical Class	Product Class	Conc. Tested	Amount Tested[1]	Purity	MW	pH	Dermal Corrosivity	# of Animals Tested	Water Solubility	Log Kow	Color	Physical Form Tested	MMAS score
5459-04-1	Acetoacetic acid glycol ester	ZEBET	n.a.	Hoechst Celanese Corp. (Bulk)	Ester, Ketone	Chemical Intermediate, Pesticide	n.a.	0.1 mL or 100 mg	n.a.	230.2	?	?	3	?	?	?	?	13.7
5459-37-0	Heptyl methacrylate	ECETOC	Elf Atochem, Inc.	Elf Atochem, Inc. (Bulk)	Ester	Cosmetic Ingredient, Dental Adhesive, Perfume	100%	0.1 mL	>99%	164.3	?	?	3	?	?	?	liquid	1.3
55179-31-2	1-(4-Phenyl-phenoxy)-1-(1,2,4-triazole-1)-3,3-dimethylbutane	TSCA	Mobay Corp.	Shanghai Orgchem Co., Ltd.	Heterocyclic Compound	Anti-Fungal, Pesticide	100%	0.1 mL	96.5%	337.4	?	?	3	?	?	?	liquid	5.7
55-56-1	**Chlorhexidine**	**ECETOC**	**n.a.**	**Sigma-Aldrich Corp.**	**Amidine**	**Anti-Infective, Pharmaceutical**	**100%**	**100 mg**	**n.a.**	**505.5**	**?**	**?**	**3**	**?**	**n.a.**	**?**	**solid**	**82.3**
562-49-2	3,3-Dimethylpentane	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Hydrocarbon (acyclic)	Chemical Intermediate	100%	0.1 mL	99%	100.2	?	?	3	insoluble	?	?	liquid	0.0
56-81-5	Glycerol	ECETOC	Mallinckrodt, Inc.	Sigma-Aldrich Corp.	Alcohol	Chemical Intermediate, Cosmetic Ingredient, Food Additive, Pharmaceutical, Solvent	100%	0.1 mL	>99.5%	92.1	6.0-7.0 (10% aq.)	?	6	>500 g/L	?	?	liquid	1.7
57-09-0	**Cetyltrimethylammonium bromide**	**NIHS-Ohno**	**Japanese Cosmetic Industry Assn.**	**Sigma-Aldrich Corp.**	**Onium Compound, Salt (organic)**	**Cosmetic Ingredient**	**10%**	**0.1 mL**	**n.a.**	**364.4**	**5.9**	**noncorrosive**	**3**	**soluble (30 g/L)**	**3.18/2.26**	**?**	**liquid**	**96.0**
58-33-3	**Promethazine hydrochloride**	**ECETOC**	**n.a.**	**Sigma-Aldrich Corp.**	**Amine, Amidine, Heterocyclic Compound, Sulfur Compound (organic)**	**Pharmaceutical**	**100%**	**100 mg**	**98%**	**320.9**	**?**	**?**	**3**	**n.a.**	**n.a.**	**white to faint yellow**	**solid**	**71.7**
58-33-3	Promethazine hydrochloride	LNS	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Amine, Amidine, Heterocyclic Compound, Sulfur Compound (organic)	Pharmaceutical	20%	0.1 mL	n.a.	320.9	4.5	noncorrosive	3	n.a.	n.a.	white to faint yellow	liquid	84.0
589-10-6	4-Bromophenetole	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Ether	Chemical Intermediate	100%	0.1 mL	99%	201.1	?	?	3	?	?	?	liquid	1.3
589-34-4	3-Methylhexane	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Hydrocarbon (acyclic)	Industrial Chemical	100%	0.1 mL	99%	100.2	?	?	6	insoluble	?	?	liquid	0.7
592-42-7	1,5-Hexadiene	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (acyclic)	Chemical Intermediate, Industrial Chemical	100%	0.1 mL	97%	82.2	?	?	6	?	?	?	liquid	4.7
594-61-6	**2-Hydroxyisobutyric acid**	**ZEBET**	**n.a.**	**Sigma-Aldrich Corp.**	**Acid (organic) [carboxylic acid]**	**Industrial Chemical**	**n.a.**	**0.1 mL or 100 mg**	**n.a.**	**104.1**	**?**	**?**	**3**	**?**	**?**	**?**	**solid**	**98.7**
595-37-9	**2,2-Dimethyl butanoic acid**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Acid (organic) [carboxylic acid]**	**Pharmaceutical**	**100%**	**0.1 mL**	**96%**	**116.2**	**n.a.**	**R34**	**6**	**n.a.**	**n.a.**	**?**	**liquid**	**44.7**
598-65-2	**n,n-Dimethylguanidine sulfate**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Amidine, Salt (organic)**	**Laboratory Chemical**	**100%**	**100 mg**	**>95%**	**272.3**	**n.a.**	**noncorrosive**	**3**	**n.a.**	**n.a.**	**n.a.**	**solid**	**6.7**
598-98-1	Methyl trimethyl acetate	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Ester	Chemical Intermediate, Pharmaceutical Intermediate	100%	0.1 mL	99%	116.2	?	?	6	?	?	?	liquid	2.7
609-14-3	**Ethyl-2-methyl acetoacetate**	**ECETOC**	**Fluka, Inc.**	**Sigma-Aldrich Corp.**	**Ester, Ketone**	**Chemical Intermediate**	**100%**	**0.1 mL**	**97%**	**144.2**	**7.5**	**noncorrosive**	**3**	**Slightly soluble**	**n.a.**	**?**	**liquid**	**18.0**
616-09-1	**TNO-35 (Propyl lactate)**	**TNO-Prinsen**	**n.a.**	**Cook Aromatics Ltd. (Bulk)**	**Alcohol, Ester**	**Cleaning Agent, Food Additive**	**n.a.**	**0.1 mL or 100 mg**	**n.a.**	**132.2**	**?**	**?**	**1**	**?**	**?**	**?**	**solid**	**63.0**
619-66-9	**4-Carboxybenzaldehyde**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Aldehyde, Acid (organic) [carboxylic acid]**	**Industrial Chemical**	**100%**	**0.1 mL**	**>95%**	**150.1**	**3.1**	**noncorrosive**	**3**	**Very soluble**	**n.a.**	**?**	**liquid**	**50.3**
620-14-4	3-Ethyl toluene	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Hydrocarbon (cyclic)	Industrial Chemical, Laboratory Chemical	100%	0.1 mL	99%	120.2	?	?	6	?	?	?	liquid	2.3
62-23-7	p-Nitrobenzoic acid	ZEBET	n.a.	Sigma-Aldrich Corp.	Acid (organic) [carboxylic acid], Nitro Compound	Chemical Intermediate, Pharmaceutical Intermediate	n.a.	0.1 mL or 100 mg	n.a.	167.1	?	?	3	?	?	?	solid	19.3
623-39-2	**3-Methoxy-1,2-propanediol**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Ether, Phenol**	**Laboratory Chemical**	**100%**	**0.1 mL**	**98%**	**106.1**	**?**	**?**	**3**	**soluble**	**?**	**?**	**liquid**	**0.0**
623-51-8	Ethyl thioglycolate	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Alcohol, Ester, Sulfur Compound (organic)	Chemical Intermediate, Cosmetic Ingredient, Food Additive, Industrial Chemical	100%	0.1 mL	99.1%	120.2	?	?	3	?	?	?	Liquid	24.7
625-69-4	**2,4-Pentanediol**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Alcohol**	**Chemical Intermediate**	**100%**	**0.1 mL**	**98%**	**104.2**	**n.a.**	**?**	**3**	**?**	**?**	**?**	**liquid**	**4.7**
62-76-0	**Sodium oxalate**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Acid (organic) [carboxylic acid]**	**Industrial Chemical, Laboratory Chemical**	**100%**	**100 mg**	**>99%**	**134.0**	**9.4**	**corrosive**	**3**	**soluble (37 g/L)**	**n.a.**	**?**	**solid**	**61.3**
629-03-8	1,6-Dibromohexane	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (halogenated)	Chemical Intermediate, Pharmaceutical Intermediate	100%	0.1 mL	98.4%	244.0	?	?	3	insoluble	?	colorless to yellow	liquid	6.7
629-14-1	Ethyleneglycol diethyl ether	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Ether	Chemical Intermediate, Solvent	100%	0.1 mL	98%	118.2	?	?	3	?	?	colorless	liquid	10.7
629-19-6	Di-*n*-propyl disulfide	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Sulfur Compound (organic)	Food Additive, Industrial Agent	100%	0.1 mL	99.2%	150.3	?	?	3	insoluble	?	colorless	liquid	4.0

CASRN	Substance	GHS Classification	Corneal score	Irital score	Conjunctival score	NICEATM Category 1 SubClass.[2]	Tested in BCOP	Tested in HET-CAM	Tested in ICE	Tested in IRE	EPA Classification	EU Classification	FHSA Classification	Human Exposure Summary
5459-04-1	Acetoacetic acid glycol ester	Category 2B	-	-	-	-	-	-	-	-	Category III	R36	SCNM	?
5459-37-0	Heptyl methacrylate	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	?
55179-31-2	1-(4-Phenyl-phenoxy)-1-(1,2,4-triazole-1)-3,3-dimethylbutane	nonirritant	-	-	-	-	-	-	-	-	Category III	nonirritant	nonirritant	?
55-56-1	**Chlorhexidine**	**Category 1**	**n=1/3, CO=4**	**-**	**-**	**4**	**X**	**X**	**X**	**X**	**SCNM**	**R41**	**SCNM**	**Acutely toxic when applied to the eye. Irreversible corneal injuries and opacification attributed to Hibiclens (chlorhexidine gluconate, a 4% topical preparation), reported in 4 female patients, aged 9 months to 83 year, in whom the drug was accidentally introduced into the eye during surgical preparation. Inadvertently used as an intraocular irrigating solution in three patients undergoing surgery. In two of the three patients, corneal endothelium damage was so severe that penetrating keratoplasty had to be performed. Further effects included pronounced iris atrophy, anterior chamber applanation, and a retrocorneal membrane. (25, 28, 31)**
562-49-2	3,3-Dimethylpentane	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	?
56-81-5	Glycerol	nonirritant	-	-	-	-	X	X	X	X	Category IV	nonirritant	nonirritant	?
57-09-0	**Cetyltrimethylammonium bromide**	**Category 1**	**n=3/3, CO=4**	**-**	**n=1/3, CR=3, n=3/3, CC=2 D14**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**SCNM**	**In 179 patients treated with eye drops containing cetrimide (Cetyltrimethylammonium bromide) for 30 days, adverse effects were reported for 21 patients. The adverse events consisted of discomfort, blurred vision, hyperemia, burning and itching. Accidental application of cetrimide occurred during cataract surgery. This resulted in immediate corneal edema which in turn resulted in a bullous keratopathy. Four patients underwent a penetrating keratoplasty. In one patient the cornea was covered with a conjunctival flap. Light microscopy of the corneas included epithelial edema, loss of keratocytes, and a disrupted and sometimes absent endothelial cell layer. (3, 29)**
58-33-3	**Promethazine hydrochloride**	**Category 1**	**n=3/3, CO=3**	**n=3/3, IR=2**	**-**	**3**	**X**	**X**	**X**	**X**	**Category I**	**R41**	**SCNM**	**Severe eye irritant (17)**
58-33-3	Promethazine hydrochloride	Category 1	n=3/3, CO=4	-	-	4	-	-	-	-	Category I	R41	SCNM	Severe eye irritant (17)
589-10-6	4-Bromophenetole	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	?
589-34-4	3-Methylhexane	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant	?
592-42-7	1,5-Hexadiene	nonirritant	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM	?
594-61-6	**2-Hydroxyisobutyric acid**	**Category 1**	**n=3/3, CO=4**	**-**	**n=1/3, CR=3, n=3/3, CC=4**	**4**	**-**	**X**	**-**	**-**	**SCNM**	**R41**	**SCNM**	**Human data not located**
595-37-9	**2,2-Dimethyl butanoic acid**	**Category 1**	**n=1/6, CO=3 D14**	**n=1/6, IR=2 D14**	**-**	**1**	**X**	**X**	**X**	**X**	**Category I**	**R41**	**irritant**	**Human data not located**
598-65-2	**n,n-Dimethylguanidine sulfate**	**nonirritant**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category III**	**nonirritant**	**SCNM**	**Human data not located**
598-98-1	Methyl trimethyl acetate	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant	?
609-14-3	**Ethyl-2-methyl acetoacetate**	**Category 2B**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**X**	**Category III**	**nonirritant**	**SCNM**	**Human data not located**
616-09-1	**TNO-35 (Propyl lactate)**	**Category 1**	**n=1/1, CO>0 D21**	**n=1/1, IR>0 D21**	**n=1/1, CC>0 D21**	**1**	**-**	**-**	**X**	**-**	**Category I**	**R41**	**SCNM**	**Human data not located**
619-66-9	**4-Carboxybenzaldehyde**	**Category 2A**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**-**	**Category II**	**R36**	**SCNM**	**Human data not located**
620-14-4	3-Ethyl toluene	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant	?
62-23-7	p-Nitrobenzoic acid	Category 2B	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM	?
623-39-2	**3-Methoxy-1,2-propanediol**	**nonirritant**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category IV**	**nonirritant**	**SCNM**	**Human data not located**
623-51-8	Ethyl thioglycolate	nonirritant	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM	?
625-69-4	**2,4-Pentanediol**	**nonirritant**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category IV**	**nonirritant**	**SCNM**	**Human data not located**
62-76-0	**Sodium oxalate**	**Category 1**	**n=1/3, CO=4**	**n=1/3, IR=2 D14**	**-**	**4**	**X**	**X**	**X**	**-**	**Category I**	**R41**	**SCNM**	**Human data not located**
629-03-8	1,6-Dibromohexane	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	?
629-14-1	Ethyleneglycol diethyl ether	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	?
629-19-6	Di-*n*-propyl disulfide	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	?

CASRN	Substance	Animal Exposure Summary for Category 1(H) Substances	Notes
5459-04-1	Acetoacetic acid glycol ester	?	
5459-37-0	Heptyl methacrylate	?	
55179-31-2	1-(4-Phenyl-phenoxy)-1-(1,2,4-triazole-1)-3,3-dimethylbutane	?	
55-56-1	**Chlorhexidine**		
562-49-2	3,3-Dimethylpentane	?	
56-81-5	Glycerol	?	
57-09-0	**Cetyltrimethylammonium bromide**		
58-33-3	**Promethazine hydrochloride**		
58-33-3	Promethazine hydrochloride		ECETOC study noted irital effects when tested at 100% as a solid
589-10-6	4-Bromophenetole	?	
589-34-4	3-Methylhexane	?	
592-42-7	1,5-Hexadiene	?	
594-61-6	**2-Hydroxyisobutyric acid**		
595-37-9	**2,2-Dimethyl butanoic acid**		
598-65-2	**n,n-Dimethylguanidine sulfate**		
598-98-1	Methyl trimethyl acetate	?	
609-14-3	**Ethyl-2-methyl acetoacetate**		
616-09-1	**TNO-35 (Propyl lactate)**		
619-66-9	**4-Carboxybenzaldehyde**		
620-14-4	3-Ethyl toluene	?	
62-23-7	p-Nitrobenzoic acid	?	
623-39-2	**3-Methoxy-1,2-propanediol**		
623-51-8	Ethyl thioglycolate	?	
625-69-4	**2,4-Pentanediol**		
62-76-0	**Sodium oxalate**		
629-03-8	1,6-Dibromohexane	?	
629-14-1	Ethyleneglycol diethyl ether	?	
629-19-6	Di-*n*-propyl disulfide	?	

CASRN	Substance	In Vivo Data Source	Substance Source	Commercial Availability	Chemical Class	Product Class	Conc. Tested	Amount Tested[1]	Purity	MW	pH	Dermal Corrosivity	# of Animals Tested	Water Solubility	Log Kow	Color	Physical Form Tested	MMAS score
64-19-7	**Acetic Acid**	**NIHS-Ohno**	**Japanese Cosmetic Industry Assn.**	**Sigma-Aldrich Corp.**	**Acid (organic) [carboxylic acid]**	**Industrial Chemical; Laboratory Agent, Solvent**	**10%**	**0.1 mL**	**n.a.**	**60.1**	**2.4**	**R35 (60%)**	**3**	**soluble**	**-0.17 (60%)**	**colorless**	**liquid**	**68.0**
6424-85-7	**Acid blue 40**	**TSCA**	**Crompton and Knowles Corp.**	**Sigma-Aldrich Corp.**	**Amine, Quinone, Salt (organic)**	**Industrial Chemical**	**n.a.**	**100 mg**	**n.a.**	**473.4**	**8.0**	**noncorrosive**	**6**	**soluble (30 g/L@ 80C)**	**2.2**	**deep blue**	**solid**	**39.7**
6484-52-2	**Ammonium nitrate**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Onium Compound, Nitrate, Salt (organic)**	**Industrial Chemical**	**100%**	**100 mg**	**99.999%**	**80.0**	**4.8**	**noncorrosive**	**3**	**soluble (1920 g/L)**	**n.a.**	**white, hot concentrate**	**solid**	**18.3**
65558-69-2	**1,3-Diiminobenz (f)-isoindoline**	**TSCA**	**Hoechst Celanese Corp.**	**Sigma-Aldrich Corp.**	**Amine, Heterocyclic Compound**	**Dye, Laboratory Chemical**	**100%**	**100 mg**	**n.a.**	**195.2**	**n.a.**	**?**	**3**	**?**	**?**	**?**	**solid**	**93.0**
67-64-1	**Acetone**	**ECETOC**	**Fisher Scientific International, Inc.**	**Sigma-Aldrich Corp.**	**Ketone**	**Chemical Intermediate, Cleaning Agent, Industrial Chemical, Pharmaceutical Intermediate, Preservative, Solvent**	**100%**	**0.1 mL**	**99%**	**58.1**	**5.3**	**noncorrosive**	**4**	**soluble**	**-0.24**	**?**	**liquid**	**65.8**
67-66-3	**Chloroform**	**-**	**n.a.**	**Sigma-Aldrich Corp.**	**Hydrocarbon (acyclic)**	**Anesthetic, Chemical Intermediate, Cleaning Agent, Industrial Chemical, Pharmaceutical Intermediate, Solvent**	**-**	**-**	**-**	**119.4**	**-**	**-**	**-**	**n.a.**	**n.a.**	**?**	**liquid**	**-**
69-05-6	Quinacrine	LNS	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Amine, Heterocyclic Compound, Polycyclic Compound	Pharmaceutical	20%	0.1 mL	n.a.	472.9	3.8	noncorrosive	3	soluble (1 g/36 mL)	n.a.	?	liquid	52.3
69-05-6	**Quinacrine**	**ECETOC**	**n.a.**	**Sigma-Aldrich Corp.**	**Amine, Heterocyclic Compound, Polycyclic Compound**	**Pharmaceutical**	**100%**	**100 mg**	**90%**	**472.9**	**?**	**noncorrosive**	**3**	**soluble (1 g/36 mL)**	**n.a.**	**?**	**solid**	**82.0**
6940-78-9	1-Bromo-4-chlorobutane	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (halogenated)	Industrial Chemical	100%	0.1 mL	98%	171.5	?	?	3	soluble in ethanol, ethyl ether	?	colorless to yellow	liquid	4.0
71-36-3	**n-Butanol**	**NIHS-Ohno**	**Japanese Cosmetic Industry Assn.**	**Sigma-Aldrich Corp.**	**Alcohol**	**Chemical Intermediate, Cosmetic Ingredient, Food Additive, Industrial Chemcial, Pesticide Intermediate, Pharmaceutical Intermediate, Solvent, Veterinary Chemical**	**10%**	**0.1 mL**	**n.a.**	**74.1**	**n.a.**	**noncorrosive**	**3**	**insoluble**	**0.88**	**colorless**	**liquid**	**34.0**
71-36-3	*n*-Butanol	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Alcohol	Chemical Intermediate, Cosmetic Ingredient, Food Additive, Industrial Chemcial, Pesticide Intermediate, Pharmaceutical Intermediate, Solvent, Veterinary Chemical	100%	0.1 mL	99.8%	74.1	n.a.	noncorrosive	4	insoluble	0.88	colorless	liquid	60.8
71-36-3	*n*-Butanol	ZEBET	n.a.	Sigma-Aldrich Corp.	Alcohol	Chemical Intermediate, Cosmetic Ingredient, Food Additive, Industrial Chemcial, Pesticide Intermediate, Pharmaceutical Intermediate, Solvent, Veterinary Chemical	n.a.	0.1 mL or 100 mg	n.a.	74.1	?	noncorrosive	3	insoluble	0.88	colorless	liquid	17.7
75-26-3	**iso-Propyl bromide**	**ECETOC**	**Fluka, Inc.**	**Sigma-Aldrich Corp.**	**Hydrocarbon (halogenated)**	**Chemical Intermediate, Pharmaceutical Intermediate**	**100%**	**0.1 mL**	**>99%**	**123.0**	**?**	**?**	**3**	**3 g/L**	**1.9**	**?**	**liquid**	**9.7**
76-02-8	**Trichloroacetyl chloride**	**TSCA**	**Rhone-Poulenc, Inc.**	**Sigma-Aldrich Corp.**	**Acyl Halide**	**Chemical Intermediate, Industrial Chemical**	**n.a.**	**0.1 mL**	**n.a.**	**163.4**	**?**	**?**	**4**	**?**	**?**	**?**	**liquid**	**91.0**
76-03-9	**Trichloroacetic acid**	**ECETOC**	**Fisher Scientific International, Inc.**	**Sigma-Aldrich Corp.**	**Acid (organic) [carboxylic acid]**	**Caustic Agent, Herbicide**	**30%**	**0.1 mL**	**Reagent Grade**	**163.4**	**0.7**	**R34 (0.6N); R35 (undiluted)**	**1**	**soluble (10 g/mL)**	**1.33**	**?**	**liquid**	**106.0**
7646-85-7	**Zinc chloride**	**-**	**-**	**Sigma-Aldrich Corp.**	**Salt (inorganic)**	**Anti-Infective, Flame Retardant, Herbicide, Industrial Chemical. Pesticide, Preservative**	**-**	**-**	**-**	**136.3**	**-**	**-**	**-**	**n.a.**	**n.a.**	**?**	**solid**	**-**
7659-86-12	2-Ethylhexylthioglycolate	ECETOC	Elf Atochem, Inc.	Elf Atochem, Inc. (Bulk)	Alcohol, Ester, Sulfur Compound (organic)	Chemical Intermediate, Cosmetic Ingredient	100%	0.1 mL	99.4%	204.3	?	?	3	?	?	?	liquid	2.7

CASRN	Substance	GHS Classification	Corneal score	Irital score	Conjunctival score	NICEATM Category 1 SubClass.[2]	Tested in BCOP	Tested in HET-CAM	Tested in ICE	Tested in IRE	EPA Classification	EU Classification	FHSA Classification	Human Exposure Summary
64-19-7	**Acetic Acid**	**Category 1**	**n=2/3, CO=4**	**-**	**-**	**4**	**-**	**X**	**X**	**X**	**Category I**	**R41**	**SCNM**	**Has caused extreme eye and nasal irritation at concentrations in air in excess of 25 ppm. Has caused conjunctivitis at concentrations below 10 ppm. Concentrations of 200 ppm caused conjunctival hyerperemia. Glacial (100%) acetic acid has caused permanent corneal opacification. A splash of vinegar (4 to 10% acetic acid solution) in the eye causes immediate pain and conjunctival hyperemia, sometimes with injury of the corneal epithelium (2 patients). Accidental application of glacial acetic acid to the eyes followed very quickly by irrigation with water resulted in immediate corneal opacification. These corneas cleared sufficiently in a few days to reveal severe iritis and small pupils fixed by posterior synechiae. Regeneration of the epithelium took many months, but corneal anesthesia and opacity were permanent. In workers exposed to aerosol concentrations of 60 ppm for 7-12 years, with daily exposures as high as 100-200 ppm, investigators found conjunctivitis (in addition to bronchitis, pharyngitis, and erosion of exposed teeth) (1, 13, 18)**
6424-85-7	**Acid blue 40**	**Category 1**	**n=2/6, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**SCNM**	**R36**	**irritant**	**Human data not located**
6484-52-2	**Ammonium nitrate**	**Category 2B**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**X**	**Category III**	**R36**	**SCNM**	**Human data not located**
65558-69-2	**1,3-Diiminobenz (f)-isoindoline**	**Category 1**	**n=4/4, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**SCNM**	**R41**	**SCNM**	**Human data not located**
67-64-1	**Acetone**	**Category 2A**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**X**	**Category II**	**R36**	**SCNM**	**Acute exposures of humans to atmospheric concentrations have been reported to produce eye irritation. Exposure of15 minutes to aerosol concentrations of 1660 ppm also reportedly causes eye irritation. Direct contact with the eyes may produce irritation and corneal injury. (14, 16, 30, 32)**
67-66-3	**Chloroform**	**Category 1(H)**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Splash of liquid chloroform in the eyes causes immediate burning pain, tearing and reddening of the conjunctiva. The corneal corneal epithelium corneal epithelium is usually injured and partially lost. Exposure to liquid or gaseous chloroform causes keratitis, corneal opacities, and ulceration (11, 37, 38, 39, 40, 41)**
69-05-6	Quinacrine	Category 1	n=1/3, CO=4	n=3/3, IR=2 D14	-	1	-	-	-	-	Category I	R41	SCNM	Direct contact with the eye causes yellow staining of the bulbar conjunctiva and cornea; in more severe reactions striate keratopathy or wrinkling of the posterior surface of cornea develops, presumably due to corneal edema (11)
69-05-6	**Quinacrine**	**Category 1**	**n=3/3, CO=3**	**n=3/3, IR=2**	**-**	**3**	**X**	**X**	**X**	**-**	**Category I**	**R41**	**SCNM**	**Direct contact with the eye causes yellow staining of the bulbar conjunctiva and cornea; in more severe reactions striate keratopathy or wrinkling of the posterior surface of cornea develops, presumably due to corneal edema (11)**
6940-78-9	1-Bromo-4-chlorobutane	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	?
71-36-3	**n-Butanol**	**Category 1**	**n=1/3, CO=4**	**-**	**-**	**4**	**-**	**X**	**-**	**-**	**SCNM**	**R41**	**SCNM**	**Is reported to cause irritation of the eyes from exposure to either vapor or liquid. Circumstantial evidence points to butyl alcohol vapor as cause of a special vacuolar keratopathy in some patients; the most severely affected it has been associated with pain & tearing, characteristically most marked on first opening eyes in morning. It can cause transient mild edema of conjunctiva of the eye. Vapor: Irritating to eyes. Considered a strong irritant of the eyes. (9, 11, 13, 27)**
71-36-3	*n*-Butanol	Category 2A	-	-	-	-	-	X	X	X	Category II	R36	SCNM	Is reported to cause irritation of the eyes from exposure to either vapor or liquid. Circumstantial evidence points to butyl alcohol vapor as cause of a special vacuolar keratopathy in some patients; the most severely affected it has been associated with pain & tearing, characteristically most marked on first opening eyes in morning. It can cause transient mild edema of conjunctiva of the eye. Vapor: Irritating to eyes. Considered a strong irritant of the eyes. (9, 11, 13, 27)
71-36-3	*n*-Butanol	Category 1	n=1/3, CO=4	-	-	4	-	-	-	-	SCNM	Review Data	SCNM	Is reported to cause irritation of the eyes from exposure to either vapor or liquid. Circumstantial evidence points to butyl alcohol vapor as cause of a special vacuolar keratopathy in some patients; the most severely affected it has been associated with pain & tearing, characteristically most marked on first opening eyes in morning. It can cause transient mild edema of conjunctiva of the eye. Vapor: Irritating to eyes. Considered a strong irritant of the eyes. (9, 11, 13, 27)
75-26-3	**iso-Propyl bromide**	**nonirritant**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category IV**	**nonirritant**	**SCNM**	**Human data not located**
76-02-8	**Trichloroacetyl chloride**	**Category 1**	**n=4/4, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**SCNM**	**Reported to be irritating and very painful to the human eye (15, 19)**
76-03-9	**Trichloroacetic acid**	**Category 1**	**n=1/1, CO=4**	**n=1/1, IR=2 D21**	**n=1/1, CR/CC=2 D21**	**4**	**X**	**X**	**X**	**X**	**Category I**	**R41**	**SCNM**	**Reported to be irritating and very painful to the human eye (15, 19)**
7646-85-7	**Zinc chloride**	**Category 1(H)**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**An unstated concentration of zinc chloride solution splashed in 1 eye of a workman at first only caused redness and discomfort, but within 6 days grayish corneal opacities had developed, with irregularity of the overlying epithelium. A patient who had an eye burned with one drop of 50% zinc chloride solution there was immediate severe pain, erosion of the corneal epithelium, corneal vascularization, severe iritis and iridial hemorrhage (11, 27, 54)**
7659-86-12	2-Ethylhexylthioglycolate	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	?

CASRN	Substance	Animal Exposure Summary for Category 1(H) Substances	Notes
64-19-7	**Acetic Acid**		
6424-85-7	**Acid blue 40**		
6484-52-2	**Ammonium nitrate**		
65558-69-2	**1,3-Diiminobenz (f)-isoindoline**		
67-64-1	**Acetone**		
67-66-3	**Chloroform**	**Liquid chloroform produced slight injury to the eyes which took over a week to heal. (62)**	
69-05-6	Quinacrine		In ECETOC study, tested at 100% as a solid
69-05-6	**Quinacrine**		
6940-78-9	1-Bromo-4-chlorobutane	?	
71-36-3	**n-Butanol**		
71-36-3	*n*-Butanol		Used results when tested at lower concentration
71-36-3	*n*-Butanol		Conc. tested provided in other study
75-26-3	**iso-Propyl bromide**		
76-02-8	**Trichloroacetyl chloride**		
76-03-9	**Trichloroacetic acid**		
7646-85-7	**Zinc chloride**	**10% zinc chloride was classified as a mild or non-irritant when test in the rabbit eye. A 50% solution of zinc chloride applied repeatedly during 1 day to 1 eye of an albino rabbit caused immediate corneal opacity. 6 days after exposure, the eye had become very hard, with extensive hemorrhage in the anterior segment, accompanied by infiltration with inflammatory cells, loss of corneal endothelium and clouding of the anterior portion of the lens. (11, 61)**	
7659-86-12	2-Ethylhexylthioglycolate	?	

CASRN	Substance	In Vivo Data Source	Substance Source	Commercial Availability	Chemical Class	Product Class	Conc. Tested	Amount Tested[1]	Purity	MW	pH	Dermal Corrosivity	# of Animals Tested	Water Solubility	Log Kow	Color	Physical Form Tested	MMAS score
7664-41-7	**Ammonia**	-	-	**Sigma-Aldrich Corp.**	**Alkali**	**Anti-Fungal, Chemical Intermediate, Cleaning Agent, Fertilizer, Herbicide, Industrial Chemical, Refrigerant**	-	-	-	**17.0**	-	-	-	**n.a.**	**n.a.**	**?**	**Liquid**	-
7664-93-9	**Sulfuric acid**	-	-	**Sigma-Aldrich Corp.**	**Acid (inorganic), Sulfur Compound (inorganic)**	**Battery Acid, Chemical Intermediate, Cleaning Agent, Fertilizer, Food Additive, Industrial Chemical, Laboratory Chemical**	-	-	-	**98.1**	-	-	-	**n.a.**	**n.a.**	**?**	**liquid**	-
7681-38-1	**Sodium hydrogen sulfate**	**ZEBET**	**n.a.**	**Sigma-Aldrich Corp.**	**Salt (inorganic)**	**Cleaning Agent, Laboratory Chemical, Pesticide**	**n.a.**	**0.1 mL or 100 mg**	**n.a.**	**120.1**	**?**	**?**	**1**	**?**	**?**	**?**	**solid**	**8.0**
7697-37-2	**Nitric acid**	-	-	**Sigma-Aldrich Corp.**	**Acid, Salt (inorganic)**	**Chemical Intermediate, Industrial Chemical, Laboratory Reagent, Pharmaceutical Intermediate**	-	-	-	**63.0**	-	-	-	**n.a.**	**n.a.**	**colorless to yellow**	**liquid**	-
7761-88-8	**Silver nitrate**	-	-	**Sigma-Aldrich Corp.**	**Nitrate, Salt (inorganic)**	**Anti-Infective, Chemical Intermediate, Dye, Industrial Chemical, Laboratory Chemical, Pharmaceutical, Pharmaceutical Intermediate**	-	-	-	**169.9**	-	-	-	**n.a.**	**n.a.**	**white to grayish-black**	**liquid**	-
77-75-8	**Methylpentynol**	**ZEBET**	**n.a.**	**Sigma-Aldrich Corp.**	**Alcohol**	**Pharmaceutical, Veterinary Chemical**	**n.a.**	**0.1 mL or 100 mg**	**n.a.**	**98.1**	**?**	**?**	**1**	**?**	**?**	**?**	**liquid**	**34.0**
78-76-2	Bromo-2-butane	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (halogenated)	Chemical Intermediate	100%	0.1 mL	>99%	137.0	?	?	3	?	?	?	liquid	0.0
78-83-1	iso-Butanol	ECETOC	n.a.	Sigma-Aldrich Corp.	Alcohol	Chemical Intermediate, Food Additive, Pesticide, Pharmaceutical Intermediate, Solvent	100%	0.1 mL	99.9%	74.1	7.0	noncorrosive	4	soluble (95 g/L)	0.76	?	liquid	60.3
78-83-1	iso-Butanol	ZEBET	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Alcohol	Chemical Intermediate, Food Additive, Pesticide, Pharmaceutical Intermediate, Solvent	n.a.	0.1 mL or 100 mg	n.a.	74.1	5.7	noncorrosive	3	soluble (95 g/L)	0.76	?	liquid	11.7
78-93-3	**Methyl ethyl ketone**	**ECETOC**	**Fisher Scientific International, Inc.**	**Sigma-Aldrich Corp.**	**Ketone**	**Solvent**	**100%**	**0.1 mL**	**99%**	**72.1**	**5.5**	**noncorrosive**	**4**	**soluble (353 g/L)**	**0.29**	**colorless**	**liquid**	**50.0**
79-20-9	**Methyl acetate**	**ECETOC**	**Fisher Scientific International, Inc.**	**Sigma-Aldrich Corp.**	**Ester**	**Chemical Intermediate, Food Additive, Herbicide, Laboratory Chemical,Solvent**	**100%**	**0.1 mL**	**98%**	**74.1**	**n.a.**	**?**	**4**	**243 g/L**	**0.18**	**colorless**	**liquid**	**39.5**
79-20-9	Methyl acetate	ZEBET	n.a.	Sigma-Aldrich Corp.	Ester	Chemical Intermediate, Food Additive, Herbicide, Laboratory Chemical,Solvent	n.a.	0.1 mL	n.a.	74.1	7.0	?	3	243 g/L	0.18	colorless	liquid	16.3
79-92-5	Camphen	ZEBET	n.a.	Sigma-Aldrich Corp.	Hydrocarbon (cyclic)	Chemical Intermediate, Cosmetic Ingredient, Food Additive, Pesticide Intermediate	n.a.	0.1 mL or 100 mg	n.a.	136.2	?	?	3	?	?	colorless	solid	15.0
8001-54-5	**Benzalkonium chloride**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Onium Compound**	**Surfactant (cationic)**	**5%**	**0.1 mL**	**98%**	**471.5**	**3.1**	**R34 (50%)**	**4**	**soluble**	**n.a.**	**clear**	**liquid**	**4.8**
8001-54-5	Benzalkonium chloride	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Onium Compound	Surfactant (cationic)	10%	0.1 mL	98%	471.5	3.2	R34 (50%)	3	soluble	n.a.	clear	liquid	108.0
80-54-6	**Protectol PP**	**TSCA**	**BASF**	**Sigma-Aldrich Corp.**	**Aldehyde**	**Food Additive, Perfume**	**100%**	**0.1 mL**	**84.8%**	**204.3**	**n.a.**	**noncorrosive**	**3**	**n.a.**	**?**	**white powder**	**liquid**	**34.3**

CASRN	Substance	GHS Classification	Corneal score	Irital score	Conjunctival score	NICEATM Category 1 SubClass.[2]	Tested in BCOP	Tested in HET-CAM	Tested in ICE	Tested in IRE	EPA Classification	EU Classification	FHSA Classification	Human Exposure Summary
7664-41-7	**Ammonia**	**Category 1(H)**	-	-	-	-	-	-	-	-	-	-	-	**Ammonia vapors cause irritation of eyes, with high concentrations causing conjunctivitis. Corneal edema and semi-dilated, fixed pupils are typical. Ammonia has a greater tendency than other alkalies to penetrate and damage the iris, and to cause cataract. In severe burns, iritis may be accompanied by hypopyon or hemorrhages, extensive loss of pigment and severe glaucoma. Exposure to high gas concentrations of ammonia may cause temporary blindness and severe eye damage. Direct contact of the eyes with liquid anhydrous ammonia will produce serious eye burns. 2 cases of ocular injuries with a rise in intraocular pressure and cataract formation after ammonia of unknown concentration had been squirted into the victims' eyes during robberies were reported. In both cases, the more severely affected eyes showed marked injection and edema of the conjunctiva; diffuse corneal damage; semi-dilated, oval, and fixed pupils; and a marked increase of the intraocular pressure, which persisted and was controlled only with drugs. Glaucoma was observed to be associated with an open angle**
7664-93-9	**Sulfuric acid**	**Category 1(H)**	-	-	-	-	-	-	-	-	-	-	-	**At aerosol concentrations of 1.1 to 2.1 mg/cu m, 40% of human subjects noticed irritation of the eyes. At 2.4 to 6.0 mg/cu m, all subjects experienced eye irritation. Contact of concentrated sulfuric acid with the eye may cause total loss of vision in addition to corneal necrosis, opacification, scarring, ulceration and vascularization. (1, 44, 51, 52)**
7681-38-1	**Sodium hydrogen sulfate**	**Category 1**	**n=1/1, CO=4**	-	-	**4**	-	-	-	-	**SCNM**	**Review Data**	**SCNM**	**Human data not located**
7697-37-2	**Nitric acid**	**Category 1(H)**	-	-	-	-	-	-	-	-	-	-	-	**Contact of nitric acid with the eye causes immediate opacification of the corneal and conjunctival epithelium. It also causes symblepharon, shrinkage of the globe, keratitis, corneal ulceration and corneal and conjunctival necrosis (11, 17, 46)**
7761-88-8	**Silver nitrate**	**Category 1(H)**	-	-	-	-	-	-	-	-	-	-	-	**Solid silver nitrate, known as lunar caustic, can be very injurious to the eye. Particles of solid silver nitrate in the conjunctival sac have been known to cause severe inflammation with deep injury to surrounding tissues, scarring, and symblepharon. In a most unusual case of severe injury from solid nitrate the cornea became dark brown, and the lens became cataractous. Concentration solutions of silver nitrate from 5%-50% applied by mistake or accidentally splashed in the eye have caused severe injury, with permanent corneal opacification in some cases. Solutions of high concentration cause rapid appearance of edema of the conjunctiva and lids, with bloody purulent discharge from the conjunctival sac. Opacification of the cornea may result and may be permanent (5, 11, 13, 48, 49, 50)**
77-75-8	**Methylpentynol**	**Category 1**	**n=1/1, CO=4**	-	-	**4**	-	**X**	-	-	**Category I**	**R41**	**SCNM**	**Human data not located**
78-76-2	Bromo-2-butane	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	?
78-83-1	iso-Butanol	Category 2A	-	-	-	-	-	X	X	X	Category I	R41	SCNM	Irritation of the skin, eyes, and throat have been reported from exposure to vapor or liquid. Irritation of the eyes and throat, formation of vacuoles in the superficial layers of the cornea, were reported among workers subjected to an undetermined, but apparently high concn of isobutyl alcohol & butyl acetate. (9, 20)+AH12
78-83-1	iso-Butanol	Category 1	n=1/3, CO=3 D14	-	-	1	-	-	-	-	Category II	R36	SCNM	Irritation of the skin, eyes, and throat have been reported from exposure to vapor or liquid. Irritation of the eyes and throat, formation of vacuoles in the superficial layers of the cornea, were reported among workers subjected to an undetermined, but apparently high concn of isobutyl alcohol & butyl acetate. (9, 20)+AH12
78-93-3	**Methyl ethyl ketone**	**Category 2A**	-	-	-	-	**X**	**X**	**X**	**X**	**Category III**	**R36**	**SCNM**	**High atmospheric concentrations are irritating to the eyes. May produce painful irritation and corneal injury if splashed in the eyes. Workers exposed to 33,000 and100,000 ppm in air reported intolerable irritation of the eyes. Implicated as the cause of retrobulbar neuritis in one patient. A workman splashed his eye accidentally with methyl ethyl ketone, but the next day had only slight conjunctival hyperemia and no residual corneal injury. (2, 5, 11, 20)**
79-20-9	**Methyl acetate**	**Category 2A**	-	-	-	-	**X**	**X**	**X**	**X**	**Category II**	**R36**	**SCNM**	**Cases of slight poisoning under industrial conditions were manifested by eye burns and lacrimation. One case of blindness has been reported. (1, 13, 18)**
79-20-9	Methyl acetate	Category 2B	-	-	-	-	-	-	-	-	Category III	R36	Insufficient Animal Data	Cases of slight poisoning under industrial conditions were manifested by eye burns and lacrimation. One case of blindness has been reported. (1, 13, 18)
79-92-5	Camphen	Category 2B	-	-	-	-	-	X	-	-	Category III	R36	SCNM	?
8001-54-5	**Benzalkonium chloride**	**Category 1**	**n=1/4, CO=4; n=2/4, CO=3; n=2/4, CO>0 D21**	**n=1/4, IR>1.5 D21**	**n=1/4, CR/CC>0 D21**	**3**	**X**	**X**	**X**	**X**	**Category I**	**R41**	**SCNM**	**A severe irritant to the human eye. Concentrations as low as 0.1 to 0.5% cause mild discomfort and conjunctival irritation. Slit lamp examination within 90 seconds of exposure to a single drop of 0.1% shows fine gray dots of keratitis epithelias in the corneal epithelium. Within 10 minutes of exposure, a gray haze may be seen in the corneal surface; superficial desquamation of the conjunctival epithelium may follow. These effects disappear in a day or less. (9, 17)**
8001-54-5	Benzalkonium chloride	Category 1	n=3/3, CO=4	n=3/3, IR=2 D21	n=1/3, CR>0, n=2/3, CC>0 D21	4	X	X	X	X	Category I	R41	SCNM	A severe irritant to the human eye. Concentrations as low as 0.1 to 0.5% cause mild discomfort and conjunctival irritation. Slit lamp examination within 90 seconds of exposure to a single drop of 0.1% shows fine gray dots of keratitis epithelias in the corneal epithelium. Within 10 minutes of exposure, a gray haze may be seen in the corneal surface; superficial desquamation of the conjunctival epithelium may follow. These effects disappear in a day or less. (9, 17)
80-54-6	**Protectol PP**	**Category 1**	**n=2/3, CO>0 D21**	-	**n=3/3, CR>0 D21**	**1**	-	-	-	-	**Category I**	**R41**	**SCNM**	**Severe eye irritant (17)**

CASRN	Substance	Animal Exposure Summary for Category 1(H) Substances	Notes
7664-41-7	**Ammonia**	**Corneal opacity was observed in rabbits following continuous exposure to ammonia vapor (470 mg/M3). Swine exposed to ammonia for 2 to 6 weeks at 100 PPM in air developed conjunctival irritation. Continuous exposure of rabbits to 470 mg/cu m for several weeks produced opacities over ¼ to ½ of the cornea. Even fairly low airborne concentrations of ammonia produce rapid eye and nose irritation. Contact with concentrated ammonia solutions, such as some industrial cleaners, can cause serious corrosive injury (6, 11, 56).**	
7664-93-9	**Sulfuric acid**	**Animals in the vicinity of potato fields sprayed with sulfuric acid during spraying, or gaining access to such fields soon after spraying, may develop eye burns from the spray. (63)**	
7681-38-1	**Sodium hydrogen sulfate**		
7697-37-2	**Nitric acid**	**Animal Data Not Located**	
7761-88-8	**Silver nitrate**	**Treatment of rat eyes with a single 3-drops 0.66% silver nitrate soln caused deposition of silver in the cornea, conjunctiva, subconjunctiva, Bowman's layer, reticular fibers of the corneal stroma, Descemete's membrane and the posterior corneal epithelium. Morphologic evolution of the early events of corneal vascularization in the rat cornea induced by silver nitrate cautery was followed by light and electron microscopy. An initial acute inflammatory response occurred within the first 6 hours after cautery as evidenced by vascular dilation, diapedesis of leukocytes, and an increased vascular permeability, as manifested by distended lymphatics and the presence of extravascular fibrin. At 33 hours after cautery, the first new vessels were observed as sprouts from the capillary arcade and postcapillary venules. Adult male Sprague-Dawley rats were anesthetized with halothane gas, and the centers of their right corneas treated with a silver nitrate applicator stick (75% silver nitrate, 25% potassium nitrate) to produce a discrete lesion 1 mm in diameter. Edema of the corneal stroma and elevated immune cell counts became significant 4 hour**	
77-75-8	**Methylpentynol**		
78-76-2	Bromo-2-butane	?	
78-83-1	iso-Butanol		Discordant GHS classification
78-83-1	iso-Butanol		Discordant GHS classification
78-93-3	**Methyl ethyl ketone**		
79-20-9	**Methyl acetate**		
79-20-9	Methyl acetate		Conc. tested unknown
79-92-5	Camphen	?	
8001-54-5	**Benzalkonium chloride**		
8001-54-5	Benzalkonium chloride		Severe effects at 5% in other study
80-54-6	**Protectol PP**		

CASRN	Substance	In Vivo Data Source	Substance Source	Commercial Availability	Chemical Class	Product Class	Conc. Tested	Amount Tested[1]	Purity	MW	pH	Dermal Corrosivity	# of Animals Tested	Water Solubility	Log Kow	Color	Physical Form Tested	MMAS score
80-55-7	**2-Hydroxyisobutyric acid ethylester**	**ZEBET**	**n.a.**	**Sigma-Aldrich Corp.**	**Alcohol, Ester**	**Industrial Chemical**	**n.a.**	**0.1 mL or 100 mg**	**n.a.**	**132.2**	**?**	**?**	**3**	**?**	**?**	**?**	**solid**	**81.0**
818-61-1	**Hydroxyethyl acrylate**	**TSCA**	**n.a.**	**Dow Chemical Co. (Bulk)**	**Alcohol, Ester**	**Chemical Intermediate**	**100%**	**0.1 mL**	**n.a.**	**116.1**	**?**	**?**	**6**	**?**	**?**	**?**	**liquid**	**96.7**
82985-35-1	**Organofunctional Silane 45-49**	**TSCA**	**Union Carbide Corp.**	**Sigma-Aldrich Corp.**	**Amine, Organosilicon Compound**	**Polish**	**100%**	**0.005 mL**	**n.a.**	**341.6**	**?**	**?**	**6**	**?**	**?**	**?**	**liquid**	**54.2**
86-87-3	**1-Naphthaleneacetic acid (solid)**	**ECETOC**	**US EPA**	**Sigma-Aldrich Corp.**	**Acid (organic) [carboxylic acid], Polycyclic Compound**	**Pesticide**	**100%**	**100 mg**	**96%**	**186.2**	**3.3**	**noncorrosive**	**6**	**insoluble (420 mg/L)**	**2.24**	**?**	**solid**	**46.7**
89-86-1	**beta-Resorcylic acid**	**ZEBET**	**n.a.**	**Sigma-Aldrich Corp.**	**Acid (organic) [carboxylic acid], Phenol**	**Chemical Intermediate, Dye**	**n.a.**	**0.1 mL or 100 mg**	**n.a.**	**154.1**	**?**	**?**	**1**	**?**	**?**	**?**	**solid**	**63.0**
9002-92-0	Polyoxyethylene 23 lauryl ether (BRIJ-35)	LNS	n.a.	Sigma-Aldrich Corp.	Alcohol	Pharmaceutical	10%	0.1 mL	n.a.	230.4	?	?	3	?	?	colorless	liquid	0.0
9002-93-1	**Triton X-100**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Ether**	**Surfactant (nonionic)**	**1%**	**0.1 mL**	**98%**	**250.4**	**7.2**	**noncorrosive**	**6**	**soluble**	**n.a.**	**colorless**	**liquid**	**1.7**
9002-93-1	**Triton X-100**	**ECETOC**	**n.a.**	**Sigma-Aldrich Corp.**	**Ether**	**Surfactant (nonionic)**	**5%**	**0.1 mL**	**98%**	**250.4**	**n.a.**	**noncorrosive**	**6**	**soluble**	**n.a.**	**colorless**	**liquid**	**33.8**
9002-93-1	**Triton X-100**	**ECETOC**	**n.a.**	**Sigma-Aldrich Corp.**	**Ether**	**Surfactant (nonionic)**	**5%**	**0.1 mL**	**98%**	**250.4**	**n.a.**	**noncorrosive**	**6**	**soluble**	**n.a.**	**colorless**	**liquid**	**33.8**
9002-93-1	Triton X-100	ECETOC	Union Carbide Corp.	Sigma-Aldrich Corp.	Ether	Surfactant (nonionic)	10%	0.1 mL	98%	250.4	n.a.	noncorrosive	6	soluble	n.a.	colorless	liquid	68.7
9002-93-1	**Triton X-100**	**TSCA**	**Union Carbide Corp.**	**Sigma-Aldrich Corp.**	**Ether**	**Surfactant (nonionic)**	**100%**	**0.1 mL**	**n.a.**	**250.4**	**n.a.**	**noncorrosive**	**6**	**soluble**	**n.a.**	**colorless**	**liquid**	**65.8**
9002-93-1	Triton X-100	NIHS-Ohno	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Ether	Surfactant (nonionic)	100%	0.1 mL	n.a.	250.4	6.8	noncorrosive	3	soluble	n.a.	colorless	liquid	41.3
9002-93-1	Triton X-100	TSCA	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Ether	Surfactant (nonionic)	100%	100 mg	n.a.	250.4	9.7 (100%)	noncorrosive	6	soluble	n.a.	colorless	solid	51.7
9005-64-5	Tween 20	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Ester, Ether	Food Additive, Laboratory Chemical, Pesticide Intermediate, Surfactant (nonionic)	100%	0.1 mL	98%	1227.5	n.a.	noncorrosive	4	100 g/L	n.a.	?	liquid	40.0
9016-45-9	Polyethylene glycol nonylphenyl ether (Surfonic HDL-1)	TSCA	Texaco, Inc.	Houghton Chemical Corp.	Alcohol, Ether	Cleaning Agent, Industrial Chemical, Pesticide, Surfactant (nonionic)	100%	0.1 mL	n.a.	308.5	?	?	6	?	?	?	liquid	35.0
9016-45-9	Polyethylene glycol nonylphenyl ether (Surfonic N-102)	TSCA	Texaco, Inc.	Houghton Chemical Corp.	Alcohol, Ether	Cleaning Agent, Industrial Chemical, Pesticide, Surfactant (nonionic)	100%	0.1 mL	n.a.	308.5	?	?	6	?	?	?	liquid	38.3
9016-45-9	**Polyethylene glycol nonylphenyl ether (Surfonic HDL-1)**	**TSCA**	**Texaco, Inc.**	**Houghton Chemical Corp.**	**Alcohol, Ether**	**Cleaning Agent, Industrial Chemical, Pesticide, Surfactant (nonionic)**	**100%**	**0.1 mL**	**n.a.**	**308.5**	**?**	**?**	**6**	**?**	**?**	**?**	**liquid**	**52.3**
919-30-2	**gamma-Aminopropyltriethoxy silane**	**TSCA**	**Union Carbide Corp.**	**Sigma-Aldrich Corp.**	**Amine, Amidine, Organosilicon Compound**	**Industrial Chemical**	**100%**	**0.1 mL**	**99%**	**221.4**	**?**	**R34**	**6**	**?**	**?**	**?**	**liquid**	**78.7**
92-84-2	Phenothiazine	TSCA	ICI Americas, Inc.	Fisher Scientific International, Inc.	Amine, Sulfur Compound (organic)	Pesticide, Pharmaceutical Intermediate	n.a.	100 mg	99.8%	199.3	?	?	6	?	?	?	solid	0.0
931-88-4	*cis*-Cyclo-octene	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (cyclic)	Chemical Intermediate, Industrial Chemical, Laboratory Chemical	100%	0.1 mL	95%	110.2	?	?	6	?	?	?	liquid	3.3
96-05-9	Allyl methacrylate	ECETOC	Elf Atochem, Inc.	Sigma-Aldrich Corp.	Ester	Chemical Intermediate	100%	0.1 mL	99.6%	126.2	?	?	6	4 g/L	?	?	liquid	5.8
96-37-7	Methyl cyclopentane	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (cyclic)	Solvent	100%	0.1 mL	>99%	84.2	?	?	6	?	?	colorless	liquid	3.7
96-41-3	**Cyclopentanol**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Alcohol**	**Pharmaceutical Intermediate**	**100%**	**0.1 mL**	**99%**	**86.1**	**n.a.**	**noncorrosive**	**3**	**slightly soluble**	**0.71**	**colorless**	**liquid**	**21.7**
96-48-0	**gamma-Butyrolactone**	**ECETOC**	**Shell Oil Co. of California**	**Sigma-Aldrich Corp.**	**Heterocyclic Compound, Lactone**	**Solvent**	**100%**	**0.1 mL**	**>99%**	**86.1**	**4.5**	**noncorrosive**	**6**	**miscible**	**-0.57**	**colorless**	**liquid**	**43.0**
96568-04-6	**2,6-Dichloro-5-fluoro-beta-oxo-3-pyridinepropanoate**	**GSK**	**n.a.**	**Sigma-Aldrich Corp.**	**Ester, Heterocyclic Compound, Ketone**	**Industrial Chemical, Pharmaceutical Intermediate**	**100%**	**0.1 mL or 100 mg**	**n.a.**	**280.1**	**?**	**?**	**3**	**?**	**?**	**white**	**solid**	**21.3**
98-07-7	**Benzotrichloride**	**TSCA**	**Velsicol Chemical Corp.**	**Sigma-Aldrich Corp.**	**Hydrocarbon (cyclic)**	**Chemical Intermediate**	**100%**	**0.1 mL**	**n.a.**	**195.5**	**?**	**?**	**6**	**?**	**?**	**?**	**liquid**	**11.7**
98-09-9	**Benzenesulfonyl chloride**	**TSCA**	**n.a.**	**Fisher Scientific International, Inc.**	**Acyl Halide, Sulfur Compound (organic)**	**Chemical Intermediate, Pesticide**	**n.a.**	**0.1 mL**	**99.6%**	**176.6**	**?**	**R34**	**6**	**?**	**?**	**brown**	**liquid**	**80.7**
98-09-9	**Di(2-ethylhexyl) sodium sulfosuccinate**	**NIHS-Ohno**	**Japanese Cosmetic Industry Assn.**	**Sigma-Aldrich Corp.**	**Ester, Salt (organic), Sulfur Compound (organic)**	**Adjuvant, Cleaner, Solubilizer, Wetting Agent**	**10%**	**0.1 mL**	**n.a.**	**444.6**	**6.5**	**noncorrosive**	**3**	**soluble (15 g/L)**	**n.a.**	**?**	**liquid**	**57.0**
98-29-3	**4-tert-Butylcatechol**	**TSCA**	**n.a.**	**Sigma-Aldrich Corp.**	**Phenol**	**Chemical Intermediate, Laboratory Chemical**	**85%**	**0.1 mL**	**n.a.**	**166.2**	**?**	**?**	**6**	**?**	**?**	**?**	**liquid**	**83.7**
98-36-2	**4-Chloro-methanilic acid**	**ZEBET**	**n.a.**	**Fisher Scientific International, Inc.**	**Amine, Sulfur Compound (organic)**	**Chemical Intermediate, Laboratory Chemical**	**n.a.**	**0.1 mL or 100 mg**	**n.a.**	**207.6**	**?**	**?**	**1**	**?**	**?**	**?**	**solid**	**17.0**
98-54-4	**p-tert-Butylphenol**	**TSCA**	**Union Carbide Corp.**	**Sigma-Aldrich Corp.**	**Phenol**	**Chemical Intermediate, Perfume, Pesticide**	**100%**	**80 mg**	**n.a.**	**150.2**	**?**	**?**	**6**	**?**	**?**	**?**	**solid**	**71.3**
98-54-4	p-tert-Butylphenol	TSCA	Union Carbide Corp.	Sigma-Aldrich Corp.	Phenol	Chemical Intermediate, Perfume, Pesticide	n.a.	10 mg	n.a.	150.2	?	?	6	?	?	?	solid	49.7
99-62-7	1,3-Di-iso-propyl benzene	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Hydrocarbon (cyclic)	Chemical Intermediate, Solvent	100%	0.1 mL	96%	162.3	?	?	6	soluble with Alcohol, Ether, acetone	?	?	liquid	2.0
99-65-0	*m*-Dinitrobenzene	ZEBET	n.a.	Sigma-Aldrich Corp.	Nitro Compound	Chemical Intermediate	n.a.	0.1 mL or 100 mg	n.a.	168.1	?	?	3	?	?	?	solid	15.7
mixture of isomers	Dichlorotoluenes	ECETOC	Elf Atochem, Inc.	Elf Atochem, Inc. (Bulk)	Hydrocarbon (halogenated)	Industrial Chemical	100%	0.1 mL	99-99.8%	n.a.	?	?	3	?	?	?	liquid	0.0
n.a.	HZA - Shampoo No. 7	CTFA	Battelle Columbus Lab.	yes	Formulation	Shampoos, Hair	100%	0.1 mL	n.a.	n.a.	n.a.	n.a.	6	n.a.	n.a.	?	liquid	34.2

CASRN	Substance	GHS Classification	Corneal score	Irital score	Conjunctival score	NICEATM Category 1 SubClass.[2]	Tested in BCOP	Tested in HET-CAM	Tested in ICE	Tested in IRE	EPA Classification	EU Classification	FHSA Classification	Human Exposure Summary
80-55-7	**2-Hydroxyisobutyric acid ethylester**	**Category 1**	**n=3/3, CO=3**	**-**	**-**	**2**	**-**	**-**	**-**	**-**	**SCNM**	**R41**	**SCNM**	**Human data not located**
818-61-1	**Hydroxyethyl acrylate**	**Category 1**	**n=4/6, CO=4**	**n=6/6, IR=2 D14**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**SCNM**	**Severe eye irritant (27)**
82985-35-1	**Organofunctional Silane 45-49**	**Category 1**	**n=2/6, CO>0 D21**	**n=2/6, IR>0 D21**	**n=2/6, CR>0 D21**	**1**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**SCNM**	**Human data not located**
86-87-3	**1-Naphthaleneacetic acid (solid)**	**Category 1**	**n=1/6, CO=4**	**-**	**-**	**4**	**X**	**X**	**X**	**-**	**Category I**	**R41**	**irritant**	**Has been reported to cause severe irritation to the human eye (17)**
89-86-1	**beta-Resorcylic acid**	**Category 1**	**n=1/1, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**SCNM**	**Review Data**	**SCNM**	**Human data not located**
9002-92-0	Polyoxyethylene 23 lauryl ether (BRIJ-35)	nonirritant	-	-	-	-	-	X	-	-	Category IV	nonirritant	nonirritant	?
9002-93-1	**Triton X-100**	**nonirritant**	**-**	**-**	**-**	**-**	**X**	**-**	**-**	**-**	**Category II**	**R36**	**irritant**	**Human data not located**
9002-93-1	**Triton X-100**	**Category 2B**	**-**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**Category I**	**R41**	**SCNM**	**Human data not located**
9002-93-1	**Triton X-100**	**Category 2A**	**-**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**Category I**	**R41**	**SCNM**	**Human data not located**
9002-93-1	Triton X-100	Category 1	-	n=2/6, IR>1.5	n=1/6, CR>0	3	X	X	X	X	SCNM	R41	irritant	Human data not located
9002-93-1	**Triton X-100**	**Category 1**	**n=2/6, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**SCNM**	**Review Data**	**irritant**	**Human data not located**
9002-93-1	Triton X-100	Category 1	n=1/3, CO=3 D14	-	-	1	-	-	-	-	Category III	nonirritant	irritant	?
9002-93-1	Triton X-100	Category 1	-	n=5/6, IR>1.5	-	2	-	-	-	-	Category III	nonirritant	SCNM	Human data not located
9005-64-5	Tween 20	nonirritant	-	-	-	-	X	X	X	X	Category III	nonirritant	SCNM	Human data not located
9016-45-9	Polyethylene glycol nonylphenyl ether (Surfonic HDL-1)	Category 1	-	-	-	0	-	-	-	-	SCNM	Review Data	irritant	?
9016-45-9	Polyethylene glycol nonylphenyl ether (Surfonic N-102)	Category 1	n=2/6, CO=4	-	-	4	-	-	-	-	Category I	R41	irritant	Human data not located
9016-45-9	**Polyethylene glycol nonylphenyl ether (Surfonic HDL-1)**	**Category 1**	**n=5/6, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**irritant**	**Human data not located**
919-30-2	**gamma-Aminopropyltriethoxy silane**	**Category 1**	**n=5/6, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**SCNM**	**Review Data**	**irritant**	**Human data not located**
92-84-2	Phenothiazine	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant	?
931-88-4	*cis*-Cyclo-octene	nonirritant	-	-	-	-	-	-	-	-	Category III	nonirritant	irritant	?
96-05-9	Allyl methacrylate	nonirritant	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM	?
96-37-7	Methyl cyclopentane	nonirritant	-	-	-	-	X	X	X	-	Category III	nonirritant	nonirritant	?
96-41-3	**Cyclopentanol**	**Category 2B**	**-**	**-**	**-**	**-**	**-**	**-**	**X**	**-**	**Category II**	**R36**	**SCNM**	**Human data not located**
96-48-0	**gamma-Butyrolactone**	**Category 2A**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**X**	**Category II**	**R36**	**irritant**	**Human data not located**
96568-04-6	**2,6-Dichloro-5-fluoro-beta-oxo-3-pyridinepropanoate**	**Category 2B**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category III**	**nonirritant**	**SCNM**	**Human data not located**
98-07-7	**Benzotrichloride**	**Category 2A**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category II**	**nonirritant**	**irritant**	**Human data not located**
98-09-9	**Benzenesulfonyl chloride**	**Category 1**	**n=5/6, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**irritant**	**Human data not located**
98-09-9	**Di(2-ethylhexyl) sodium sulfosuccinate**	**Category 1**	**n=1/3, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**SCNM**	**R41**	**SCNM**	**In ophthalmological formulations, concentrations of greater than 0.1% may cause conjunctival irritation; repeated use of such drugs may delay healing of corneal lesions. (7)**
98-29-3	**4-tert-Butylcatechol**	**Category 1**	**n=6/6, CO=4**	**n=2/6, IR=2 D21**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**irritant**	**Human data not located**
98-36-2	**4-Chloro-methanilic acid**	**Category 1**	**n=1/1, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**SCNM**	**Review Data**	**SCNM**	**Human data not located**
98-54-4	**p-tert-Butylphenol**	**Category 1**	**n=4/6, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**irritant**	**Human data not located**
98-54-4	p-tert-Butylphenol	Category 1	n=4/6, CO>0 D21	-	-	1	-	-	-	-	Category I	R41	irritant	?
99-62-7	1,3-Di-iso-propyl benzene	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant	?
99-65-0	*m*-Dinitrobenzene	Category 2B	-	-	-	-	-	-	-	-	Category III	R36	SCNM	?
mixture of isomers	Dichlorotoluenes	nonirritant	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	?
n.a.	HZA - Shampoo No. 7	Category 1	n=2/6, CO=1 D21	-	-	1	-	X	-	-	Category I	nonirritant	irritant	?

CASRN	Substance	Animal Exposure Summary for Category 1(H) Substances	Notes
80-55-7	**2-Hydroxyisobutyric acid ethylester**		
818-61-1	**Hydroxyethyl acrylate**		
82985-35-1	**Organofunctional Silane 45-49**		
86-87-3	**1-Naphthaleneacetic acid (solid)**		
89-86-1	**beta-Resorcylic acid**		
9002-92-0	Polyoxyethylene 23 lauryl ether (BRIJ-35)	?	
9002-93-1	**Triton X-100**		
9002-93-1	**Triton X-100**		
9002-93-1	**Triton X-100**		
9002-93-1	Triton X-100		Decided to use Triton X-100 at different conc.; this was maximum concentration tested
9002-93-1	**Triton X-100**		
9002-93-1	Triton X-100	?	
9002-93-1	Triton X-100		All other concn. tested as a liquid; excluded to be consistent
9005-64-5	Tween 20		
9016-45-9	Polyethylene glycol nonylphenyl ether (Surfonic HDL-1)	?	Used study demonstrating most consistent animal responses
9016-45-9	Polyethylene glycol nonylphenyl ether (Surfonic N-102)		Used study demonstrating most consistent animal responses
9016-45-9	**Polyethylene glycol nonylphenyl ether (Surfonic HDL-1)**		
919-30-2	**gamma-Aminopropyltriethoxy silane**		
92-84-2	Phenothiazine	?	
931-88-4	*cis*-Cyclo-octene	?	
96-05-9	Allyl methacrylate	?	
96-37-7	Methyl cyclopentane	?	
96-41-3	**Cyclopentanol**		
96-48-0	**gamma-Butyrolactone**		
96568-04-6	**2,6-Dichloro-5-fluoro-beta-oxo-3-pyridinepropanoate**		
98-07-7	**Benzotrichloride**		
98-09-9	**Benzenesulfonyl chloride**		
98-09-9	**Di(2-ethylhexyl) sodium sulfosuccinate**		
98-29-3	**4-tert-Butylcatechol**		
98-36-2	**4-Chloro-methanilic acid**		
98-54-4	**p-tert-Butylphenol**		
98-54-4	p-tert-Butylphenol	?	Conc. tested provided in other study
99-62-7	1,3-Di-iso-propyl benzene	?	
99-65-0	*m*-Dinitrobenzene	?	
mixture of isomers	Dichlorotoluenes	?	
n.a.	HZA - Shampoo No. 7	?	Formulations excluded

CASRN	Substance	In Vivo Data Source	Substance Source	Commercial Availability	Chemical Class	Product Class	Conc. Tested	Amount Tested[1]	Purity	MW	pH	Dermal Corrosivity	# of Animals Tested	Water Solubility	Log Kow	Color	Physical Form Tested	MMAS score
n.a.	HZD Shampoo No. 5	CTFA	Battelle Columbus Lab.	yes	Formulation	Shampoos, Hair	100%	0.1 mL	n.a.	n.a.	n.a.	n.a.	3	n.a.	n.a.	n.a.	liquid	33.7
n.a.	HZF - Baby Shampoo No. 2	CTFA	Battelle Columbus Lab.	yes	Formulation	Shampoos, Hair	100%	0.1 mL	n.a.	n.a.	n.a.	n.a.	6	n.a.	n.a.	n.a.	liquid	34.5
n.a.	HZI - Skin Cleanser	CTFA	Battelle Columbus Lab.	yes	Formulation	Formulation	100%	0.1 mL	n.a.	n.a.	n.a.	n.a.	6	n.a.	n.a.	n.a.	liquid	37.2
n.a.	HZK - Bubble Bath	CTFA	Battelle Columbus Lab.	yes	Formulation	Formulation	100%	0.1 mL	n.a.	n.a.	n.a.	n.a.	6	n.a.	n.a.	n.a.	liquid	39.7
n.a.	HZS - Shower Gel	CTFA	Battelle Columbus Lab.	yes	Formulation	Formulation	100%	0.1 mL	n.a.	n.a.	n.a.	n.a.	6	n.a.	n.a.	n.a.	gel	39.0
n.a.	HZX - Shampoo No. 2	CTFA	Battelle Columbus Lab.	yes	Formulation	Shampoos, Hair	100%	0.1 mL	n.a.	n.a.	n.a.	n.a.	6	n.a.	n.a.	n.a.	liquid	39.3
n.a.	HZY - Anti-Dandruff Shampoo	CTFA	Battelle Columbus Lab.	yes	Formulation	Shampoos, Hair	100%	0.1 mL	n.a.	n.a.	n.a.	n.a.	6	n.a.	n.a.	n.a.	liquid	37.2

CASRN	Substance	GHS Classification	Corneal score	Irital score	Conjunctival score	NICEATM Category 1 SubClass.[2]	Tested in BCOP	Tested in HET-CAM	Tested in ICE	Tested in IRE	EPA Classification	EU Classification	FHSA Classification	Human Exposure Summary
n.a.	HZD Shampoo No. 5	Category 2B	-	-	-	-	-	X	-	-	Category III	nonirritant	SCNM	?
n.a.	HZF - Baby Shampoo No. 2	Category 1	n=2/6, CO=1 D21	-	n=2/6, CR=2 D21	1	-	X	-	-	Category I	R41	irritant	?
n.a.	HZI - Skin Cleanser	Category 1	n=3/6, CO=1 D21	-	-	1	-	X	-	-	Category I	R36	irritant	?
n.a.	HZK - Bubble Bath	Category 1	n=5/6, CO=1 D21	-	n=3/6, CR=2 D21	1	-	X	-	-	Category I	R41	irritant	?
n.a.	HZS - Shower Gel	Category 1	n=2/6, CO>1 D21	-	n=2/6, CR=2 D21	1	-	X	-	-	Category I	R41	irritant	?
n.a.	HZX - Shampoo No. 2	Category 1	n=2/6, CO=1 D21	-	-	1	-	X	-	-	Category I	R36	irritant	?
n.a.	HZY - Anti-Dandruff Shampoo	Category 1	n=2/6, CO=1 D21	-	-	1	-	X	-	-	Category I	R41	irritant	?

CASRN	Substance	Animal Exposure Summary for Category 1(H) Substances	Notes
n.a.	HZD Shampoo No. 5	?	Formulations excluded.
n.a.	HZF - Baby Shampoo No. 2	?	Formulations excluded
n.a.	HZI - Skin Cleanser	?	Formulations excluded
n.a.	HZK - Bubble Bath	?	Formulations excluded
n.a.	HZS - Shower Gel	?	Formulations excluded
n.a.	HZX - Shampoo No. 2	?	Formulations excluded
n.a.	HZY - Anti-Dandruff Shampoo	?	Formulations excluded

Abbreviations: ? = Data has not been obtained at this time; - = not applicable; AG = Aktiengesellschaft (incorporated); Assn. = Association; BASF = Badische Anilin- & Soda Fabrik AG; BCOP = Bovine Corneal Opacity and Permeability; CASRN = Chemical Abstracts Service Registry Number; CC = Conjunctival Chemosis; Co. = Company; CO = Corneal Opacity; Conc. = concentration; Corp. = Corporation; CR = Conjunctival Redness; CTFA = Cosmetic, Toiletries and Fragrance Association; D = Day; ECETOC= European Center for Ecotoxicology and Toxicology of Chemicals; GmbH = Gesellschaft mit beschränkter Haftung (Inc.); GSK = Glaxo Smith-Kline; HET-CAM = Hen's Egg Test- Chorioallantoic Membrane; ICE = Isolated Chicken Eye; IRE = Isolated Rabbit Eye; ISOPA = European Diisocyanate and Polyol Producers Association; I = Iritis; Lab. = Laboratory; LNS= Laboratoire National de la Sante; Log Kow = octanol/water partition coefficient; Ltd. = Limited; LLC = Limited Liability Company; MeSH = Medical Subject Headings, information on chemical class criteria can be obtained at www.nlm.nih.gov/mesh; MG CU/ M = Milligrams Per Cubic Meter; MMAS = Modified Maximum Average Score; the highest (maximum) average of the individual animal weighted scores for observation times greater than or equal to 24 hours after test substance instillation.; MW = molecular weight; n = number of animals; n.a. = not available; noncorrosive = not classified as a dermal corrosive; NIHS-Ohno = National Institute of Health Sciences, Japan, Yasuo Ohno; PPM = Parts Per Million; R34 = causes burns; R35 = causes severe burns; SCNM = Study Criteria Not Met; (H) = classification based on inducing severe ocular damage in humans; TNO-Prinsen = Institute CIVO, Menk Prinsen; TSCA = Toxic Substances Control Act; ZEBET = German Center for Documentation and Evaluation of Alternative Methods to Animal Experiments; X = Where a substance has been tested in BCOP, HET-CAM, ICE, or IRE, the presence of an "X" indicates that the substance has been tested in the proposed version of this test method.

NICEATM Cat. 1 Subcat. = Category 1 subcategories = NICEATM-assigned subcategories for GHS Category 1 substances (ocular corrosives and severe irritants) were assigned based on the following: 0 = not classifiable; 1 = positive response based on a persistent lesion involving the cornea, iris, and/or conjunctiva through to day 21 in at least one of three rabbits and not on severity; 2 = positive response based on mean for first 3 days (corneal opacity [CO] score >3 and <4 or iritis [IR] score >1.5) in at least two of three rabbits but lesions do not persist through day 21; 3 = positive response based on mean for first 3 days (CO >3 and <4 or IR >1.5) in at least two of three rabbits and a persistent (>21 days) lesion in at least one rabbit; 4 = CO score of 4 at any time in at least one of three rabbits

“100 mg or 0.1 mL” indicates studies which were conducted according to Draize, but for which the amount tested was not provided in the study information provided or obtained.

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APPENDIX V-A2

CANDIDATE SUBSTANCES FOR THE LIST OF PROPOSED REFERENCE SUBSTANCES FOR VALIDATION STUDIES OF *IN VITRO* TEST METHODS FOR THE IDENTIFICATION OF OCULAR CORROSIVES/SEVERE IRRITANTS (SORTED BY GHS OCULAR HAZARD CATEGORY AND SUBSTANCE NAME)

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Candidate Substances (Sorted by GHS Classification and Substance Name)

GHS Classification	Substance	CASRN	In Vivo Data Source	Substance Source	Commercial Availability	Chemical Class	Product Class	Conc. Tested	Amount Tested[1]	Purity	MW	pH	Dermal Corrosivity	# of Animals Tested	Water Solubility	Log Kow	Color
Category 1	Acetic Acid	64-19-7	NIHS-Ohno	Japanese Cosmetic Industry Assn.	Sigma-Aldrich Corp.	Acid (organic) [carboxylic acid]	Industrial Chemical; Laboratory Agent, Solvent	10%	0.1 mL	n.a.	60.1	2.4	R35 (60%)	3	soluble	-0.17 (60%)	colorless
Category 1	Acid blue 40	6424-85-7	TSCA	Crompton and Knowles Corp.	Sigma-Aldrich Corp.	Amine, Quinone, Salt (organic)	Industrial Chemical	n.a.	100 mg	n.a.	473.4	8.0	noncorrosive	6	soluble (30 g/L@ 80C)	2.2	deep blue
Category 1	Methoxyethyl acrylate	3121-61-7	ECETOC	Elf Atochem, Inc.	Sigma-Aldrich Corp.	Ester, Ether	Chemical Intermediate, Industrial Chemical, Laboratory Chemical	100%	0.1 mL	99.6%	130.1	n.a.	noncorrosive	3	Soluble	0.08	?
Category 1	Aluminum chloride	16603-84-2	TSCA	Monsanto Co.	Fisher Scientific International, Inc.	Salt (inorganic)	Chemical Intermediate, Dye, Industrial Chemical, Laboratory Chemical, Pesticide, Preservative	n.a.	0.1 mL	n.a.	98.9	?	?	6	?	?	light yellow-green
Category 1	gamma-Aminopropyltriethoxy silane	919-30-2	TSCA	Union Carbide Corp.	Sigma-Aldrich Corp.	Amine, Amidine, Organosilicon Compound	Industrial Chemical	100%	0.1 mL	99%	221.4	?	R34	6	?	?	?
Category 1	Antimony oxide	1309-64-4	TSCA	Monsanto Co.	Sigma-Aldrich Corp.	Salt (inorganic)	Flame Retardant, Industrial Chemical, Laboratory Chemical, Pharmaceutical Intermediate	100%	100 mg	83.5%	291.5	?	noncorrosive	6	?	?	white powder
Category 1	Benzalkonium chloride	8001-54-5	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Onium Compound	Surfactant (cationic)	5%	0.1 mL	98%	471.5	3.1	R34 (50%)	4	soluble	n.a.	clear
Category 1	Benzalkonium chloride	8001-54-5	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Onium Compound	Surfactant (cationic)	10%	0.1 mL	98%	471.5	3.2	R34 (50%)	3	soluble	n.a.	clear
Category 1	Benzenesulfonyl chloride	98-09-9	TSCA	n.a.	Fisher Scientific International, Inc.	Acyl Halide, Sulfur Compound (organic)	Chemical Intermediate, Pesticide	n.a.	0.1 mL	99.6%	176.6	?	R34	6	?	?	brown
Category 1	Benzethonium chloride	121-54-0	LNS	n.a.	Sigma-Aldrich Corp.	Amine, Onium Compound	Anti-Infective, Pharmaceutical, Veterinary Chemical	10%	0.1 mL	n.a.	448.1	?	?	3	?	?	?
Category 1	2-Benzyl-4-chlorophenol	120-32-1	TSCA	Monsanto Co.	Sigma-Aldrich Corp.	Phenol	Anti-Fungal, Anti-Infective, Herbicide	100%	100 mg	95%	218.7	?	?	6	?	?	light brown
Category 1	2-Benzyl-4-chlorophenol	120-32-1	TSCA	Monsanto Co.	Sigma-Aldrich Corp.	Phenol	Anti-Fungal, Anti-Infective, Herbicide	n.a.	0.1 mL	n.a.	218.7	?	?	6	?	?	light brown
Category 1	2,2-Dimethyl butanoic acid	595-37-9	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Acid (organic) [carboxylic acid]	Pharmaceutical	100%	0.1 mL	96%	116.2	n.a.	R34	6	n.a.	n.a.	?
Category 1	iso-Butanol	78-83-1	ZEBET	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Alcohol	Chemical Intermediate, Food Additive, Pesticide, Pharmaceutical Intermediate, Solvent	n.a.	0.1 mL or 100 mg	n.a.	74.1	5.7	noncorrosive	3	soluble (95 g/L)	0.76	?
Category 1	n-Butanol	71-36-3	NIHS-Ohno	Japanese Cosmetic Industry Assn.	Sigma-Aldrich Corp.	Alcohol	Chemical Intermediate, Cosmetic Ingredient, Food Additive, Industrial Chemcial, Pesticide Intermediate, Pharmaceutical Intermediate, Solvent, Veterinary Chemical	10%	0.1 mL	n.a.	74.1	n.a.	noncorrosive	3	insoluble	0.88	colorless
Category 1	*n*-Butanol	71-36-3	ZEBET	n.a.	Sigma-Aldrich Corp.	Alcohol	Chemical Intermediate, Cosmetic Ingredient, Food Additive, Industrial Chemcial, Pesticide Intermediate, Pharmaceutical Intermediate, Solvent, Veterinary Chemical	n.a.	0.1 mL or 100 mg	n.a.	74.1	?	noncorrosive	3	insoluble	0.88	colorless

GHS Classification	Substance	Physical Form Tested	MMAS score	Corneal score	Irital score	Conjunctival score	NICEATM Category 1 SubClass.[2]	Tested in BCOP	Tested in HET-CAM	Tested in ICE	Tested in IRE	EPA Classification	EU Classification	FHSA Classification
Category 1	**Acetic Acid**	**liquid**	**68.0**	**n=2/3, CO=4**	**-**	**-**	**4**	**-**	**X**	**X**	**X**	**Category I**	**R41**	**SCNM**
Category 1	**Acid blue 40**	**solid**	**39.7**	**n=2/6, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**SCNM**	**R36**	**irritant**
Category 1	**Methoxyethyl acrylate**	**liquid**	**45.0**	**n=2/3, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**SCNM**	**R36**	**SCNM**
Category 1	**Aluminum chloride**	**liquid**	**82.7**	**n=5/6, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**irritant**
Category 1	**gamma-Aminopropyltriethoxy silane**	**liquid**	**78.7**	**n=5/6, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**SCNM**	**Review Data**	**irritant**
Category 1	**Antimony oxide**	**solid**	**107.3**	**n=6/6, CO=4**	**n=6/6, IR=2 D14**	**n=6/6, CR=3, n=3/6, CC=4 D14**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**irritant**
Category 1	**Benzalkonium chloride**	**liquid**	**4.8**	**n=1/4, CO=4; n=2/4, CO=3; n=2/4, CO>0 D21**	**n=1/4, IR>1.5 D21**	**n=1/4, CR/CC>0 D21**	**3**	**X**	**X**	**X**	**X**	**Category I**	**R41**	**SCNM**
Category 1	Benzalkonium chloride	liquid	108.0	n=3/3, CO=4	n=3/3, IR=2 D21	n=1/3, CR>0, n=2/3, CC>0 D21	4	X	X	X	X	Category I	R41	SCNM
Category 1	**Benzenesulfonyl chloride**	**liquid**	**80.7**	**n=5/6, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**irritant**
Category 1	**Benzethonium chloride**	**liquid**	**76.3**	**n=2/3, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**SCNM**
Category 1	**2-Benzyl-4-chlorophenol**	**solid**	**100.0**	**n=6/6, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**irritant**
Category 1	2-Benzyl-4-chlorophenol	liquid	71.5	n=5/6, CO>0 D21	n=5/6, IR>0 D21	n=5/6, CR/CC>0 D21	1	-	-	-	-	Category I	R41	irritant
Category 1	**2,2-Dimethyl butanoic acid**	**liquid**	**44.7**	**n=1/6, CO=3 D14**	**n=1/6, IR=2 D14**	**-**	**1**	**X**	**X**	**X**	**X**	**Category I**	**R41**	**irritant**
Category 1	iso-Butanol	liquid	11.7	n=1/3, CO=3 D14	-	-	1	-	-	-	-	Category II	R36	SCNM
Category 1	**n-Butanol**	**liquid**	**34.0**	**n=1/3, CO=4**	**-**	**-**	**4**	**-**	**X**	**-**	**-**	**SCNM**	**R41**	**SCNM**
Category 1	*n*-Butanol	liquid	17.7	n=1/3, CO=4	-	-	4	-	-	-	-	SCNM	Review Data	SCNM

GHS Classification	Substance	Human Exposure Summary	Animal Exposure Summary for Category 1(H) Substances	Notes
Category 1	**Acetic Acid**	**Has caused extreme eye and nasal irritation at concentrations in air in excess of 25 ppm. Has caused conjunctivitis at concentrations below 10 ppm. Concentrations of 200 ppm caused conjunctival hyerperemia. Glacial (100%) acetic acid has caused permanent corneal opacification. A splash of vinegar (4 to 10% acetic acid solution) in the eye causes immediate pain and conjunctival hyperemia, sometimes with injury of the corneal epithelium (2 patients). Accidental application of glacial acetic acid to the eyes followed very quickly by irrigation with water resulted in immediate corneal opacification. These corneas cleared sufficiently in a few days to reveal severe iritis and small pupils fixed by posterior synechiae. Regeneration of the epithelium took many months, but corneal anesthesia and opacity were permanent. In workers exposed to aerosol concentrations of 60 ppm for 7-12 years, with daily exposures as high as 100-200 ppm, investigators found conjunctivitis (in addition to bronchitis, pharyngeitis, and erosion of exposed teeth) (1, 13, 18)**		
Category 1	**Acid blue 40**	**Human data not located**		
Category 1	**Methoxyethyl acrylate**	**Human data not located**		
Category 1	**Aluminum chloride**	**Is caustic and irritating to the human eye, but in only 1 out of 55 instances of industrial corneal burns has healing been delayed beyond 2 days (10)**		
Category 1	**gamma-Aminopropyltriethoxy silane**	**Human data not located**		
Category 1	**Antimony oxide**	**Chronic exposure causes eye irritation (6, 53)**		
Category 1	**Benzalkonium chloride**	**A severe irritant to the human eye. Concentrations as low as 0.1 to 0.5% cause mild discomfort and conjunctival irritation. Slit lamp examination within 90 seconds of exposure to a single drop of 0.1% shows fine gray dots of keratitis epithelias in the corneal epithelium. Within 10 minutes of exposure, a gray haze may be seen in the corneal surface; superficial desquamation of the conjunctival epithelium may follow. These effects disappear in a day or less. (9, 17)**		
Category 1	Benzalkonium chloride	A severe irritant to the human eye. Concentrations as low as 0.1 to 0.5% cause mild discomfort and conjunctival irritation. Slit lamp examination within 90 seconds of exposure to a single drop of 0.1% shows fine gray dots of keratitis epithelias in the corneal epithelium. Within 10 minutes of exposure, a gray haze may be seen in the corneal surface; superficial desquamation of the conjunctival epithelium may follow. These effects disappear in a day or less. (9, 17)		Severe effects at 5% in other study
Category 1	**Benzenesulfonyl chloride**	**Human data not located**		
Category 1	**Benzethonium chloride**	**Human data not located**		
Category 1	**2-Benzyl-4-chlorophenol**	**Human data not located**		
Category 1	2-Benzyl-4-chlorophenol	Human data not located		Tested as a solid in other study
Category 1	**2,2-Dimethyl butanoic acid**	**Human data not located**		
Category 1	iso-Butanol	Irritation of the skin, eyes, and throat have been reported from exposure to vapor or liquid. Irritation of the eyes and throat, formation of vacuoles in the superficial layers of the cornea, were reported among workers subjected to an undetermined, but apparently high concn of isobutyl alcohol & butyl acetate. (9, 20)+AH12		Discordant GHS classification
Category 1	**n-Butanol**	**Is reported to cause irritation of the eyes from exposure to either vapor or liquid. Circumstantial evidence points to butyl alcohol vapor as cause of a special vacuolar keratopathy in some patients; the most severely affected it has been associated with pain & tearing, characteristically most marked on first opening eyes in morning. It can cause transient mild edema of conjunctiva of the eye. Vapor: Irritating to eyes. Considered a strong irritant of the eyes. (9, 11, 13, 27)**		
Category 1	*n*-Butanol	Is reported to cause irritation of the eyes from exposure to either vapor or liquid. Circumstantial evidence points to butyl alcohol vapor as cause of a special vacuolar keratopathy in some patients; the most severely affected it has been associated with pain & tearing, characteristically most marked on first opening eyes in morning. It can cause transient mild edema of conjunctiva of the eye. Vapor: Irritating to eyes. Considered a strong irritant of the eyes. (9, 11, 13, 27)		Conc. tested provided in other study

GHS Classification	Substance	CASRN	In Vivo Data Source	Substance Source	Commercial Availability	Chemical Class	Product Class	Conc. Tested	Amount Tested[1]	Purity	MW	pH	Dermal Corrosivity	# of Animals Tested	Water Solubility	Log Kow	Color
Category 1	Butyl cellosolve	111-76-2	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Alcohol	Solvent	100%	0.1 mL	99%	118.2	n.a.	noncorrosive	3	soluble (5 g/L)	0.83	?
Category 1	4-tert-Butylcatechol	98-29-3	TSCA	n.a.	Sigma-Aldrich Corp.	Phenol	Chemical Intermediate, Laboratory Chemical	85%	0.1 mL	n.a.	166.2	?	?	6	?	?	?
Category 1	p-tert-Butylphenol	98-54-4	TSCA	Union Carbide Corp.	Sigma-Aldrich Corp.	Phenol	Chemical Intermediate, Perfume, Pesticide	100%	80 mg	n.a.	150.2	?	?	6	?	?	?
Category 1	p-tert-Butylphenol	98-54-4	TSCA	Union Carbide Corp.	Sigma-Aldrich Corp.	Phenol	Chemical Intermediate, Perfume, Pesticide	n.a.	10 mg	n.a.	150.2	?	?	6	?	?	?
Category 1	Captan 90-concentrate (solid)	133-06-2	ECETOC	US EPA	Gustafson, LLC	Heterocyclic Compound, Sulfur Compound (organic)	Pesticide	100%	100 mg	90%	300.6	8.0	noncorrosive	3	soluble (5.1 mg/L)	2.35	white
Category 1	Cetylpyridinium bromide	140-72-7	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Onium Compound, Heterocyclic Compound	Anti-Infective; Laboratory Chemical; Surfactant (cationic)	6%	0.1 mL	99%	384.4	6.0-8.0 (0.5%)	noncorrosive	4	soluble (5 g/L)	1.83 (100%)	faintly beige
Category 1	Cetylpyridinium bromide	140-72-7	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Onium Compound, Heterocyclic Compound	Anti-Infective; Laboratory Chemical; Surfactant (cationic)	10%	0.1 mL	99%	384.4	6.0-8.0 (0.5%)	noncorrosive	6	soluble (5 g/L)	1.83 (100%)	faintly beige
Category 1	Cetyltrimethylammonium bromide	57-09-0	NIHS-Ohno	Japanese Cosmetic Industry Assn.	Sigma-Aldrich Corp.	Onium Compound, Salt (organic)	Cosmetic Ingredient	10%	0.1 mL	n.a.	364.4	5.9	noncorrosive	3	soluble (30 g/L)	3.18/2.26	?
Category 1	Chlorhexidine	55-56-1	ECETOC	n.a.	Sigma-Aldrich Corp.	Amidine	Anti-Infective, Pharmaceutical	100%	100 mg	n.a.	505.5	?	?	3	?	n.a.	?
Category 1	Cyclohexanol	108-93-0	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Alcohol	Solvent	100%	0.1 mL	97%	100.2	4.5	noncorrosive	4	soluble (3.6 mg/100 mL)	1.23	colorless
Category 1	3,4-Dichlorophenyl isocyanate	102-36-3	TSCA	Mobay Corp.	Fisher Scientific International, Inc.	Isocyanate	Chemical Intermediate, Industrial Chemical	100%	0.1 mL	n.a.	188.0	?	?	3	?	?	?
Category 1	Diethylaminopropionitrile	5351-04-2	ECETOC	Elf Atochem, Inc.	Fisher Scientific International, Inc.	Amine, Nitrile	Industrial Chemical	100%	0.1 mL	>98.8 %	126.2	n.a.	noncorrosive	3	soluble	0.77	yellow
Category 1	Diethylethanolamine	100-37-8	TSCA	Union Carbide Corp.	Sigma-Aldrich Corp.	Alcohol, Amine	Chemical Intermediate, Pharmaceutical Intermediate	25%	0.1 mL	n.a.	117.2	?	?	6	?	?	colorless
Category 1	Diethylethanolamine	100-37-8	TSCA	Union Carbide Corp.	Sigma-Aldrich Corp.	Alcohol, Amine	Chemical Intermediate, Pharmaceutical Intermediate	50%	0.1 mL	n.a.	117.2	?	?	6	?	?	colorless
Category 1	Diethylethanolamine	100-37-8	TSCA	Union Carbide Corp.	Sigma-Aldrich Corp.	Alcohol, Amine	Chemical Intermediate, Pharmaceutical Intermediate	100%	0.1 mL	n.a.	117.2	?	?	6	?	?	colorless
Category 1	1,3-Diiminobenz (f)-isoindoline	65558-69-2	TSCA	Hoechst Celanese Corp.	Sigma-Aldrich Corp.	Amine, Heterocyclic Compound	Dye, Laboratory Chemical	100%	100 mg	n.a.	195.2	n.a.	?	3	?	?	?
Category 1	2,5-Dimethylhexanediol	110-03-2	ECETOC	BASF	Sigma-Aldrich Corp.	Alcohol	Chemical Intermediate	100%	40 mg	99.5%	146.2	5.7	noncorrosive	3	soluble	n.a.	?
Category 1	Bis-(3-aminopropyl) tetramethyl disiloxane	2469-55-8	TSCA	General Electric Co.	Sigma-Aldrich Corp.	Amine, Amidine, Organosilicon Compound	Industrial Chemical	100%	0.1 mL	n.a.	248.5	n.a.	R34	2	n.a.	n.a.	?
Category 1	Domiphen bromide	538-71-6	NIHS-Ohno	Japanese Cosmetic Industry Assn.	Sigma-Aldrich Corp.	Ether, Onium Compound, Salt (organic)	Anti-Infective, Pharmaceutical	10%	0.1 mL	n.a.	414.5	6.2	noncorrosive	3	n.a.	n.a.	?
Category 1	Granuform	30525-89-4	ZEBET	n.a.	Sigma-Aldrich Corp.	Aldehyde, Ether	Anti-Fungal, Anti-Infective, Industrial Chemical, Laboratory Chemical	n.a.	0.1 mL or 100 mg	n.a.	30.0	4.0	?	3	?	?	?
Category 1	Hydroxyethyl acrylate	818-61-1	TSCA	n.a.	Dow Chemical Co. (Bulk)	Alcohol, Ester	Chemical Intermediate	100%	0.1 mL	n.a.	116.1	?	?	6	?	?	?
Category 1	2-Hydroxyisobutyric acid ethylester	80-55-7	ZEBET	n.a.	Sigma-Aldrich Corp.	Alcohol, Ester	Industrial Chemical	n.a.	0.1 mL or 100 mg	n.a.	132.2	?	?	3	?	?	?
Category 1	2-Hydroxyisobutyric acid	594-61-6	ZEBET	n.a.	Sigma-Aldrich Corp.	Acid (organic) |carboxylic acid|	Industrial Chemical	n.a.	0.1 mL or 100 mg	n.a.	104.1	?	?	3	?	?	?
Category 1	HZA - Shampoo No. 7	n.a.	CTFA	Battelle Columbus Lab.	yes	Formulation	Shampoos, Hair	100%	0.1 mL	n.a.	n.a.	n.a.	n.a.	6	n.a.	n.a.	?
Category 1	HZF - Baby Shampoo No. 2	n.a.	CTFA	Battelle Columbus Lab.	yes	Formulation	Shampoos, Hair	100%	0.1 mL	n.a.	n.a.	n.a.	n.a.	6	n.a.	n.a.	n.a.
Category 1	HZI - Skin Cleanser	n.a.	CTFA	Battelle Columbus Lab.	yes	Formulation	Formulation	100%	0.1 mL	n.a.	n.a.	n.a.	n.a.	6	n.a.	n.a.	n.a.

GHS Classification	Substance	Physical Form Tested	MMAS score	Corneal score	Irital score	Conjunctival score	NICEATM Category 1 SubClass.[2]	Tested in BCOP	Tested in HET-CAM	Tested in ICE	Tested in IRE	EPA Classification	EU Classification	FHSA Classification
Category 1	**Butyl cellosolve**	**liquid**	**68.7**	-	-	**n=2/3, CR>0, n=1/3, CC>0 D21**	**1**	**X**	-	-	-	**Category II**	**R36**	**SCNM**
Category 1	**4-tert-Butylcatechol**	**liquid**	**83.7**	**n=6/6, CO=4**	**n=2/6, IR=2 D21**	-	**4**	-	-	-	-	**Category I**	**R41**	**irritant**
Category 1	**p-tert-Butylphenol**	**solid**	**71.3**	**n=4/6, CO=4**	-	-	**4**	-	-	-	-	**Category I**	**R41**	**irritant**
Category 1	p-tert-Butylphenol	solid	49.7	n=4/6, CO>0 D21	-	-	1	-	-	-	-	Category I	R41	irritant
Category 1	**Captan 90-concentrate (solid)**	**solid**	**83.0**	**n=3/3, CO=4**	**n=1/3, IR>0 D21**	**n=2/3, CR/CC>0 D21**	**4**	**X**	**X**	**X**	-	**Category I**	**R41**	**SCNM**
Category 1	**Cetylpyridinium bromide**	**liquid**	**85.8**	-	**n=3/4, I>1.5**	-	**2**	**X**	-	**X**	**X**	**Category II**	**R36**	**irritant**
Category 1	Cetylpyridinium bromide	liquid	89.7	n=3/6, CO=4	n=6/6, I>1.5	-	4	X	X	X	X	Category III	nonirritant	SCNM
Category 1	**Cetyltrimethylammonium bromide**	**liquid**	**96.0**	**n=3/3, CO=4**	-	**n=1/3, CR=3, n=3/3, CC=2 D14**	**4**	-	-	-	-	**Category I**	**R41**	**SCNM**
Category 1	**Chlorhexidine**	**solid**	**82.3**	**n=1/3, CO=4**	-	-	**4**	**X**	**X**	**X**	**X**	**SCNM**	**R41**	**SCNM**
Category 1	**Cyclohexanol**	**liquid**	**79.8**	**n=3/4, CO=3**	-	-	**2**	**X**	**X**	**X**	**X**	**Category I**	**R41**	**SCNM**
Category 1	**3,4-Dichlorophenyl isocyanate**	**liquid**	**10.3**	**n=3/3, CO>0 D21**	-	-	**1**	-	-	-	-	**Category I**	**R41**	**SCNM**
Category 1	**Diethylaminopropionitrile**	**liquid**	**62.3**	**n=3/3, CO=4**	-	-	**4**	-	-	-	-	**Category II**	**R41**	**SCNM**
Category 1	**Diethylethanolamine**	**liquid**	**94.7**	**n=6/6, CO=4**	**n=3/3, IR=2 D14**	-	**4**	-	-	-	-	**Category I**	**R41**	**irritant**
Category 1	Diethylethanolamine	liquid	95.0	n=6/6, CO=4	-	n=6/6, CR/CC>0 D21	4	-	-	-	-	Category I	R41	irritant
Category 1	Diethylethanolamine	liquid	82.5	n=5/6, CO=4	-	-	4	-	-	-	-	Category I	R41	irritant
Category 1	**1,3-Diiminobenz (f)-isoindoline**	**solid**	**93.0**	**n=4/4, CO=4**	-	-	**4**	-	-	-	-	**SCNM**	**R41**	**SCNM**
Category 1	**2,5-Dimethylhexanediol**	**solid**	**28.3**	-	**n=1/3, IR = 1 D21**	**n=1/3, CR=2 D21**	**1**	**X**	**X**	**X**	-	**Category I**	**R41**	**SCNM**
Category 1	**Bis-(3-aminopropyl) tetramethyl disiloxane**	**liquid**	**109.0**	**n=2/2, CO=4**	**n=2/2, IR=2**	**n=2/2, CR=3, CC=4**	**4**	-	-	-	-	**Category I**	**Review Data**	**SCNM**
Category 1	**Domiphen bromide**	**liquid**	**96.3**	**n=3/3, CO=4**	-	-	**4**	-	**X**	-	-	**Category I**	**R41**	**SCNM**
Category 1	**Granuform**	**solid**	**75.3**	**n=1/3, CO=4**	-	-	**4**	-	**X**	-	-	**SCNM**	**Review Data**	**SCNM**
Category 1	**Hydroxyethyl acrylate**	**liquid**	**96.7**	**n=4/6, CO=4**	**n=6/6, IR=2 D14**	-	**4**	-	-	-	-	**Category I**	**R41**	**SCNM**
Category 1	**2-Hydroxyisobutyric acid ethylester**	**solid**	**81.0**	**n=3/3, CO=3**	-	-	**2**	-	-	-	-	**SCNM**	**R41**	**SCNM**
Category 1	**2-Hydroxyisobutyric acid**	**solid**	**98.7**	**n=3/3, CO=4**	-	**n=1/3, CR=3, n=3/3, CC=4**	**4**	-	**X**	-	-	**SCNM**	**R41**	**SCNM**
Category 1	HZA - Shampoo No. 7	liquid	34.2	n=2/6, CO=1 D21	-	-	1	-	X	-	-	Category I	nonirritant	irritant
Category 1	HZF - Baby Shampoo No. 2	liquid	34.5	n=2/6, CO=1 D21	-	n=2/6, CR=2 D21	1	-	X	-	-	Category I	R41	irritant
Category 1	HZI - Skin Cleanser	liquid	37.2	n=3/6, CO=1 D21	-	-	1	-	X	-	-	Category I	R36	irritant

GHS Classification	Substance	Human Exposure Summary	Animal Exposure Summary for Category 1(H) Substances	Notes
Category 1	**Butyl cellosolve**	**An irritant to the human eye. In several, single 8 hour exposures to concentrations of 100 to 200 ppm in air, participants reported discomfort and mild eye irritation. 7 workers exposed to aerosol concentrations of 200 to 300 ppm reported intense eye irritation, followed by recurrent ocular irritation after the initial exposure. (1, 14, 21, 24, 30)**		
Category 1	**4-tert-Butylcatechol**	**Human data not located**		
Category 1	**p-tert-Butylphenol**	**Human data not located**		
Category 1	p-tert-Butylphenol	?	?	Conc. tested provided in other study
Category 1	**Captan 90-concentrate (solid)**	**Has been reported to cause conjunctivitis (12)**		
Category 1	**Cetylpyridinium bromide**	**Human data not located**		
Category 1	Cetylpyridinium bromide	Human data not located		Severe response at 6% in other study, severity based on irital effects
Category 1	**Cetyltrimethylammonium bromide**	**In 179 patients treated with eye drops containing cetrimide (Cetyltrimethylammonium bromide) for 30 days, adverse effects were reported for 21 patients. The adverse events consisted of discomfort, blurred vision, hyperemia, burning and itching. Accidental application of cetrimide occurred during cataract surgery. This resulted in immediate corneal edema which in turn resulted in a bullous keratopathy. Four patients underwent a penetrating keratoplasty. In one patient the cornea was covered with a conjunctival flap. Light microscopy of the corneas included epithelial edema, loss of keratocytes, and a disrupted and sometimes absent endothelial cell layer. (3, 29)**		
Category 1	**Chlorhexidine**	**Acutely toxic when applied to the eye. Irreversible corneal injuries and opacification attributed to Hibiclens (chlorhexidine gluconate, a 4% topical preparation), reported in 4 female patients, aged 9 months to 83 year, in whom the drug was accidentally introduced into the eye during surgical preparation. Inadvertently used as an intraocular irrigating solution in three patients undergoing surgery. In two of the three patients, corneal endothelium damage was so severe that penetrating keratoplasty had to be performed. Further effects included pronounced iris atrophy, anterior chamber applanation, and a retrocorneal membrane. (25, 28, 31)**		
Category 1	**Cyclohexanol**	**Irritation to the eyes of human subjects results at air concentrations of 100 ppm, and which occurs after 3 to 5 minutes exposure (13, 22)**		
Category 1	**3,4-Dichlorophenyl isocyanate**	**An irritant to the human eye, causing lacrimation, and (rarely), conjunctivitis (13, 17)**		
Category 1	**Diethylaminopropionitrile**	**Human data not located**		
Category 1	**Diethylethanolamine**	**A human eye irritant (18, 42, 43)**		
Category 1	Diethylethanolamine	A human eye irritant (18, 42, 43)		Severe response at 25% conc. in other study
Category 1	Diethylethanolamine	A human eye irritant (18, 42, 43)		Severe response at 25% conc. in other study
Category 1	**1,3-Diiminobenz (f)-isoindoline**	**Human data not located**		
Category 1	**2,5-Dimethylhexanediol**	**Human data not located**		
Category 1	**Bis-(3-aminopropyl) tetramethyl disiloxane**	**Human data not located**		
Category 1	**Domiphen bromide**	**Human data not located**		
Category 1	**Granuform**	**A human eye irritant (27, 55)**		
Category 1	**Hydroxyethyl acrylate**	**Severe eye irritant (27)**		
Category 1	**2-Hydroxyisobutyric acid ethylester**	**Human data not located**		
Category 1	**2-Hydroxyisobutyric acid**	**Human data not located**		
Category 1	HZA - Shampoo No. 7	?	?	Formulations excluded
Category 1	HZF - Baby Shampoo No. 2	?	?	Formulations excluded
Category 1	HZI - Skin Cleanser	?	?	Formulations excluded

GHS Classification	Substance	CASRN	In Vivo Data Source	Substance Source	Commercial Availability	Chemical Class	Product Class	Conc. Tested	Amount Tested[1]	Purity	MW	pH	Dermal Corrosivity	# of Animals Tested	Water Solubility	Log Kow	Color
Category 1	HZK - Bubble Bath	n.a.	CTFA	Battelle Columbus Lab.	yes	Formulation	Formulation	100%	0.1 mL	n.a.	n.a.	n.a.	n.a.	6	n.a.	n.a.	n.a.
Category 1	HZS - Shower Gel	n.a.	CTFA	Battelle Columbus Lab.	yes	Formulation	Formulation	100%	0.1 mL	n.a.	n.a.	n.a.	n.a.	6	n.a.	n.a.	n.a.
Category 1	HZX - Shampoo No. 2	n.a.	CTFA	Battelle Columbus Lab.	yes	Formulation	Shampoos, Hair	100%	0.1 mL	n.a.	n.a.	n.a.	n.a.	6	n.a.	n.a.	n.a.
Category 1	HZY - Anti-Dandruff Shampoo	n.a.	CTFA	Battelle Columbus Lab.	yes	Formulation	Shampoos, Hair	100%	0.1 mL	n.a.	n.a.	n.a.	n.a.	6	n.a.	n.a.	n.a.
Category 1	Imidazole	288-32-4	LNS	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Heterocyclic Compound	Anti-Fungal	20%	0.1 mL	n.a.	68.1	10.3	R34	3	soluble (633 g/L)	n.a.	?
Category 1	**Imidazole**	**288-32-4**	**ECETOC**	**n.a.**	**Sigma-Aldrich Corp.**	**Heterocyclic Compound**	**Anti-Fungal**	**100%**	**100 mg**	**99%**	**68.1**	**10.3**	**R34**	**3**	**soluble (633 g/L)**	**n.a.**	**?**
Category 1	**Cyclohexyl isocyanate**	**3173-53-3**	**TSCA**	**Mobay Corp.**	**Sigma-Aldrich Corp.**	**Isocyanate**	**Anesthetic, Chemical Intermediate, Cleaning Agent, Industrial Chemical, Pharmaceutical Intermediate, Solvent**	**100%**	**0.1 mL**	**Technical Grade**	**125.2**	**n.a.**	**R34**	**2**	**insoluble**	**6.11**	**?**
Category 1	**alpha-Ketoglutaric acid alpha**	**328-50-7**	**ZEBET**	**n.a.**	**Sigma-Aldrich Corp.**	**Acid (organic) [carboxylic acid]**	**Chemical Intermediate, Laboratory Chemical, Pharmaceutical,**	**n.a.**	**0.1 mL or 100 mg**	**n.a.**	**146.1**	**?**	**?**	**3**	**?**	**?**	**?**
Category 1	**Lactic Acid**	**50-21-5**	**NIHS-Ohno**	**Japanese Cosmetic Industry Assn.**	**Sigma-Aldrich Corp.**	**Alcohol, Acid (organic) [carboxylic acid]**	**Cosmetic Ingredient**	**100%**	**0.1 mL**	**n.a.**	**90.1**	**1.9**	**R34**	**3**	**soluble**	**-0.72**	**colorless**
Category 1	**Lauric acid**	**143-07-7**	**ECETOC**	**Unichema International, Inc.**	**Sigma-Aldrich Corp.**	**Acid (organic) [carboxylic acid]**	**Surfactant (anionic)**	**100%**	**52 mg**	**>92%**	**200.3**	**4.2**	**noncorrosive**	**3**	**insoluble**	**4.20**	**colorless**
Category 1	**4-Chloro-methanilic acid**	**98-36-2**	**ZEBET**	**n.a.**	**Fisher Scientific International, Inc.**	**Amine, Sulfur Compound (organic)**	**Chemical Intermediate, Laboratory Chemical**	**n.a.**	**0.1 mL or 100 mg**	**n.a.**	**207.6**	**?**	**?**	**1**	**?**	**?**	**?**
Category 1	***n*-Acetyl-methionine**	**1115-47-5**	**ZEBET**	**n.a.**	**Sigma-Aldrich Corp.**	**Amide, Amino Acid**	**Cosmetic Ingredient, Food Additive, Laboratory Chemical**	**n.a.**	**0.1 mL or 100 mg**	**n.a.**	**191.3**	**2.2**	**?**	**3**	**?**	**?**	**?**
Category 1	**2-Methylbutyric acid**	**116-53-0**	**TSCA**	**Union Carbide Corp.**	**Sigma-Aldrich Corp.**	**Acid (organic) [carboxylic acid]**	**Chemical Intermediate, Cosmetic Ingredient, Solvent**	**100%**	**0.005 mL**	**97.9%**	**102.1**	**?**	**R34**	**6**	**?**	**1.18**	**?**
Category 1	**Methylpentynol**	**77-75-8**	**ZEBET**	**n.a.**	**Sigma-Aldrich Corp.**	**Alcohol**	**Pharmaceutical, Veterinary Chemical**	**n.a.**	**0.1 mL or 100 mg**	**n.a.**	**98.1**	**?**	**?**	**1**	**?**	**?**	**?**
Category 1	**Methylthioglycolate**	**2365-48-2**	**ECETOC**	**Elf Atochem, Inc.**	**Sigma-Aldrich Corp.**	**Ester, Sulfur Compound (organic)**	**Industrial Chemical**	**100%**	**0.1 mL**	**99.7%**	**106.1**	**pKa 8.22**	**noncorrosive**	**3**	**Soluble**	**0.65**	**?**
Category 1	**1-Naphthaleneacetic acid (solid)**	**86-87-3**	**ECETOC**	**US EPA**	**Sigma-Aldrich Corp.**	**Acid (organic) [carboxylic acid], Polycyclic Compound**	**Pesticide**	**100%**	**100 mg**	**96%**	**186.2**	**3.3**	**noncorrosive**	**6**	**insoluble (420 mg/L)**	**2.24**	**?**
Category 1	***n*-Octylamine**	**111-86-4**	**TSCA**	**Hoechst Celanese Corp.**	**Sigma-Aldrich Corp.**	**Amine**	**Chemical Intermediate, Laboratory Chemical**	**100%**	**0.1 mL**	**n.a.**	**129.2**	**?**	**?**	**4**	**?**	**?**	**?**
Category 1	**tetra-N-Octylammonium bromide**	**14866-33-2**	**GSK**	**n.a.**	**Sigma-Aldrich Corp.**	**Onium Compound**	**Industrial Chemical, Laboratory Chemical**	**100%**	**0.1 mL or 100 mg**	**n.a.**	**546.8**	**?**	**?**	**1**	**?**	**?**	**?**
Category 1	**Organofunctional Silane 45-49**	**82985-35-1**	**TSCA**	**Union Carbide Corp.**	**Sigma-Aldrich Corp.**	**Amine, Organosilicon Compound**	**Polish**	**100%**	**0.005 mL**	**n.a.**	**341.6**	**?**	**?**	**6**	**?**	**?**	**?**
Category 1	**4-(1,1,3,3-Tetramethylbutyl)phenol**	**140-66-9**	**TSCA**	**Rohm and Haas Co.**	**Sigma-Aldrich Corp.**	**Phenol**	**Chemical Intermediate**	**100%**	**100 mg**	**n.a.**	**206.3**	**?**	**?**	**6**	**?**	**?**	**?**
Category 1	**Phosphorodicloridic acid, ethyl ester**	**1498-51-7**	**TSCA**	**Rhone-Poulenc, Inc.**	**Sigma-Aldrich Corp.**	**Ester, Organophosphorus Compound**	**Chemical Intermediate, Pesticide**	**100%**	**0.1 mL**	**96%**	**162.9**	**?**	**R34**	**6**	**?**	**?**	**?**
Category 1	Polyethylene glycol nonylphenyl ether (Surfonic HDL-1)	9016-45-9	TSCA	Texaco, Inc.	Houghton Chemical Corp.	Alcohol, Ether	Cleaning Agent, Industrial Chemical, Pesticide, Surfactant (nonionic)	100%	0.1 mL	n.a.	308.5	?	?	6	?	?	?
Category 1	Polyethylene glycol nonylphenyl ether (Surfonic N-102)	9016-45-9	TSCA	Texaco, Inc.	Houghton Chemical Corp.	Alcohol, Ether	Cleaning Agent, Industrial Chemical, Pesticide, Surfactant (nonionic)	100%	0.1 mL	n.a.	308.5	?	?	6	?	?	?
Category 1	**Polyethylene glycol nonylphenyl ether (Surfonic HDL-1)**	**9016-45-9**	**TSCA**	**Texaco, Inc.**	**Houghton Chemical Corp.**	**Alcohol, Ether**	**Cleaning Agent, Industrial Chemical, Pesticide, Surfactant (nonionic)**	**100%**	**0.1 mL**	**n.a.**	**308.5**	**?**	**?**	**6**	**?**	**?**	**?**
Category 1	**Potassium laurate**	**10124-65-9**	**NIHS-Ohno**	**Japanese Cosmetic Industry Assn.**	**Pfaltz & Bauer, Inc.**	**Acid (organic) [carboxylic acid], Salt (organic)**	**Cosmetic Ingredient, Pesticide**	**10%**	**0.1 mL**	**n.a.**	**238.4**	**?**	**?**	**3**	**?**	**?**	**?**
Category 1	**Promethazine hydrochloride**	**58-33-3**	**ECETOC**	**n.a.**	**Sigma-Aldrich Corp.**	**Amine, Amidine, Heterocyclic Compound, Sulfur Compound (organic)**	**Pharmaceutical**	**100%**	**100 mg**	**98%**	**320.9**	**?**	**?**	**3**	**n.a.**	**n.a.**	**white to faint yellow**

GHS Classification	Substance	Physical Form Tested	MMAS score	Corneal score	Irital score	Conjunctival score	NICEATM Category 1 SubClass.[2]	Tested in BCOP	Tested in HET-CAM	Tested in ICE	Tested in IRE	EPA Classification	EU Classification	FHSA Classification
Category 1	HZK - Bubble Bath	liquid	39.7	n=5/6, CO=1 D21	-	n=3/6, CR=2 D21	1	-	X	-	-	Category I	R41	irritant
Category 1	HZS - Shower Gel	gel	39.0	n=2/6, CO>1 D21	-	n=2/6, CR=2 D21	1	-	X	-	-	Category I	R41	irritant
Category 1	HZX - Shampoo No. 2	liquid	39.3	n=2/6, CO=1 D21	-	-	1	-	X	-	-	Category I	R36	irritant
Category 1	HZY - Anti-Dandruff Shampoo	liquid	37.2	n=2/6, CO=1 D21	-	-	1	-	X	-	-	Category I	R41	irritant
Category 1	Imidazole	liquid	48.7	n=1/3, CO=3 D14	-	-	1	-	-	-	-	Category I	R41	SCNM
Category 1	**Imidazole**	**solid**	**59.3**	**n=2/3, CO=4**	**n=2/3, I>1.5**	**-**	**4**	**X**	**X**	**X**	**X**	**Category I**	**R41**	**SCNM**
Category 1	**Cyclohexyl isocyanate**	**liquid**	**101.0**	**n=2/2, CO=4**	**-**	**-**	**4**	**-**	**-**	**X**	**-**	**Category I**	**R41**	**SCNM**
Category 1	**alpha-Ketoglutaric acid alpha**	**solid**	**93.0**	**n=2/3, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**SCNM**	**R41**	**SCNM**
Category 1	**Lactic Acid**	**liquid**	**102.7**	**n=3/3, CO=4**	**-**	**n=3/3, CR/CC=2 D14**	**4**	**-**	**X**	**-**	**-**	**Category I**	**R41**	**SCNM**
Category 1	**Lauric acid**	**solid**	**38.0**	**n=3/3, CO>1 D21**	**-**	**n=3/3, CR=1 D21**	**1**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**SCNM**
Category 1	**4-Chloro-methanilic acid**	**solid**	**17.0**	**n=1/1, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**SCNM**	**Review Data**	**SCNM**
Category 1	***n*-Acetyl-methionine**	**solid**	**57.3**	**n=1/3, CO=4**	**-**	**-**	**4**	**-**	**X**	**-**	**-**	**SCNM**	**R41**	**SCNM**
Category 1	**2-Methylbutyric acid**	**liquid**	**38.3**	**n=2/6, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**Review Data**	**SCNM**
Category 1	**Methylpentynol**	**liquid**	**34.0**	**n=1/1, CO=4**	**-**	**-**	**4**	**-**	**X**	**-**	**-**	**Category I**	**R41**	**SCNM**
Category 1	**Methylthioglycolate**	**liquid**	**53.0**	**n=1/3, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**Category II**	**R36**	**SCNM**
Category 1	**1-Naphthaleneacetic acid (solid)**	**solid**	**46.7**	**n=1/6, CO=4**	**-**	**-**	**4**	**X**	**X**	**X**	**-**	**Category I**	**R41**	**irritant**
Category 1	***n*-Octylamine**	**liquid**	**79.5**	**n=4/4, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**SCNM**
Category 1	**tetra-N-Octylammonium bromide**	**solid**	**0.0**	**-**	**-**	**-**	**0 (likely 4)**	**-**	**-**	**-**	**X**	**Category I**	**R41**	**SCNM**
Category 1	**Organofunctional Silane 45-49**	**liquid**	**54.2**	**n=2/6, CO>0 D21**	**n=2/6, IR>0 D21**	**n=2/6, CR>0 D21**	**1**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**SCNM**
Category 1	**4-(1,1,3,3-Tetramethylbutyl)phenol**	**solid**	**90.0**	**n=6/6, CO=3**	**n=6/6, IR=2**	**-**	**2**	**-**	**-**	**-**	**-**	**SCNM**	**R41**	**SCNM**
Category 1	**Phosphorodicloridic acid, ethyl ester**	**liquid**	**100.0**	**n=6/6, CO=4**	**-**	**n=6/6, CR=3, CC=4 D21**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**irritant**
Category 1	Polyethylene glycol nonylphenyl ether (Surfonic HDL-1)	liquid	35.0	-	-	-	0	-	-	-	-	SCNM	Review Data	irritant
Category 1	Polyethylene glycol nonylphenyl ether (Surfonic N-102)	liquid	38.3	n=2/6, CO=4	-	-	4	-	-	-	-	Category I	R41	irritant
Category 1	**Polyethylene glycol nonylphenyl ether (Surfonic HDL-1)**	**liquid**	**52.3**	**n=5/6, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**irritant**
Category 1	**Potassium laurate**	**liquid**	**33.7**	**n=1/3, CO=4 D14**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**SCNM**
Category 1	**Promethazine hydrochloride**	**solid**	**71.7**	**n=3/3, CO=3**	**n=3/3, IR=2**	**-**	**3**	**X**	**X**	**X**	**X**	**Category I**	**R41**	**SCNM**

GHS Classification	Substance	Human Exposure Summary	Animal Exposure Summary for Category 1(H) Substances	Notes
Category 1	HZK - Bubble Bath	?	?	Formulations excluded
Category 1	HZS - Shower Gel	?	?	Formulations excluded
Category 1	HZX - Shampoo No. 2	?	?	Formulations excluded
Category 1	HZY - Anti-Dandruff Shampoo	?	?	Formulations excluded
Category 1	Imidazole	Human data not located		Tested as a solid in other study
Category 1	**Imidazole**	**Human data not located**		
Category 1	**Cyclohexyl isocyanate**	**Human data not located**		
Category 1	**alpha-Ketoglutaric acid alpha**	**Human data not located**		
Category 1	**Lactic Acid**	**Effect on the eye is similar to that of other acids of moderate strength, causing initial epithelial coagulation on the cornea and conjunctiva; more concentrated solutions can cause severe burns of the skin or eye (10, 20)**		
Category 1	**Lauric acid**	**Human data not located**		
Category 1	**4-Chloro-methanilic acid**	**Human data not located**		
Category 1	***n*-Acetyl-methionine**	**Human data not located**		
Category 1	**2-Methylbutyric acid**	**Human data not located**		
Category 1	**Methylpentynol**	**Human data not located**		
Category 1	**Methylthioglycolate**	**Human data not located**		
Category 1	**1-Naphthaleneacetic acid (solid)**	**Has been reported to cause severe irritation to the human eye (17)**		
Category 1	***n*-Octylamine**	**Human data not located**		
Category 1	**tetra-N-Octylammonium bromide**	**Human data not located**		
Category 1	**Organofunctional Silane 45-49**	**Human data not located**		
Category 1	**4-(1,1,3,3-Tetramethylbutyl)phenol**	**A human eye irritant (23)**		
Category 1	**Phosphorodicloridic acid, ethyl ester**	**Vapor causes eye irritation; liquid causes sever burns to eye (27)**		
Category 1	Polyethylene glycol nonylphenyl ether (Surfonic HDL-1)	?	?	Used study demonstrating most consistent animal responses
Category 1	Polyethylene glycol nonylphenyl ether (Surfonic N-102)	Human data not located		Used study demonstrating most consistent animal responses
Category 1	**Polyethylene glycol nonylphenyl ether (Surfonic HDL-1)**	**Human data not located**		
Category 1	**Potassium laurate**	**Human data not located**		
Category 1	**Promethazine hydrochloride**	**Severe eye irritant (17)**		

GHS Classification	Substance	CASRN	In Vivo Data Source	Substance Source	Commercial Availability	Chemical Class	Product Class	Conc. Tested	Amount Tested[1]	Purity	MW	pH	Dermal Corrosivity	# of Animals Tested	Water Solubility	Log Kow	Color
Category 1	Promethazine hydrochloride	58-33-3	LNS	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Amine, Amidine, Heterocyclic Compound, Sulfur Compound (organic)	Pharmaceutical	20%	0.1 mL	n.a.	320.9	4.5	noncorrosive	3	n.a.	n.a.	white to faint yellow
Category 1	**Protectol PP**	**80-54-6**	**TSCA**	**BASF**	**Sigma-Aldrich Corp.**	**Aldehyde**	**Food Additive, Perfume**	**100%**	**0.1 mL**	**84.8%**	**204.3**	**n.a.**	**noncorrosive**	**3**	**n.a.**	**?**	**white powder**
Category 1	**Pyridine**	**110-86-1**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Heterocyclic Compound**	**Pesticide Intermediate, Pharmaceutical Intermediate, Solvent**	**100%**	**0.1 mL**	**99.9+%**	**79.1**	**9.9**	**noncorrosive**	**3**	**soluble**	**0.65**	**?**
Category 1	Quinacrine	69-05-6	LNS	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Amine, Heterocyclic Compound, Polycyclic Compound	Pharmaceutical	20%	0.1 mL	n.a.	472.9	3.8	noncorrosive	3	soluble (1 g/36 mL)	n.a.	?
Category 1	**Quinacrine**	**69-05-6**	**ECETOC**	**n.a.**	**Sigma-Aldrich Corp.**	**Amine, Heterocyclic Compound, Polycyclic Compound**	**Pharmaceutical**	**100%**	**100 mg**	**90%**	**472.9**	**?**	**noncorrosive**	**3**	**soluble (1 g/36 mL)**	**n.a.**	**?**
Category 1	**beta-Resorcylic acid**	**89-86-1**	**ZEBET**	**n.a.**	**Sigma-Aldrich Corp.**	**Acid (organic) [carboxylic acid], Phenol**	**Chemical Intermediate, Dye**	**n.a.**	**0.1 mL or 100 mg**	**n.a.**	**154.1**	**?**	**?**	**1**	**?**	**?**	**?**
Category 1	**Sodium hydrogen sulfate**	**7681-38-1**	**ZEBET**	**n.a.**	**Sigma-Aldrich Corp.**	**Salt (inorganic)**	**Cleaning Agent, Laboratory Chemical, Pesticide**	**n.a.**	**0.1 mL or 100 mg**	**n.a.**	**120.1**	**?**	**?**	**1**	**?**	**?**	**?**
Category 1	**Sodium hydroxide**	**1310-73-2**	**ECETOC**	**Fisher Scientific International, Inc.**	**Sigma-Aldrich Corp.**	**Alkali**	**Caustic Agent, Chemical Intermediate, Industrial Chemical, Pharmaceutical Intermediate, Veterinary Chemical**	**10%**	**0.1 mL**	**Reagent Grade**	**40.0**	**12.7**	**R35 (5%)**	**1**	**soluble (1 g/0.9 mL)**	**"virtually 0"**	**?**
Category 1	**Sodium oxalate**	**62-76-0**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Acid (organic) [carboxylic acid]**	**Industrial Chemical, Laboratory Chemical**	**100%**	**100 mg**	**>99%**	**134.0**	**9.4**	**corrosive**	**3**	**soluble (37 g/L)**	**n.a.**	**?**
Category 1	**Sodium perborate tetrahydrate**	**10486-00-7**	**ECETOC**	**Dupont Corp.**	**Sigma-Aldrich Corp.**	**Boron Compound, Salt (inorganic)**	**Cleaning Agent**	**100%**	**60 mg**	**98.6%**	**153.9**	**10.0**	**noncorrosive**	**6**	**n.a.**	**n.a.**	**?**
Category 1	**Di(2-ethylhexyl) sodium sulfosuccinate**	**98-09-9**	**NIHS-Ohno**	**Japanese Cosmetic Industry Assn.**	**Sigma-Aldrich Corp.**	**Ester, Salt (organic), Sulfur Compound (organic)**	**Adjuvant, Cleaner, Solubilizer, Wetting Agent**	**10%**	**0.1 mL**	**n.a.**	**444.6**	**6.5**	**noncorrosive**	**3**	**soluble (15 g/L)**	**n.a.**	**?**
Category 1	Dibenzoyl-L-tartaric acid	2743-38-6	LNS	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Acid (organic) [carboxylic acid], Ester	Chemical Intermediate	20%	0.1 mL	n.a.	358.3	2.4	noncorrosive	3	slightly soluble	n.a.	?
Category 1	**Dibenzoyl-L-tartaric acid**	**2743-38-6**	**ECETOC**	**n.a.**	**Sigma-Aldrich Corp.**	**Acid (organic) [carboxylic acid], Ester**	**Chemical Intermediate**	**100%**	**100 mg**	**98%**	**358.3**	**n.a.**	**noncorrosive**	**3**	**slightly soluble**	**n.a.**	**?**
Category 1	**Tetraethylene glycol diacrylate**	**17831-71-9**	**TSCA**	**Rhone-Poulenc, Inc.**	**Sigma-Aldrich Corp.**	**Ether, Nitro Compound**	**Chemical Intermediate, Industrial Chemical**	**100%**	**0.1 mL**	**n.a.**	**302.3**	**?**	**?**	**6**	**?**	**?**	**?**
Category 1	**Tetrahydrofuran**	**109-99-9**	**TSCA**	**International Specialty Products Co.**	**Sigma-Aldrich Corp.**	**Ether, Heterocyclic Compound**	**Chemical Intermediate, Industrial Chemical, Pharmaceutical Intermediate, Solvent**	**100%**	**0.1 mL**	**n.a.**	**72.1**	**?**	**?**	**6**	**?**	**?**	**?**
Category 1	**N,N,N',N`-Tetramethylhexanediamine**	**111-18-2**	**TSCA**	**Union Carbide Corp.**	**Sigma-Aldrich Corp.**	**Amine**	**Anti-Infective, Industrial Chemical, Laboratory Chemical**	**100%**	**0.005 mL**	**n.a.**	**172.3**	**?**	**?**	**6**	**?**	**?**	**?**
Category 1	**2-Nitro-4-thiocyanoaniline**	**54029-45-7**	**GSK**	**n.a.**	**Sigma-Aldrich Corp.**	**Amine, Nitro Compound, Sulfur Compound (organic)**	**Industrial Chemical**	**100%**	**0.1 mL or 100 mg**	**n.a.**	**195.2**	**?**	**?**	**1**	**?**	**?**	**?**
Category 1	**TNO-35 (Propyl lactate)**	**616-09-1**	**TNO-Prinsen**	**n.a.**	**Cook Aromatics Ltd. (Bulk)**	**Alcohol, Ester**	**Cleaning Agent, Food Additive**	**n.a.**	**0.1 mL or 100 mg**	**n.a.**	**132.2**	**?**	**?**	**1**	**?**	**?**	**?**
Category 1	**1,2,4-Triazole, sodium salt**	**41253-21-8**	**ECETOC**	**Elf Atochem, Inc.**	**Sigma-Aldrich Corp.**	**Heterocyclic Compound, Salt (organic)**	**Anti-Fungal**	**100%**	**100 mg**	**99%**	**91.1**	**n.a.**	**noncorrosive**	**1**	**soluble**	**n.a.**	**brown**
Category 1	**Trichloroacetic acid**	**76-03-9**	**ECETOC**	**Fisher Scientific International, Inc.**	**Sigma-Aldrich Corp.**	**Acid (organic) [carboxylic acid]**	**Caustic Agent, Herbicide**	**30%**	**0.1 mL**	**Reagent Grade**	**163.4**	**0.7**	**R34 (0.6N); R35 (undiluted)**	**1**	**soluble (10 g/mL)**	**1.33**	**?**
Category 1	**Trichloroacetyl chloride**	**76-02-8**	**TSCA**	**Rhone-Poulenc, Inc.**	**Sigma-Aldrich Corp.**	**Acyl Halide**	**Chemical Intermediate, Industrial Chemical**	**n.a.**	**0.1 mL**	**n.a.**	**163.4**	**?**	**?**	**4**	**?**	**?**	**?**
Category 1	Triton X-100	9002-93-1	ECETOC	Union Carbide Corp.	Sigma-Aldrich Corp.	Ether	Surfactant (nonionic)	10%	0.1 mL	98%	250.4	n.a.	noncorrosive	6	soluble	n.a.	colorless
Category 1	**Triton X-100**	**9002-93-1**	**TSCA**	**Union Carbide Corp.**	**Sigma-Aldrich Corp.**	**Ether**	**Surfactant (nonionic)**	**100%**	**0.1 mL**	**n.a.**	**250.4**	**n.a.**	**noncorrosive**	**6**	**soluble**	**n.a.**	**colorless**
Category 1	Triton X-100	9002-93-1	NIHS-Ohno	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Ether	Surfactant (nonionic)	100%	0.1 mL	n.a.	250.4	6.8	noncorrosive	3	soluble	n.a.	colorless
Category 1	Triton X-100	9002-93-1	TSCA	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Ether	Surfactant (nonionic)	100%	100 mg	n.a.	250.4	9.7 (100%)	noncorrosive	6	soluble	n.a.	colorless

GHS Classification	Substance	Physical Form Tested	MMAS score	Corneal score	Irital score	Conjunctival score	NICEATM Category 1 SubClass.[2]	Tested in BCOP	Tested in HET-CAM	Tested in ICE	Tested in IRE	EPA Classification	EU Classification	FHSA Classification
Category 1	Promethazine hydrochloride	liquid	84.0	n=3/3, CO=4	-	-	4	-	-	-	-	Category I	R41	SCNM
Category 1	**Protectol PP**	**liquid**	**34.3**	**n=2/3, CO>0 D21**	**-**	**n=3/3, CR>0 D21**	**1**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**SCNM**
Category 1	**Pyridine**	**liquid**	**48.0**	**n=1/3, CO=4**	**n=1/3, IR=2 D14**	**-**	**4**	**X**	**X**	**X**	**-**	**Category I**	**R41**	**SCNM**
Category 1	Quinacrine	liquid	52.3	n=1/3, CO=4	n=3/3, IR=2 D14	-	1	-	-	-	-	Category I	R41	SCNM
Category 1	**Quinacrine**	**solid**	**82.0**	**n=3/3, CO=3**	**n=3/3, IR=2**	**-**	**3**	**X**	**X**	**X**	**-**	**Category I**	**R41**	**SCNM**
Category 1	**beta-Resorcylic acid**	**solid**	**63.0**	**n=1/1, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**SCNM**	**Review Data**	**SCNM**
Category 1	**Sodium hydrogen sulfate**	**solid**	**8.0**	**n=1/1, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**SCNM**	**Review Data**	**SCNM**
Category 1	**Sodium hydroxide**	**liquid**	**108.0**	**n=1/1, CO=4**	**n=1/1, IR=2 D21**	**n=1/1, CR/CC=3 D21**	**4**	**X**	**X**	**X**	**X**	**Category I**	**R41**	**SCNM**
Category 1	**Sodium oxalate**	**solid**	**61.3**	**n=1/3, CO=4**	**n=1/3, IR=2 D14**	**-**	**4**	**X**	**X**	**X**	**-**	**Category I**	**R41**	**SCNM**
Category 1	**Sodium perborate tetrahydrate**	**solid**	**30.5**	**n=4/6, CO>1 D21**	**-**	**-**	**1**	**X**	**X**	**X**	**-**	**Category I**	**R41**	**SCNM**
Category 1	**Di(2-ethylhexyl) sodium sulfosuccinate**	**liquid**	**57.0**	**n=1/3, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**SCNM**	**R41**	**SCNM**
Category 1	Dibenzoyl-L-tartaric acid	liquid	33.7	n=2/3, CO=4	-	-	4	-	-	X	-	SCNM	R41	SCNM
Category 1	**Dibenzoyl-L-tartaric acid**	**solid**	**36.7**	**n=3/3, CO=3**	**-**	**-**	**3**	**X**	**X**	**X**	**-**	**Category I**	**R41**	**SCNM**
Category 1	**Tetraethylene glycol diacrylate**	**liquid**	**103.3**	**n=5/6, CO=4**	**n=6/6, IR=2 D14**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**irritant**
Category 1	**Tetrahydrofuran**	**liquid**	**31.2**	**n=2/6, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**SCNM**	**Review Data**	**irritant**
Category 1	**N,N,N',N`-Tetramethylhexanediamine**	**liquid**	**96.0**	**n=6/6, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**irritant**
Category 1	**2-Nitro-4-thiocyanoaniline**	**solid**	**63.0**	**-**	**-**	**-**	**0 (likely 4)**	**-**	**-**	**-**	**X**	**Category I**	**R41**	**SCNM**
Category 1	**TNO-35 (Propyl lactate)**	**solid**	**63.0**	**n=1/1, CO>0 D21**	**n=1/1, IR>0 D21**	**n=1/1, CC>0 D21**	**1**	**-**	**-**	**X**	**-**	**Category I**	**R41**	**SCNM**
Category 1	**1,2,4-Triazole, sodium salt**	**solid**	**104.0**	**n=1/1, CO=4**	**n=1/1, IR=2**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**SCNM**
Category 1	**Trichloroacetic acid**	**liquid**	**106.0**	**n=1/1, CO=4**	**n=1/1, IR=2 D21**	**n=1/1, CR/CC=2 D21**	**4**	**X**	**X**	**X**	**X**	**Category I**	**R41**	**SCNM**
Category 1	**Trichloroacetyl chloride**	**liquid**	**91.0**	**n=4/4, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**Category I**	**R41**	**SCNM**
Category 1	Triton X-100	liquid	68.7	-	n=2/6, IR>1.5	n=1/6, CR>0	3	X	X	X	X	SCNM	R41	irritant
Category 1	**Triton X-100**	**liquid**	**65.8**	**n=2/6, CO=4**	**-**	**-**	**4**	**-**	**-**	**-**	**-**	**SCNM**	**Review Data**	**irritant**
Category 1	Triton X-100	liquid	41.3	n=1/3, CO=3 D14	-	-	1	-	-	-	-	Category III	nonirritant	irritant
Category 1	Triton X-100	solid	51.7	-	n=5/6, IR>1.5	-	2	-	-	-	-	Category III	nonirritant	SCNM

GHS Classification	Substance	Human Exposure Summary	Animal Exposure Summary for Category 1(H) Substances	Notes
Category 1	Promethazine hydrochloride	Severe eye irritant (17)		ECETOC study noted irital effects when tested at 100% as a solid
Category 1	**Protectol PP**	**Severe eye irritant (17)**		
Category 1	**Pyridine**	**Causes irritation upon contact with the eyes (6, 20)**		
Category 1	Quinacrine	Direct contact with the eye causes yellow staining of the bulbar conjunctiva and cornea; in more severe reactions striate keratopathy or wrinkling of the posterior surface of cornea develops, presumably due to corneal edema (11)		In ECETOC study, tested at 100% as a solid
Category 1	**Quinacrine**	**Direct contact with the eye causes yellow staining of the bulbar conjunctiva and cornea; in more severe reactions striate keratopathy or wrinkling of the posterior surface of cornea develops, presumably due to corneal edema (11)**		
Category 1	**beta-Resorcylic acid**	**Human data not located**		
Category 1	**Sodium hydrogen sulfate**	**Human data not located**		
Category 1	**Sodium hydroxide**	**Contact with the eyes causes disintegration and sloughing of conjunctival and corneal epithelia, corneal opacification, marked edema, and ulceration; after 7 to 13 days either gradual recovery begins, or there is progression of ulceration and corneal opacification. Opacification may be so severe that iris markings are not discernable. Complications of severe eye burns are symblepharon, with overgrowth of the cornea by a vascularized membrane, progressive or recurrent corneal ulceration, permanent corneal opacification, necrosis of the bulbar conjunctiva, blanched and necrotic corneal cul-de-sac, and blindness. Eye contact; Levels of toxic effect: (1) Irritation. (2) Conjunctivitis, corneal burns. (3) Photophobia. (4) Disintegration and sloughing of conjunctival and corneal epithelium. (5) Corneal edema, ulceration, and opacification. (6) Symblepharon. (7) Overgrowth of the cornea by a vascularized membrane. (8) Permanent corneal opacification. (11, 18)**		
Category 1	**Sodium oxalate**	**Human data not located**		
Category 1	**Sodium perborate tetrahydrate**	**Very few cases of eye irritation were observed (26)**		
Category 1	**Di(2-ethylhexyl) sodium sulfosuccinate**	**In ophthalmological formulations, concentrations of greater than 0.1% may cause conjunctival irritation; repeated use of such drugs may delay healing of corneal lesions. (7)**		
Category 1	Dibenzoyl-L-tartaric acid	Human data not located		Tested as a solid in other study
Category 1	**Dibenzoyl-L-tartaric acid**	**Human data not located**		
Category 1	**Tetraethylene glycol diacrylate**	**Human data not located**		
Category 1	**Tetrahydrofuran**	**A human eye irritant (27)**		
Category 1	**N,N,N',N`-Tetramethylhexanediamine**	**Human data not located**		
Category 1	**2-Nitro-4-thiocyanoaniline**	**Human data not located**		
Category 1	**TNO-35 (Propyl lactate)**	**Human data not located**		
Category 1	**1,2,4-Triazole, sodium salt**	**Human data not located**		
Category 1	**Trichloroacetic acid**	**Reported to be irritating and very painful to the human eye (15, 19)**		
Category 1	**Trichloroacetyl chloride**	**Reported to be irritating and very painful to the human eye (15, 19)**		
Category 1	Triton X-100	Human data not located		Decided to use Triton X-100 at different conc.; this was maximum concentration tested
Category 1	**Triton X-100**	**Human data not located**		
Category 1	Triton X-100	?	?	
Category 1	Triton X-100	Human data not located		All other concn. tested as a liquid; excluded to be consistent

GHS Classification	Substance	CASRN	In Vivo Data Source	Substance Source	Commercial Availability	Chemical Class	Product Class	Conc. Tested	Amount Tested[1]	Purity	MW	pH	Dermal Corrosivity	# of Animals Tested	Water Solubility	Log Kow	Color
Category 1(H)	Ammonia	7664-41-7	-	-	Sigma-Aldrich Corp.	Alkali	Anti-Fungal, Chemical Intermediate, Cleaning Agent, Fertilizer, Herbicide, Industrial Chemical, Refrigerant	-	-	-	17.0	-	-	-	n.a.	n.a.	?
Category 1(H)	Chloroform	67-66-3	-	n.a.	Sigma-Aldrich Corp.	Hydrocarbon (acyclic)	Anesthetic, Chemical Intermediate, Cleaning Agent, Industrial Chemical, Pharmaceutical Intermediate, Solvent	-	-	-	119.4	-	-	-	n.a.	n.a.	?
Category 1(H)	Lime	1305-78-8	-	-	Sigma-Aldrich Corp.	Salt (inorganic)	Building Material, Chemical Intermediate, Cleaning Agent, Fertilizer, Industrial Chemical	-	-	-	56.1	-	-	-	n.a.	n.a.	white to grayish
Category 1(H)	Magnesium hydroxide	12141-11-6	-	-	Sigma-Aldrich Corp.	Salt (inorganic)	Chemical Intermediate, Flame Retardant, Industrial Chemical, Pharmaceutical, Veterinary Agent	-	-	-	42.3	-	-	-	n.a.	n.a.	?
Category 1(H)	Nitric acid	7697-37-2	-	-	Sigma-Aldrich Corp.	Acid, Salt (inorganic)	Chemical Intermediate, Industrial Chemical, Laboratory Reagent, Pharmaceutical Intermediate	-	-	-	63.0	-	-	-	n.a.	n.a.	colorless to yellow
Category 1(H)	Potassium hydroxide	1310-58-3	-	-	Sigma-Aldrich Corp.	Alkali, Salt (inorganic)	Chemical Intermediate, Cleaning Agent, Fertilizer, Food Additive, Industrial Chemical, Veterinary Chemical	-	-	-	56.1	-	-	-	n.a.	n.a.	?
Category 1(H)	Silver nitrate	7761-88-8	-	-	Sigma-Aldrich Corp.	Nitrate, Salt (inorganic)	Anti-Infective, Chemical Intermediate, Dye, Industrial Chemical, Laboratory Chemical, Pharmaceutical, Pharmaceutical Intermediate	-	-	-	169.9	-	-	-	n.a.	n.a.	white to grayish-black
Category 1(H)	Sodium hydrogen difluoride	1333-83-1	-	-	Sigma-Aldrich Corp.	Salt (inorganic)	Anti-Infective, Cleaning Agent, Industrial Chemical, Preservative	-	-	-	62.0	-	-	-	n.a.	n.a.	?
Category 1(H)	Sulfuric acid	7664-93-9	-	-	Sigma-Aldrich Corp.	Acid (inorganic), Sulfur Compound (inorganic)	Battery Acid, Chemical Intermediate, Cleaning Agent, Fertilizer, Food Additive, Industrial Chemical, Laboratory Chemical	-	-	-	98.1	-	-	-	n.a.	n.a.	?
Category 1(H)	Zinc chloride	7646-85-7	-	-	Sigma-Aldrich Corp.	Salt (inorganic)	Anti-Infective, Flame Retardant, Herbicide, Industrial Chemical. Pesticide, Preservative	-	-	-	136.3	-	-	-	n.a.	n.a.	?
Category 2A	Methyl acetate	79-20-9	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Ester	Chemical Intermediate, Food Additive, Herbicide, Laboratory Chemical,Solvent	100%	0.1 mL	98%	74.1	n.a.	?	4	243 g/L	0.18	colorless

GHS Classification	Substance	Physical Form Tested	MMAS score	Corneal score	Irital score	Conjunctival score	NICEATM Category 1 SubClass.[2]	Tested in BCOP	Tested in HET-CAM	Tested in ICE	Tested in IRE	EPA Classification	EU Classification	FHSA Classification
Category 1(H)	Ammonia	Liquid	-	-	-	-	-	-	-	-	-	-	-	-
Category 1(H)	Chloroform	liquid	-	-	-	-	-	-	-	-	-	-	-	-
Category 1(H)	Lime	solid	-	-	-	-	-	-	-	-	-	-	-	-
Category 1(H)	Magnesium hydroxide	solid	-	-	-	-	-	-	-	-	-	-	-	-
Category 1(H)	Nitric acid	liquid	-	-	-	-	-	-	-	-	-	-	-	-
Category 1(H)	Potassium hydroxide	solid	-	-	-	-	-	-	-	-	-	-	-	-
Category 1(H)	Silver nitrate	liquid	-	-	-	-	-	-	-	-	-	-	-	-
Category 1(H)	Sodium hydrogen difluoride	liquid	-	-	-	-	-	-	-	-	-	-	-	-
Category 1(H)	Sulfuric acid	liquid	-	-	-	-	-	-	-	-	-	-	-	-
Category 1(H)	Zinc chloride	solid	-	-	-	-	-	-	-	-	-	-	-	-
Category 2A	Methyl acetate	liquid	39.5	-	-	-	-	X	X	X	X	Category II	R36	SCNM

GHS Classification	Substance	Human Exposure Summary	Animal Exposure Summary for Category 1(H) Substances	Notes
Category 1(H)	Ammonia	Ammonia vapors cause irritation of eyes, with high concentrations causing conjunctivitis. Corneal edema and semi-dilated, fixed pupils are typical. Ammonia has a greater tendency than other alkalies to penetrate and damage the iris, and to cause cataract. In severe burns, iritis may be accompanied by hypopyon or hemorrhages, extensive loss of pigment and severe glaucoma. Exposure to high gas concentrations of ammonia may cause temporary blindness and severe eye damage. Direct contact of the eyes with liquid anhydrous ammonia will produce serious eye burns. 2 cases of ocular injuries with a rise in intraocular pressure and cataract formation after ammonia of unknown concentration had been squirted into the victims' eyes during robberies were reported. In both cases, the more severely affected eyes showed marked injection and edema of the conjunctiva; diffuse corneal damage; semi-dilated, oval, and fixed pupils; and a marked increase of the intraocular pressure, which persisted and was controlled only with drugs. Glaucoma was observed to be associated with an open angle	Corneal opacity was observed in rabbits following continuous exposure to ammonia vapor (470 mg/M3). Swine exposed to ammonia for 2 to 6 weeks at 100 PPM in air developed conjunctival irritation. Continuous exposure of rabbits to 470 mg/cu m for several weeks produced opacities over ¼ to ½ of the cornea. Even fairly low airborne concentrations of ammonia produce rapid eye and nose irritation. Contact with concentrated ammonia solutions, such as some industrial cleaners, can cause serious corrosive injury (6, 11, 56).	
Category 1(H)	Chloroform	Splash of liquid chloroform in the eyes causes immediate burning pain, tearing and reddening of the conjunctiva. The corneal corneal epithelium corneal epithelium is usually injured and partially lost. Exposure to liquid or gaseous chloroform causes keratitis, corneal opacities, and ulceration (11, 37, 38, 39, 40, 41)	Liquid chloroform produced slight injury to the eyes which took over a week to heal. (62)	
Category 1(H)	Lime	The major complaints of workers exposed to lime consist of eye and skin irritation. Calcium oxide dust irritates the eyes primarily because of its alkalinity. Exposure to lime has been reported to cause conjunctival necrosis, symblepharon, keratitis, corneal necrosis, corneal opacities, corneal scarring, corneal ulceration, corneal vascularization and iritis (1,5,44)	Animal Data Not Located	
Category 1(H)	Magnesium hydroxide	Human ocular exposure to magnesium hydroxide produces combined thermal and alkali injury. Reported effects of exposure to magnesium hydroxide are conjunctival necrosis, symblepharon, keratitis, corneal necrosis, corneal opacities, corneal scarring, corneal ulceration, corneal vascularization and iritis (44, 45)	Milk of magnesia applied to rabbit eyes twice a day for three or four days caused damage to the corneal epithelium, demonstrable by staining with fluorescein. After the applications were discontinued, the corneas returned to normal in two or three days. (10)	
Category 1(H)	Nitric acid	Contact of nitric acid with the eye causes immediate opacification of the corneal and conjunctival epithelium. It also causes symblepharon, shrinkage of the globe, keratitis, corneal ulceration and corneal and conjunctival necrosis (11, 17, 46)	Animal Data Not Located	
Category 1(H)	Potassium hydroxide	Eye contact with concentrated alkalis such as potassium hydroxide causes conjunctival edema and corneal destruction. Potassium hydroxide (caustic potash) is one of the strongest alkalies. It is extremely corrosive, and many reports have been made of devastating damage of the eye from contact with either the solid or solutions of potassium hydroxide. The type of injury is essentially the same as that produced by sodium hydroxide and other strong alkalies, and includes iritis, conjunctival necrosis, symblepharon, keratitis, corneal necrosis, opacities, scarring, ulceration and vascularization (1, 11, 27, 45, 47)	Animal Data Not Located	
Category 1(H)	Silver nitrate	Solid silver nitrate, known as lunar caustic, can be very injurious to the eye. Particles of solid silver nitrate in the conjunctival sac have been known to cause severe inflammation with deep injury to surrounding tissues, scarring, and symblepharon. In a most unusual case of severe injury from solid nitrate the cornea became dark brown, and the lens became cataractous. Concentration solutions of silver nitrate from 5%-50% applied by mistake or accidentally splashed in the eye have caused severe injury, with permanent corneal opacification in some cases. Solutions of high concentration cause rapid appearance of edema of the conjunctiva and lids, with bloody purulent discharge from the conjunctival sac. Opacification of the cornea may result and may be permanent (5, 11, 13, 48, 49, 50)	Treatment of rat eyes with a single 3-drops 0.66% silver nitrate soln caused deposition of silver in the cornea, conjunctiva, subconjunctiva, Bowman's layer, reticular fibers of the corneal stroma, Descemete's membrane and the posterior corneal epithelium. Morphologic evolution of the early events of corneal vascularization in the rat cornea induced by silver nitrate cautery was followed by light and electron microscopy. An initial acute inflammatory response occurred within the first 6 hours after cautery as evidenced by vascular dilation, diapedesis of leukocytes, and an increased vascular permeability, as manifested by distended lymphatics and the presence of extravascular fibrin. At 33 hours after cautery, the first new vessels were observed as sprouts from the capillary arcade and postcapillary venules. Adult male Sprague-Dawley rats were anesthetized with halothane gas, and the centers of their right corneas treated with a silver nitrate applicator stick (75% silver nitrate, 25% potassium nitrate) to produce a discrete	
Category 1(H)	Sodium hydrogen difluoride	Exposure to concentrated sodium hydrogen difluoride has caused corneal necrosis, opacification, scarring, ulceration, vascularization (11, 23)	This substance causes the formation of hydrofluoric acid when exposed to mucous membranes. Ocular toxicity is caused by hydrofluoric acid. In inhalation studies in rabbits and guinea pigs, a concentration of 50 MG/CU M, hydrogen fluoride induced discharge from the eyes. Experimental splash burns of hydrofluoric acid into the eyes of rabbits have shown a 20% solution to cause immediate damage with total corneal opacification with conjunctival ischemia, and with corneal stromal edema within an hour, followed by necrosis of anterior ocular structures. An 8% solution produced ischemia and corneal stromal edema persisting for 40-65 days, accompanied by corneal vascularization. Even a 2% a solution caused mild persistent stromal edema and vascularization,. (6, 11)	
Category 1(H)	Sulfuric acid	At aerosol concentrations of 1.1 to 2.1 mg/cu m, 40% of human subjects noticed irritation of the eyes. At 2.4 to 6.0 mg/cu m, all subjects experienced eye irritation. Contact of concentrated sulfuric acid with the eye may cause total loss of vision in addition to corneal necrosis, opacification, scarring, ulceration and vascularization. (1, 44, 51, 52)	Animals in the vicinity of potato fields sprayed with sulfuric acid during spraying, or gaining access to such fields soon after spraying, may develop eye burns from the spray. (63)	
Category 1(H)	Zinc chloride	An unstated concentration of zinc chloride solution splashed in 1 eye of a workman at first only caused redness and discomfort, but within 6 days grayish corneal opacities had developed, with irregularity of the overlying epithelium. A patient who had an eye burned with one drop of 50% zinc chloride solution there was immediate severe pain, erosion of the corneal epithelium, corneal vascularization, severe iritis and iridial hemorrhage (11, 27, 54)	10% zinc chloride was classified as a mild or non-irritant when test in the rabbit eye. A 50% solution of zinc chloride applied repeatedly during 1 day to 1 eye of an albino rabbit caused immediate corneal opacity. 6 days after exposure, the eye had become very hard, with extensive hemorrhage in the anterior segment, accompanied by infiltration with inflammatory cells, loss of corneal endothelium and clouding of the anterior portion of the lens. (11, 61)	
Category 2A	Methyl acetate	Cases of slight poisoning under industrial conditions were manifested by eye burns and lacrimation. One case of blindness has been reported. (1, 13, 18)		

GHS Classification	Substance	CASRN	In Vivo Data Source	Substance Source	Commercial Availability	Chemical Class	Product Class	Conc. Tested	Amount Tested[1]	Purity	MW	pH	Dermal Corrosivity	# of Animals Tested	Water Solubility	Log Kow	Color
Category 2A	**Acetone**	**67-64-1**	**ECETOC**	**Fisher Scientific International, Inc.**	**Sigma-Aldrich Corp.**	**Ketone**	**Chemical Intermediate, Cleaning Agent, Industrial Chemical, Pharmaceutical Intermediate, Preservative, Solvent**	**100%**	**0.1 mL**	**99%**	**58.1**	**5.3**	**noncorrosive**	**4**	**soluble**	**-0.24**	**?**
Category 2A	**Benzotrichloride**	**98-07-7**	**TSCA**	**Velsicol Chemical Corp.**	**Sigma-Aldrich Corp.**	**Hydrocarbon (cyclic)**	**Chemical Intermediate**	**100%**	**0.1 mL**	**n.a.**	**195.5**	**?**	**?**	**6**	**?**	**?**	**?**
Category 2A	iso-Butanol	78-83-1	ECETOC	n.a.	Sigma-Aldrich Corp.	Alcohol	Chemical Intermediate, Food Additive, Pesticide, Pharmaceutical Intermediate, Solvent	100%	0.1 mL	99.9%	74.1	7.0	noncorrosive	4	soluble (95 g/L)	0.76	?
Category 2A	*n*-Butanol	71-36-3	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Alcohol	Chemical Intermediate, Cosmetic Ingredient, Food Additive, Industrial Chemcial, Pesticide Intermediate, Pharmaceutical Intermediate, Solvent, Veterinary Chemical	100%	0.1 mL	99.8%	74.1	n.a.	noncorrosive	4	insoluble	0.88	colorless
Category 2A	**gamma-Butyrolactone**	**96-48-0**	**ECETOC**	**Shell Oil Co. of California**	**Sigma-Aldrich Corp.**	**Heterocyclic Compound, Lactone**	**Solvent**	**100%**	**0.1 mL**	**>99%**	**86.1**	**4.5**	**noncorrosive**	**6**	**miscible**	**-0.57**	**colorless**
Category 2A	**4-Carboxybenzaldehyde**	**619-66-9**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Aldehyde, Acid (organic) [carboxylic acid]**	**Industrial Chemical**	**100%**	**0.1 mL**	**>95%**	**150.1**	**3.1**	**noncorrosive**	**3**	**Very soluble**	**n.a.**	**?**
Category 2A	**Cetylpyridinium bromide**	**140-72-7**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Onium Compound, Heterocyclic Compound**	**Anti-Infective; Laboratory Chemical; Surfactant (cationic)**	**1%**	**0.1 mL**	**99%**	**384.4**	**6.4**	**noncorrosive**	**6**	**soluble (5 g/L)**	**1.83 (100%)**	**faintly beige**
Category 2A	**Deoxycholic acid sodium salt**	**302-95-4**	**LNS**	**n.a.**	**Sigma-Aldrich Corp.**	**Alcohol, Acid (organic) [carboxylic acid], Polycyclic Compound, Salt (organic)**	**Anti-Infective, Laboratory Chemical, Solvent**	**10%**	**0.1 mL**	**n.a.**	**414.6**	**?**	**?**	**3**	**?**	**?**	**?**
Category 2A	**Dibenzyl phosphate**	**1623-08-1**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Ester, Organophosphorus Compound**	**Pesticide**	**100%**	**100 mg**	**99%**	**278.2**	**2.4**	**noncorrosive**	**3**	**n.a.**	**n.a.**	**?**
Category 2A	**2,6-Dichlorobenzoyl chloride**	**4659-45-4**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Acyl Halide**	**Anti-Fungal, Anti-Infective**	**100%**	**0.1 mL**	**99%**	**209.5**	**2.5**	**R34**	**6**	**insoluble**	**2.57**	**slight yellow**
Category 2A	**2-Ethyl-1-hexanol**	**104-76-7**	**ECETOC**	**Fisher Scientific International, Inc.**	**Sigma-Aldrich Corp.**	**Alcohol**	**Solvent**	**100%**	**0.1 mL**	**99%**	**130.2**	**4.8**	**noncorrosive**	**4**	**slightly soluble**	**2.82**	**?**
Category 2A	***n*-Hexanol**	**111-27-3**	**ECETOC**	**Kodak Co.**	**Sigma-Aldrich Corp.**	**Alcohol**	**Solvent**	**100%**	**0.1 mL**	**98%**	**102.2**	**5.5**	**noncorrosive**	**4**	**soluble (5.8 g/L)**	**2.03**	**?**
Category 2A	**Methyl ethyl ketone**	**78-93-3**	**ECETOC**	**Fisher Scientific International, Inc.**	**Sigma-Aldrich Corp.**	**Ketone**	**Solvent**	**100%**	**0.1 mL**	**99%**	**72.1**	**5.5**	**noncorrosive**	**4**	**soluble (353 g/L)**	**0.29**	**colorless**
Category 2A	**Methyl cyanoacetate**	**105-34-0**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Ester, Nitrile**	**Chemical Intermediate**	**100%**	**0.1 mL**	**99%**	**99.1**	**5.7**	**noncorrosive**	**3**	**soluble (54 g/L)**	**n.a.**	**light yellow**
Category 2A	***n*-Octanol**	**111-87-5**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Alcohol**	**Solvent**	**100%**	**0.1 mL**	**>99%**	**130.2**	**6.1**	**noncorrosive**	**3**	**insoluble (540 mg/L)**	**3.00**	**?**
Category 2A	**Triton X-100**	**9002-93-1**	**ECETOC**	**n.a.**	**Sigma-Aldrich Corp.**	**Ether**	**Surfactant (nonionic)**	**5%**	**0.1 mL**	**98%**	**250.4**	**n.a.**	**noncorrosive**	**6**	**soluble**	**n.a.**	**colorless**
Category 2B	Methyl acetate	79-20-9	ZEBET	n.a.	Sigma-Aldrich Corp.	Ester	Chemical Intermediate, Food Additive, Herbicide, Laboratory Chemical,Solvent	n.a.	0.1 mL	n.a.	74.1	7.0	?	3	243 g/L	0.18	colorless
Category 2B	**Ethyl-2-methyl acetoacetate**	**609-14-3**	**ECETOC**	**Fluka, Inc.**	**Sigma-Aldrich Corp.**	**Ester, Ketone**	**Chemical Intermediate**	**100%**	**0.1 mL**	**97%**	**144.2**	**7.5**	**noncorrosive**	**3**	**Slightly soluble**	**n.a.**	**?**
Category 2B	Acetoacetic acid glycol ester	5459-04-1	ZEBET	n.a.	Hoechst Celanese Corp. (Bulk)	Ester, Ketone	Chemical Intermediate, Pesticide	n.a.	0.1 mL or 100 mg	n.a.	230.2	?	?	3	?	?	?
Category 2B	**Ammonium nitrate**	**6484-52-2**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Onium Compound, Nitrate, Salt (organic)**	**Industrial Chemical**	**100%**	**100 mg**	**#####**	**80.0**	**4.8**	**noncorrosive**	**3**	**soluble (1920 g/L)**	**n.a.**	**white, hot concentrate**
Category 2B	*n*-Butanal	123-72-8	ZEBET	n.a.	Sigma-Aldrich Corp.	Aldehyde	Chemical Intermediate, Food Additive	n.a.	0.1 mL or 100 mg	n.a.	72.1	?	?	3	?	?	?
Category 2B	**Butyl Dipropasol Solvent**	**29911-27-1**	**TSCA**	**Union Carbide Corp.**	**Sigma-Aldrich Corp.**	**Alcohol, Ether**	**Solvent**	**100%**	**0.1 mL**	**99%**	**176.3**	**?**	**?**	**6**	**?**	**?**	**?**
Category 2B	Camphen	79-92-5	ZEBET	n.a.	Sigma-Aldrich Corp.	Hydrocarbon (cyclic)	Chemical Intermediate, Cosmetic Ingredient, Food Additive, Pesticide Intermediate	n.a.	0.1 mL or 100 mg	n.a.	136.2	?	?	3	?	?	colorless
Category 2B	**3-Chloropropionitrile**	**542-76-7**	**ECETOC**	**Fluka, Inc.**	**Sigma-Aldrich Corp.**	**Nitrile**	**Chemical Intermediate, Pharmaceutical Intermediate**	**100%**	**0.1 mL**	**99.9%**	**89.5**	**n.a.**	**noncorrosive**	**3**	**soluble (45 g/100 mL)**	**0.18**	**?**
Category 2B	**Cyclopentanol**	**96-41-3**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Alcohol**	**Pharmaceutical Intermediate**	**100%**	**0.1 mL**	**99%**	**86.1**	**n.a.**	**noncorrosive**	**3**	**slightly soluble**	**0.71**	**colorless**
Category 2B	*m*-Dinitrobenzene	99-65-0	ZEBET	n.a.	Sigma-Aldrich Corp.	Nitro Compound	Chemical Intermediate	n.a.	0.1 mL or 100 mg	n.a.	168.1	?	?	3	?	?	?

GHS Classification	Substance	Physical Form Tested	MMAS score	Corneal score	Irital score	Conjunctival score	NICEATM Category 1 SubClass.[2]	Tested in BCOP	Tested in HET-CAM	Tested in ICE	Tested in IRE	EPA Classification	EU Classification	FHSA Classification
Category 2A	**Acetone**	**liquid**	**65.8**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**X**	**Category II**	**R36**	**SCNM**
Category 2A	**Benzotrichloride**	**liquid**	**11.7**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category II**	**nonirritant**	**irritant**
Category 2A	iso-Butanol	liquid	60.3	-	-	-	-	-	X	X	X	Category I	R41	SCNM
Category 2A	*n*-Butanol	liquid	60.8	-	-	-	-	-	X	X	X	Category II	R36	SCNM
Category 2A	**gamma-Butyrolactone**	**liquid**	**43.0**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**X**	**Category II**	**R36**	**irritant**
Category 2A	**4-Carboxybenzaldehyde**	**liquid**	**50.3**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**-**	**Category II**	**R36**	**SCNM**
Category 2A	**Cetylpyridinium bromide**	**liquid**	**36.0**	**-**	**-**	**-**	**-**	**-**	**X**	**-**	**X**	**SCNM**	**R41**	**SCNM**
Category 2A	**Deoxycholic acid sodium salt**	**liquid**	**38.0**	**-**	**-**	**-**	**-**	**X**	**-**	**-**	**-**	**Category II**	**R36**	**SCNM**
Category 2A	**Dibenzyl phosphate**	**solid**	**30.0**	**-**	**-**	**-**	**-**	**X**	**-**	**X**	**-**	**Category II**	**R36**	**SCNM**
Category 2A	**2,6-Dichlorobenzoyl chloride**	**liquid**	**23.8**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**-**	**Category II**	**R36**	**irritant**
Category 2A	**2-Ethyl-1-hexanol**	**liquid**	**51.3**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**-**	**Category II**	**R36**	**SCNM**
Category 2A	***n*-Hexanol**	**liquid**	**64.8**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**X**	**Category II**	**R36**	**SCNM**
Category 2A	**Methyl ethyl ketone**	**liquid**	**50.0**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**X**	**Category III**	**R36**	**SCNM**
Category 2A	**Methyl cyanoacetate**	**liquid**	**27.7**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**-**	**Category II**	**R36**	**SCNM**
Category 2A	***n*-Octanol**	**liquid**	**41.0**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**X**	**Category II**	**R36**	**SCNM**
Category 2A	**Triton X-100**	**liquid**	**33.8**	**-**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**Category I**	**R41**	**SCNM**
Category 2B	Methyl acetate	liquid	16.3	-	-	-	-	-	-	-	-	Category III	R36	Insufficient Animal Data
Category 2B	**Ethyl-2-methyl acetoacetate**	**liquid**	**18.0**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**X**	**Category III**	**nonirritant**	**SCNM**
Category 2B	Acetoacetic acid glycol ester	?	13.7	-	-	-	-	-	-	-	-	Category III	R36	SCNM
Category 2B	**Ammonium nitrate**	**solid**	**18.3**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**X**	**Category III**	**R36**	**SCNM**
Category 2B	*n*-Butanal	liquid	12.7	-	-	-	-	-	X	-	-	Category III	nonirritant	SCNM
Category 2B	**Butyl Dipropasol Solvent**	**liquid**	**24.7**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category III**	**nonirritant**	**irritant**
Category 2B	Camphen	solid	15.0	-	-	-	-	-	X	-	-	Category III	R36	SCNM
Category 2B	**3-Chloropropionitrile**	**liquid**	**13.7**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category III**	**nonirritant**	**SCNM**
Category 2B	**Cyclopentanol**	**liquid**	**21.7**	**-**	**-**	**-**	**-**	**-**	**-**	**X**	**-**	**Category II**	**R36**	**SCNM**
Category 2B	*m*-Dinitrobenzene	solid	15.7	-	-	-	-	-	-	-	-	Category III	R36	SCNM

GHS Classification	Substance	Human Exposure Summary	Animal Exposure Summary for Category 1(H) Substances	Notes
Category 2A	**Acetone**	**Acute exposures of humans to atmospheric concentrations have been reported to produce eye irritation. Exposure of15 minutes to aerosol concentrations of 1660 ppm also reportedly causes eye irritation. Direct contact with the eyes may produce irritation and corneal imjury. (14, 16, 30, 32)**		
Category 2A	**Benzotrichloride**	**Human data not located**		
Category 2A	iso-Butanol	Irritation of the skin, eyes, and throat have been reported from exposure to vapor or liquid. Irritation of the eyes and throat, formation of vacuoles in the superficial layers of the cornea, were reported among workers subjected to an undetermined, but apparently high concn of isobutyl alcohol & butyl acetate. (9, 20)+AH12		Discordant GHS classification
Category 2A	*n*-Butanol	Is reported to cause irritation of the eyes from exposure to either vapor or liquid. Circumstantial evidence points to butyl alcohol vapor as cause of a special vacuolar keratopathy in some patients; the most severely affected it has been associated with pain & tearing, characteristically most marked on first opening eyes in morning. It can cause transient mild edema of conjunctiva of the eye. Vapor: Irritating to eyes. Considered a strong irritant of the eyes. (9, 11, 13, 27)		Used results when tested at lower concentration
Category 2A	**gamma-Butyrolactone**	**Human data not located**		
Category 2A	**4-Carboxybenzaldehyde**	**Human data not located**		
Category 2A	**Cetylpyridinium bromide**	**Human data not located**		
Category 2A	**Deoxycholic acid sodium salt**	**Human data not located**		
Category 2A	**Dibenzyl phosphate**	**Human data not located**		
Category 2A	**2,6-Dichlorobenzoyl chloride**	**Human data not located**		
Category 2A	**2-Ethyl-1-hexanol**	**Irritation of eyes from vapor or liquid (8, 9)**		
Category 2A	***n*-Hexanol**	**Reported to cause eye burns (27)**		
Category 2A	**Methyl ethyl ketone**	**High atmospheric concentrations are irritating to the eyes. May produce painful irritation and corneal injury if splashed in the eyes. Workers exposed to 33,000 and100,000 ppm in air reported intolerable irritation of the eyes. Implicated as the cause of retrobulbar neuritis in one patient.** **A workman splashed his eye accidentally with methyl ethyl ketone, but the next day had only slight conjunctival hyperemia and no residual corneal injury. (2, 5, 11, 20)**		
Category 2A	**Methyl cyanoacetate**	**Human data not located**		
Category 2A	***n*-Octanol**	**Has caused injury of the corneal epithelium, with recovery in 48 hours (11)**		
Category 2A	**Triton X-100**	**Human data not located**		
Category 2B	Methyl acetate	Cases of slight poisoning under industrial conditions were manifested by eye burns and lacrimation. One case of blindness has been reported. (1, 13, 18)		Conc. tested unknown
Category 2B	**Ethyl-2-methyl acetoacetate**	**Human data not located**		
Category 2B	Acetoacetic acid glycol ester	?	?	
Category 2B	**Ammonium nitrate**	**Human data not located**		
Category 2B	*n*-Butanal	?	?	Conc. tested unknown
Category 2B	**Butyl Dipropasol Solvent**	**Human data not located**		
Category 2B	Camphen	?	?	
Category 2B	**3-Chloropropionitrile**	**Human data not located**		
Category 2B	**Cyclopentanol**	**Human data not located**		
Category 2B	*m*-Dinitrobenzene	?	?	

GHS Classification	Substance	CASRN	In Vivo Data Source	Substance Source	Commercial Availability	Chemical Class	Product Class	Conc. Tested	Amount Tested[1]	Purity	MW	pH	Dermal Corrosivity	# of Animals Tested	Water Solubility	Log Kow	Color
Category 2B	**3,3-Dithiodipropionic acid**	**1119-62-6**	**ECETOC**	**Fluka, Inc.**	**Sigma-Aldrich Corp.**	**Acid (organic) [carboxylic acid], Organosilicon Compound**	**Chemical Intermediate, Laboratory Chemical**	**100%**	**100 mg**	**99%**	**210.3**	**pKa 3.94**	**R34**	**3**	**Very soluble**	**1.38**	**?**
Category 2B	**Hexyl cinnamic aldehyde**	**101-86-0**	**TSCA**	**Confidential**	**International Flavors and Frangrances, Inc. (Bulk)**	**Aldehyde**	**Cosmetic Ingredient, Food Additive, Perfume**	**12.5% in Alcohol**	**0.1 mL**	**n.a.**	**216.3**	**?**	**?**	**3**	**?**	**?**	**?**
Category 2B	HZD Shampoo No. 5	n.a.	CTFA	Battelle Columbus Lab.	yes	Formulation	Shampoos, Hair	100%	0.1 mL	n.a.	n.a.	n.a.	n.a.	3	n.a.	n.a.	n.a.
Category 2B	Isopropyl acetoacetate	542-08-5	ZEBET	n.a.	Sigma-Aldrich Corp.	Ester, Ketone	Chemical Intermediate	n.a.	0.1 mL or 100 mg	n.a.	144.2	?	?	3	?	?	?
Category 2B	**N-Laurylsarcosine sodium salt**	**137-16-6**	**LNS**	**n.a.**	**Sigma-Aldrich Corp.**	**Amide, Amine, Salt (organic)**	**Cleaning Agent, Detergent, Laboratory Chemical, Surfactant (anionic)**	**10%**	**0.1 mL**	**n.a.**	**293.4**	**?**	**?**	**3**	**?**	**?**	**?**
Category 2B	**Maneb (solid)**	**12427-38-2**	**ECETOC**	**US EPA**	**Sigma-Aldrich Corp.**	**Amine, Salt (organic), Urea**	**Pesticide**	**100%**	**100 mg**	**90% (approx)**	**265.3**	**8.4**	**noncorrosive**	**6**	**Moderately soluble**	**n.a.**	**?**
Category 2B	**2-Methyl-1-pentanol**	**105-30-6**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Alcohol**	**Solvent**	**100%**	**0.1 mL**	**99%**	**102.2**	**n.a.**	**noncorrosive**	**3**	**soluble (6 g/L)**	**1.75**	**?**
Category 2B	p-Nitrobenzoic acid	62-23-7	ZEBET	n.a.	Sigma-Aldrich Corp.	Acid (organic) [carboxylic acid], Nitro Compound	Chemical Intermediate, Pharmaceutical Intermediate	n.a.	0.1 mL or 100 mg	n.a.	167.1	?	?	3	?	?	?
Category 2B	**Propasol Solvent P**	**1569-01-3**	**TSCA**	**Union Carbide Corp.**	**Sigma-Aldrich Corp.**	**Alcohol**	**Solvent**	**100%**	**0.1 mL**	**n.a.**	**118.2**	**?**	**?**	**6**	**?**	**?**	**?**
Category 2B	**6-Methyl purine**	**2004-03-7**	**TSCA**	**Monsanto Co.**	**Sigma-Aldrich Corp.**	**Heterocyclic Compound**	**Laboratory Chemical, Pharmaceutical Intermediate**	**100%**	**0.1 mL**	**n.a.**	**134.1**	**-**	**-**	**6**	**?**	**?**	**?**
Category 2B	**2,6-Dichloro-5-fluoro-beta-oxo-3-pyridinepropanoate**	**96568-04-6**	**GSK**	**n.a.**	**Sigma-Aldrich Corp.**	**Ester, Heterocyclic Compound, Ketone**	**Industrial Chemical, Pharmaceutical Intermediate**	**100%**	**0.1 mL or 100 mg**	**n.a.**	**280.1**	**?**	**?**	**3**	**?**	**?**	**white**
Category 2B	Sodium monochloroacetate	3926-62-3	ZEBET	n.a.	Sigma-Aldrich Corp.	Acid (organic) [carboxylic acid], Salt (organic)	Chemical Intermediate, Herbicide, Pharmaceutical Intermediate	n.a.	0.1 mL or 100 mg	n.a.	116.5	?	?	3	?	?	?
Category 2B	**Triton X-100**	**9002-93-1**	**ECETOC**	**n.a.**	**Sigma-Aldrich Corp.**	**Ether**	**Surfactant (nonionic)**	**5%**	**0.1 mL**	**98%**	**250.4**	**n.a.**	**noncorrosive**	**6**	**soluble**	**n.a.**	**colorless**
nonirritant	Ethyl trimethyl acetate	3938-95-2	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Ester	Industrial Chemical	100%	0.1 mL	99%	130.2	?	?	6	?	?	?
nonirritant	**iso-Octyl acrylate**	**29590-42-9**	**ECETOC**	**Elf Atochem, Inc.**	**Sigma-Aldrich Corp.**	**Ester**	**Building Material**	**100%**	**0.1 mL**	**>99%**	**184.3**	**n.a.**	**noncorrosive**	**3**	**n.a.**	**n.a.**	**?**
nonirritant	Iso-myristyl alcohol	5333-48-2	ECETOC	Elf Atochem, Inc.	Elf Atochem, Inc. (Bulk)	Alcohol	Industrial Chemical, Solvent	100%	0.1 mL	92.6%	n.a.	?	?	3	?	?	?
nonirritant	**tetra-Aminopyrimidine sulfate**	**5392-28-9**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Amine, Heterocyclic Compound, Salt (organic)**	**Chemical Intermediate**	**100%**	**100 mg**	**97%**	**238.2**	**n.a.**	**noncorrosive**	**3**	**slightly soluble**	**n.a.**	**?**
nonirritant	*n*-Amyl bromide	110-53-2	ECETOC	Elf Atochem, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (halogenated)	Chemical Intermediate, Pharmaceutical Intermediate, Solvent	100%	0.1 mL	>98.5 %	151.0	?	?	3	?	?	?
nonirritant	1,3-Di-iso-propyl benzene	99-62-7	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Hydrocarbon (cyclic)	Chemical Intermediate, Solvent	100%	0.1 mL	96%	162.3	?	?	6	soluble with Alcohol, Ether, acetone	?	?
nonirritant	4-Bromophenetole	589-10-6	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Ether	Chemical Intermediate	100%	0.1 mL	99%	201.1	?	?	3	?	?	?
nonirritant	Bromo-2-butane	78-76-2	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (halogenated)	Chemical Intermediate	100%	0.1 mL	>99%	137.0	?	?	3	?	?	?
nonirritant	*n*-Butyl acetate	123-86-4	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Ester	Chemical Intermediate, Food Additive, Industrial Chemical, Pesticide, Solvent	100%	0.1 mL	99%	116.2	?	?	4	soluble in acetone, Ether, PPG	1.82	?
nonirritant	Cellosolve acetate	111-15-9	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Ester, Ether	Chemical Intermediate, Pesticide, Pharmaceutical Intermediate, Preservative, Solvent	100%	0.1 mL	99%	305.8	?	?	4	230 g/L	?	?
nonirritant	Cetylpyridinium bromide	140-72-7	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Onium Compound, Heterocyclic Compound	Anti-Infective; Laboratory Chemical; Surfactant (cationic)	0.10%	0.1 mL	99%	384.4	4.8	noncorrosive	4	soluble (5 g/L)	1.83 (100%)	faintly beige
nonirritant	Chlorendic anhydride	115-27-5	TSCA	Velsicol Chemical Corp.	Sigma-Aldrich Corp.	Anhydride	Chemical Intermediate, Flame Retardant	n.a.	100 mg	98.8%	370.8	?	?	6	?	?	?
nonirritant	1-Bromo-4-chlorobutane	6940-78-9	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (halogenated)	Industrial Chemical	100%	0.1 mL	98%	171.5	?	?	3	soluble in ethanol, ethyl ether	?	colorless to yellow
nonirritant	Chlorpyrifos	2921-88-2	TSCA	Dow Chemical Co.	Sigma-Aldrich Corp.	Organophosphorus Compound	Pesticide	100%	0.1 mL	#####	350.6	?	?	6	?	?	white
nonirritant	Methyl cyclopentane	96-37-7	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (cyclic)	Solvent	100%	0.1 mL	>99%	84.2	?	?	6	?	?	colorless
nonirritant	1,9-Decadiene	1647-16-1	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Hydrocarbon (acyclic)	Chemical Intermediate	100%	0.1 mL	98%	138.3	?	?	6	?	?	?
nonirritant	1,4-Dibromobutane	110-52-1	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (halogenated)	Chemical Intermediate, Industrial Chemical, Laboratory Chemical	100%	0.1 mL	99.9%	215.9	?	?	3	insoluble	?	?
nonirritant	1,6-Dibromohexane	629-03-8	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (halogenated)	Chemical Intermediate, Pharmaceutical Intermediate	100%	0.1 mL	98.4%	244.0	?	?	3	insoluble	?	colorless to yellow
nonirritant	1,5-Dibromopentane	111-24-0	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (halogenated)	Pharmaceutical Intermediate	100%	0.1 mL	99.5%	230.0	?	?	3	insoluble	?	?

GHS Classification	Substance	Physical Form Tested	MMAS score	Corneal score	Irital score	Conjunctival score	NICEATM Category 1 SubClass.[2]	Tested in BCOP	Tested in HET-CAM	Tested in ICE	Tested in IRE	EPA Classification	EU Classification	FHSA Classification
Category 2B	**3,3-Dithiodipropionic acid**	**solid**	**31.7**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category II**	**nonirritant**	**SCNM**
Category 2B	**Hexyl cinnamic aldehyde**	**liquid**	**21.3**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category III**	**nonirritant**	**SCNM**
Category 2B	HZD Shampoo No. 5	liquid	33.7	-	-	-	-	-	X	-	-	Category III	nonirritant	SCNM
Category 2B	Isopropyl acetoacetate	?	12.0	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM
Category 2B	**N-Laurylsarcosine sodium salt**	**liquid**	**31.0**	**-**	**-**	**-**	**-**	**X**	**-**	**-**	**-**	**Category III**	**nonirritant**	**SCNM**
Category 2B	**Maneb (solid)**	**solid**	**14.3**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**X**	**Category III**	**R36**	**irritant**
Category 2B	**2-Methyl-1-pentanol**	**liquid**	**13.0**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category III**	**nonirritant**	**SCNM**
Category 2B	p-Nitrobenzoic acid	solid	19.3	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM
Category 2B	**Propasol Solvent P**	**liquid**	**31.2**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category II**	**nonirritant**	**irritant**
Category 2B	**6-Methyl purine**	**liquid**	**48.7**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category IV**	**R36**	**irritant**
Category 2B	**2,6-Dichloro-5-fluoro-beta-oxo-3-pyridinepropanoate**	**solid**	**21.3**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category III**	**nonirritant**	**SCNM**
Category 2B	Sodium monochloroacetate	solid	15.7	-	-	-	-	-	X	-	-	Category III	R36	SCNM
Category 2B	**Triton X-100**	**liquid**	**33.8**	**-**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**Category I**	**R41**	**SCNM**
nonirritant	Ethyl trimethyl acetate	liquid	3.8	-	-	-	-	-	X	X	-	Category III	nonirritant	nonirritant
nonirritant	**iso-Octyl acrylate**	**liquid**	**5.3**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category IV**	**nonirritant**	**SCNM**
nonirritant	Iso-myristyl alcohol	liquid	8.0	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM
nonirritant	**tetra-Aminopyrimidine sulfate**	**solid**	**10.3**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**-**	**Category III**	**nonirritant**	**SCNM**
nonirritant	*n*-Amyl bromide	liquid	4.0	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM
nonirritant	1,3-Di-iso-propyl benzene	liquid	2.0	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant
nonirritant	4-Bromophenetole	liquid	1.3	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM
nonirritant	Bromo-2-butane	liquid	0.0	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM
nonirritant	*n*-Butyl acetate	liquid	7.5	-	-	-	-	X	X	X	X	Category III	nonirritant	SCNM
nonirritant	Cellosolve acetate	liquid	15.0	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM
nonirritant	Cetylpyridinium bromide	liquid	2.7	-	-	-	-	X	X	-	-	Category I	R41	irritant
nonirritant	Chlorendic anhydride	solid	21.8	-	-	-	-	-	-	-	-	Category II	R36	irritant
nonirritant	1-Bromo-4-chlorobutane	liquid	4.0	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM
nonirritant	Chlorpyrifos	liquid	0.0	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant
nonirritant	Methyl cyclopentane	liquid	3.7	-	-	-	-	X	X	X	-	Category III	nonirritant	nonirritant
nonirritant	1,9-Decadiene	liquid	5.7	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant
nonirritant	1,4-Dibromobutane	liquid	6.0	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM
nonirritant	1,6-Dibromohexane	liquid	6.7	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM
nonirritant	1,5-Dibromopentane	liquid	4.7	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM

GHS Classification	Substance	Human Exposure Summary	Animal Exposure Summary for Category 1(H) Substances	Notes
Category 2B	**3,3-Dithiodipropionic acid**	**Human data not located**		
Category 2B	**Hexyl cinnamic aldehyde**	**Human data not located**		
Category 2B	HZD Shampoo No. 5	?	?	Formulations excluded.
Category 2B	Isopropyl acetoacetate	?	?	
Category 2B	**N-Laurylsarcosine sodium salt**	**Human data not located**		
Category 2B	**Maneb (solid)**	**Generally regarded as harmless, with no irritation, except for mild conjunctivitis (9)**		
Category 2B	**2-Methyl-1-pentanol**	**Human data not located**		
Category 2B	p-Nitrobenzoic acid	?	?	
Category 2B	**Propasol Solvent P**	**Human data not located**		
Category 2B	**6-Methyl purine**	**Human data not located**		
Category 2B	**2,6-Dichloro-5-fluoro-beta-oxo-3-pyridinepropanoate**	**Human data not located**		
Category 2B	Sodium monochloroacetate	?	?	
Category 2B	**Triton X-100**	**Human data not located**		
nonirritant	Ethyl trimethyl acetate	?	?	
nonirritant	**iso-Octyl acrylate**	**Human data not located**		
nonirritant	Iso-myristyl alcohol	?	?	
nonirritant	**tetra-Aminopyrimidine sulfate**	**Human data not located**		
nonirritant	*n*-Amyl bromide	?	?	
nonirritant	1,3-Di-iso-propyl benzene	?	?	
nonirritant	4-Bromophenetole	?	?	
nonirritant	Bromo-2-butane	?	?	
nonirritant	*n*-Butyl acetate	?	?	
nonirritant	Cellosolve acetate	Human data not located		
nonirritant	Cetylpyridinium bromide	?	?	
nonirritant	Chlorendic anhydride	?	?	
nonirritant	1-Bromo-4-chlorobutane	?	?	
nonirritant	Chlorpyrifos	?	?	
nonirritant	Methyl cyclopentane	?	?	
nonirritant	1,9-Decadiene	?	?	
nonirritant	1,4-Dibromobutane	?	?	
nonirritant	1,6-Dibromohexane	?	?	
nonirritant	1,5-Dibromopentane	?	?	

GHS Classification	Substance	CASRN	In Vivo Data Source	Substance Source	Commercial Availability	Chemical Class	Product Class	Conc. Tested	Amount Tested[1]	Purity	MW	pH	Dermal Corrosivity	# of Animals Tested	Water Solubility	Log Kow	Color
nonirritant	1,3-Dibromopropane	109-64-8	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (halogenated)	Chemical Intermediate, Pesticide Intermediate, Pharmaceutical Intermediate	100%	0.1 mL	98.4%	201.9	?	?	3	1.7 g/L	?	?
nonirritant	Dichlorotoluenes	mixture of isomers	ECETOC	Elf Atochem, Inc.	Elf Atochem, Inc. (Bulk)	Hydrocarbon (halogenated)	Industrial Chemical	100%	0.1 mL	99-99.8%	n.a.	?	?	3	?	?	?
nonirritant	**2,4-Difluoronitrobenzene**	**446-35-5**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Hydrocarbon (halogenated)**	**Pesticide, Pharmaceutical Intermediate**	**100%**	**0.1 mL**	**99%**	**159.1**	**n.a.**	**noncorrosive**	**6**	**n.a.**	**n.a.**	**n.a.**
nonirritant	1-(4-Phenyl-phenoxy)-1-(1,2,4-triazole-1)-3,3-dimethylbutane	55179-31-2	TSCA	Mobay Corp.	Shanghai Orgchem Co., Ltd.	Heterocyclic Compound	Anti-Fungal, Pesticide	100%	0.1 mL	96.5%	337.4	?	?	3	?	?	?
nonirritant	**n,n-Dimethylguanidine sulfate**	**598-65-2**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Amidine, Salt (organic)**	**Laboratory Chemical**	**100%**	**100 mg**	**>95%**	**272.3**	**n.a.**	**noncorrosive**	**3**	**n.a.**	**n.a.**	**n.a.**
nonirritant	3,3-Dimethylpentane	562-49-2	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Hydrocarbon (acyclic)	Chemical Intermediate	100%	0.1 mL	99%	100.2	?	?	3	insoluble	?	?
nonirritant	2,3-Dimethyl 2,3-dinitrobutane	3964-18-4	TSCA	Dow Chemical Co.	Dow Chemical Co. (Bulk)	Nitro Compound	Industrial Chemical	100%	100 mg	>95%	176.2	?	?	6	?	?	?
nonirritant	Di-*n*-propyl disulfide	629-19-6	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Sulfur Compound (organic)	Food Additive, Industrial Agent	100%	0.1 mL	99.2%	150.3	?	?	3	insoluble	?	colorless
nonirritant	*n*-Dodecane	112-40-3	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (acyclic)	Chemical Intermediate, Solvent	100%	0.1 mL	>99.5 %	170.3	?	?	6	?	?	?
nonirritant	**2-(n-Dodecylthio)ethanol**	**1462-55-1**	**ECETOC**	**Elf Atochem, Inc.**	**Sigma-Aldrich Corp.**	**Alcohol, Ether, Sulfur Compound (organic)**	**Chemical Intermediate**	**100%**	**100 mg**	**>99%**	**206.3**	**?**	**?**	**3**	**?**	**?**	**white**
nonirritant	2-Ethoxyethyl methacrylate	2370-63-0	ECETOC	Elf Atochem, Inc.	Sigma-Aldrich Corp.	Ester, Ether	Dental Adhesive	100%	0.1 mL	99.8%	158.2	n.a.	noncorrosive	3	n.a.	n.a.	?
nonirritant	Ethyl acetate	141-78-6	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Ester	Cleaning Agent, Food Additive, Solvent	100%	0.1 mL	99%	88.1	?	?	4	80 g/L	?	colorless
nonirritant	Ethyl thioglycolate	623-51-8	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Alcohol, Ester, Sulfur Compound (organic)	Chemical Intermediate, Cosmetic Ingredient, Food Additive, Industrial Chemical	100%	0.1 mL	99.1%	120.2	?	?	3	?	?	?
nonirritant	Ethyleneglycol diethyl ether	629-14-1	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Ether	Chemical Intermediate, Solvent	100%	0.1 mL	98%	118.2	?	?	3	?	?	colorless
nonirritant	2-Ethylhexylthioglycolate	7659-86-12	ECETOC	Elf Atochem, Inc.	Elf Atochem, Inc. (Bulk)	Alcohol, Ester, Sulfur Compound (organic)	Chemical Intermediate, Cosmetic Ingredient	100%	0.1 mL	99.4%	204.3	?	?	3	?	?	?
nonirritant	Glycerol	56-81-5	ECETOC	Mallinckrodt, Inc.	Sigma-Aldrich Corp.	Alcohol	Chemical Intermediate, Cosmetic Ingredient, Food Additive, Pharmaceutical, Solvent	100%	0.1 mL	>99.5 %	92.1	6.0-7.0 (10% aq.)	?	6	>500 g/L	?	?
nonirritant	Glycidyl methacrylate	106-91-2	ECETOC	Elf Atochem, Inc.	Sigma-Aldrich Corp.	Ether	Chemical Intermediate, Dental Adhesive, Industrial Chemical	100%	0.1 mL	>99%	142.2	?	?	3	?	?	?
nonirritant	1,5-Hexadiene	592-42-7	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (acyclic)	Chemical Intermediate, Industrial Chemical	100%	0.1 mL	97%	82.2	?	?	6	?	?	?
nonirritant	Perfluoro-n-hexane	355-42-0	TSCA	3M Corp.	Fisher Scientific International, Inc.	Hydrocarbon (halogenated)	Industrial Chemical	100%	0.1 mL	>90%	338.0	?	?	3	?	?	?
nonirritant	Perfluoro-n-hexane	355-42-0	TSCA	3M Corp.	Fisher Scientific International, Inc.	Hydrocarbon (halogenated)	Industrial Chemical	100%	0.1 mL	90%	338.0	?	?	3	?	?	?
nonirritant	*n*-Hexyl bromide	111-25-1	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (halogenated)	Industrial Chemical, Pharmaceutical Intermediate	100%	0.1 mL	>98.5 %	165.1	?	?	3	?	?	?
nonirritant	**iso-Propyl bromide**	**75-26-3**	**ECETOC**	**Fluka, Inc.**	**Sigma-Aldrich Corp.**	**Hydrocarbon (halogenated)**	**Chemical Intermediate, Pharmaceutical Intermediate**	**100%**	**0.1 mL**	**>99%**	**123.0**	**?**	**?**	**3**	**3 g/L**	**1.9**	**?**
nonirritant	**Di-iso-butyl ketone**	**108-83-8**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Ketone**	**Pharmaceutical Intermediate, Solvent**	**100%**	**0.1 mL**	**99%**	**142.2**	**n.a.**	**noncorrosive**	**3**	**0.05 g/ 100 mL**	**n.a.**	**?**
nonirritant	Methyl iso-butyl ketone	108-10-1	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Ketone	Food Additive, Solvent	100%	0.1 mL	98%	100.2	?	?	4	20 mg/mL	1.31	?
nonirritant	Allyl methacrylate	96-05-9	ECETOC	Elf Atochem, Inc.	Sigma-Aldrich Corp.	Ester	Chemical Intermediate	100%	0.1 mL	99.6%	126.2	?	?	6	4 g/L	?	?
nonirritant	Heptyl methacrylate	5459-37-0	ECETOC	Elf Atochem, Inc.	Elf Atochem, Inc. (Bulk)	Ester	Cosmetic Ingredient, Dental Adhesive, Perfume	100%	0.1 mL	>99%	164.3	?	?	3	?	?	?
nonirritant	Methyl trimethyl acetate	598-98-1	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Ester	Chemical Intermediate, Pharmaceutical Intermediate	100%	0.1 mL	99%	116.2	?	?	6	?	?	?
nonirritant	3-Methylhexane	589-34-4	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Hydrocarbon (acyclic)	Industrial Chemical	100%	0.1 mL	99%	100.2	?	?	6	insoluble	?	?
nonirritant	2-Methylpentane	107-83-5	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (acyclic)	Solvent	100%	0.1 mL	>99.5 %	86.2	n.a.	noncorrosive	6	14 mg/L	3.74	?
nonirritant	1-Methylpropyl benzene	135-98-8	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (cyclic)	Solvent	100%	0.1 mL	>99.5 %	134.2	?	?	6	0.015 g/L	?	?
nonirritant	*p*-Methylthiobenzaldehye	3446-89-7	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Aldehyde, Ether, Sulfur Compound (organic)	Chemical Intermediate	100%	0.1 mL	98.2%	152.2	?	?	3	?	?	?
nonirritant	Nonyl acrylate	2664-55-3	ECETOC	Elf Atochem, Inc.	Elf Atochem, Inc. (Bulk)	Ester	Industrial Chemical	100%	0.1 mL	99%	198.3	?	?	3	?	?	?
nonirritant	*cis*-Cyclo-octene	931-88-4	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (cyclic)	Chemical Intermediate, Industrial Chemical, Laboratory Chemical	100%	0.1 mL	95%	110.2	?	?	6	?	?	?
nonirritant	*n*-Octyl bromide	111-83-1	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (halogenated)	Chemical Intermediate, Industrial Chemical	100%	0.1 mL	>99%	193.1	?	?	3	?	?	?

GHS Classification	Substance	Physical Form Tested	MMAS score	Corneal score	Irital score	Conjunctival score	NICEATM Category 1 SubClass.[2]	Tested in BCOP	Tested in HET-CAM	Tested in ICE	Tested in IRE	EPA Classification	EU Classification	FHSA Classification
nonirritant	1,3-Dibromopropane	liquid	8.0	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM
nonirritant	Dichlorotoluenes	liquid	0.0	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM
nonirritant	**2,4-Difluoronitrobenzene**	**solid**	**4.7**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category III**	**nonirritant**	**SCNM**
nonirritant	1-(4-Phenyl-phenoxy)-1-(1,2,4-triazole-1)-3,3-dimethylbutane	liquid	5.7	-	-	-	-	-	-	-	-	Category III	nonirritant	nonirritant
nonirritant	**n,n-Dimethylguanidine sulfate**	**solid**	**6.7**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category III**	**nonirritant**	**SCNM**
nonirritant	3,3-Dimethylpentane	liquid	0.0	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM
nonirritant	2,3-Dimethyl 2,3-dinitrobutane	solid	4.3	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM
nonirritant	Di-*n*-propyl disulfide	liquid	4.0	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM
nonirritant	*n*-Dodecane	liquid	3.3	-	-	-	-	-	-	-	-	Category III	nonirritant	nonirritant
nonirritant	**2-(n-Dodecylthio)ethanol**	**solid**	**0.0**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category IV**	**nonirritant**	**SCNM**
nonirritant	2-Ethoxyethyl methacrylate	liquid	0.7	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM
nonirritant	Ethyl acetate	liquid	15.0	-	-	-	-	X	X	X	X	Category III	nonirritant	SCNM
nonirritant	Ethyl thioglycolate	Liquid	24.7	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM
nonirritant	Ethyleneglycol diethyl ether	liquid	10.7	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM
nonirritant	2-Ethylhexylthioglycolate	liquid	2.7	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM
nonirritant	Glycerol	liquid	1.7	-	-	-	-	X	X	X	X	Category IV	nonirritant	nonirritant
nonirritant	Glycidyl methacrylate	Liquid	28.0	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM
nonirritant	1,5-Hexadiene	liquid	4.7	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM
nonirritant	Perfluoro-n-hexane	liquid	0.0	-	-	-	-	-	-	-	-	Category IV	nonirritant	Insufficient Animal Data
nonirritant	Perfluoro-n-hexane	liquid	0.0	-	-	-	-	-	-	-	-	Category IV	nonirritant	Insufficient Animal Data
nonirritant	*n*-Hexyl bromide	liquid	1.3	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM
nonirritant	**iso-Propyl bromide**	**liquid**	**9.7**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category IV**	**nonirritant**	**SCNM**
nonirritant	**Di-iso-butyl ketone**	**liquid**	**7.3**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category IV**	**nonirritant**	**SCNM**
nonirritant	Methyl iso-butyl ketone	liquid	4.8	-	-	-	-	-	X	X	X	Category III	nonirritant	SCNM
nonirritant	Allyl methacrylate	liquid	5.8	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM
nonirritant	Heptyl methacrylate	liquid	1.3	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM
nonirritant	Methyl trimethyl acetate	liquid	2.7	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant
nonirritant	3-Methylhexane	liquid	0.7	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant
nonirritant	2-Methylpentane	Liquid	2.3	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant
nonirritant	1-Methylpropyl benzene	liquid	3.7	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant
nonirritant	*p*-Methylthiobenzaldehye	liquid	1.3	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM
nonirritant	Nonyl acrylate	liquid	0.0	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM
nonirritant	*cis*-Cyclo-octene	liquid	3.3	-	-	-	-	-	-	-	-	Category III	nonirritant	irritant
nonirritant	*n*-Octyl bromide	liquid	2.7	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM

GHS Classification	Substance	Human Exposure Summary	Animal Exposure Summary for Category 1(H) Substances	Notes
nonirritant	1,3-Dibromopropane	?	?	
nonirritant	Dichlorotoluenes	?	?	
nonirritant	**2,4-Difluoronitrobenzene**	**Human data not located**		
nonirritant	1-(4-Phenyl-phenoxy)-1-(1,2,4-triazole-1)-3,3-dimethylbutane	?	?	
nonirritant	**n,n-Dimethylguanidine sulfate**	**Human data not located**		
nonirritant	3,3-Dimethylpentane	?	?	
nonirritant	2,3-Dimethyl 2,3-dinitrobutane	?	?	
nonirritant	Di-*n*-propyl disulfide	?	?	
nonirritant	*n*-Dodecane	?	?	
nonirritant	**2-(n-Dodecylthio)ethanol**	**Human data not located**		
nonirritant	2-Ethoxyethyl methacrylate	Human data not located		
nonirritant	Ethyl acetate	?	?	
nonirritant	Ethyl thioglycolate	?	?	
nonirritant	Ethyleneglycol diethyl ether	?	?	
nonirritant	2-Ethylhexylthioglycolate	?	?	
nonirritant	Glycerol	?	?	
nonirritant	Glycidyl methacrylate	?	?	
nonirritant	1,5-Hexadiene	?	?	
nonirritant	Perfluoro-n-hexane	?	?	
nonirritant	Perfluoro-n-hexane	?	?	
nonirritant	*n*-Hexyl bromide	?	?	
nonirritant	**iso-Propyl bromide**	**Human data not located**		
nonirritant	**Di-iso-butyl ketone**	**Causes minor irritation to the eye (4, 20)**		
nonirritant	Methyl iso-butyl ketone	?	?	
nonirritant	Allyl methacrylate	?	?	
nonirritant	Heptyl methacrylate	?	?	
nonirritant	Methyl trimethyl acetate	?	?	
nonirritant	3-Methylhexane	?	?	
nonirritant	2-Methylpentane	A human eye irritant (23)		
nonirritant	1-Methylpropyl benzene	?	?	
nonirritant	*p*-Methylthiobenzaldehye	?	?	
nonirritant	Nonyl acrylate	?	?	
nonirritant	*cis*-Cyclo-octene	?	?	
nonirritant	*n*-Octyl bromide	Human data not located		

GHS Classification	Substance	CASRN	In Vivo Data Source	Substance Source	Commercial Availability	Chemical Class	Product Class	Conc. Tested	Amount Tested[1]	Purity	MW	pH	Dermal Corrosivity	# of Animals Tested	Water Solubility	Log Kow	Color
nonirritant	**iso-Octylthioglycolate**	**25103-09-7**	**ECETOC**	**Elf Atochem, Inc.**	**Sigma-Aldrich Corp.**	**Ester, Sulfur Compound (organic)**	**Industrial Chemical**	**100%**	**0.1 mL**	**99%**	**204.3**	**n.a.**	**noncorrosive**	**3**	**n.a.**	**n.a.**	**clear, water-white**
nonirritant	**2,4-Pentanediol**	**625-69-4**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Alcohol**	**Chemical Intermediate**	**100%**	**0.1 mL**	**98%**	**104.2**	**n.a.**	**?**	**3**	**?**	**?**	**?**
nonirritant	**2,2-Dimethyl-3-pentanol**	**3970-62-5**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Alcohol**	**Pharmaceutical**	**100%**	**0.1 mL**	**97%**	**116.2**	**n.a.**	**noncorrosive**	**3**	**insoluble**	**n.a.**	**colorless**
nonirritant	Perfluorotributylamine	311-89-7	TSCA	3M Corp.	Fisher Scientific International, Inc.	Amine	Industrial Chemical	100%	0.1 mL	80-90%	671.1	?	?	6	?	?	?
nonirritant	Phenothiazine	92-84-2	TSCA	ICI Americas, Inc.	Fisher Scientific International, Inc.	Amine, Sulfur Compound (organic)	Pesticide, Pharmaceutical Intermediate	n.a.	100 mg	99.8%	199.3	?	?	6	?	?	?
nonirritant	Phosphoric acid, tributyl ester	126-73-8	TSCA	Mobay Corp.	Sigma-Aldrich Corp.	Acid, Ester	Industrial Chemical	100%	0.1 mL	99.8%	266.3	?	?	3	?	?	?
nonirritant	Polyol 355 UCB	25791-96-2	ISOPA	Dow Europe S.A.	Dow Chemical Co. (Bulk)	Ether	Industrial Chemical	100%	0.1 mL	99.98 %	n.a.	?	?	3	?	?	?
nonirritant	Polyol XZ 95435.00	52625-13-5	ISOPA	Dow Europe GmbH	Dow Chemical Co. (Bulk)	Alcohol, Ether	Industrial Chemical	100%	0.1 mL	>99.5 %	530.7	?	?	3	?	?	?
nonirritant	Polyoxyethylene 23 lauryl ether (BRIJ-35)	9002-92-0	LNS	n.a.	Sigma-Aldrich Corp.	Alcohol	Pharmaceutical	10%	0.1 mL	n.a.	230.4	?	?	3	?	?	colorless
nonirritant	**Potassium tetrafluoroborate**	**14075-53-7**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Salt (inorganic)**	**Industrial Chemical, Pesticide**	**100%**	**100 mg**	**>99%**	**125.9**	**n.a.**	**R34**	**3**	**4.4 g/L**	**n.a.**	**n.a.**
nonirritant	**3-Methoxy-1,2-propanediol**	**623-39-2**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Ether, Phenol**	**Laboratory Chemical**	**100%**	**0.1 mL**	**98%**	**106.1**	**?**	**?**	**3**	**soluble**	**?**	**?**
nonirritant	(3-chloropropyl)trimethoxy-Silane	2530-87-2	TSCA	Union Carbide Corp.	Fisher Scientific International, Inc.	Ether	Industrial Chemical	100%	0.1 mL	96.3%	198.7	?	?	6	?	?	colorless to yellow
nonirritant	(3-chloropropyl)trimethoxy-Silane	2530-87-2	TSCA	Union Carbide Corp.	Fisher Scientific International, Inc.	Ether	Industrial Chemical	100%	0.1 mL	99.7%	198.7	?	?	6	?	?	colorless to yellow
nonirritant	**Sodium lauryl sulfate**	**151-21-3**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Acid (organic) [carboxylic acid], Salt (organic)**	**Cleaning Agent, Cosmetic Ingredient, Food Additive, Laboratory Chemical, Pesticide Intermediate, Surfactant (anionic)**	**3%**	**0.1 mL**	**98 %**	**288.4**	**8.0-10.0 (1% aq.)**	**noncorrosive**	**6**	**1 g/10 mL**	**1.60 (100%)**	**?**
nonirritant	Styrene	100-42-5	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (cyclic)	Chemical Intermediate, Industrial Chemical	100%	0.1 mL	99%	104.2	?	?	4	insoluble	?	colorless
nonirritant	Thiodiglycol	111-48-8	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Alcohol, Sulfur Compound (organic)	Industrial Chemical	100%	0.1 mL	99.8%	122.2	?	?	3	?	-0.75	?
nonirritant	**Toluene**	**108-88-3**	**ECETOC**	**Fisher Scientific International, Inc.**	**Sigma-Aldrich Corp.**	**Hydrocarbon (cyclic)**	**Chemical Intermediate, Industrial Chemical, Laboratory Chemical**	**100%**	**0.1 mL**	**99%**	**92.1**	**?**	**?**	**4**	**?**	**?**	**colorless**
nonirritant	3-Ethyl toluene	620-14-4	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Hydrocarbon (cyclic)	Industrial Chemical, Laboratory Chemical	100%	0.1 mL	99%	120.2	?	?	6	?	?	?
nonirritant	Triethyoxyoctylsilane	2943-75-1	TSCA	Union Carbide Corp.	Fisher Scientific International, Inc.	Organosilicon Compound	Industrial Chemical	100%	0.1 mL	97.3%	276.5	?	?	6	?	?	?
nonirritant	Trifluoroethyl methacrylate	392-68-7	ECETOC	Elf Atochem, Inc.	Elf Atochem, Inc. (Bulk)	Ester	Industrial Chemical	100%	0.1 mL	99.9%	n.a.	?	?	3	?	?	?
nonirritant	**Triton X-100**	**9002-93-1**	**ECETOC**	**Sigma-Aldrich Corp.**	**Sigma-Aldrich Corp.**	**Ether**	**Surfactant (nonionic)**	**1%**	**0.1 mL**	**98%**	**250.4**	**7.2**	**noncorrosive**	**6**	**soluble**	**n.a.**	**colorless**
nonirritant	Tween 20	9005-64-5	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Ester, Ether	Food Additive, Laboratory Chemical, Pesticide Intermediate, Surfactant (nonionic)	100%	0.1 mL	98%	1227.5	n.a.	noncorrosive	4	100 g/L	n.a.	?
nonirritant	Xylene	1330-20-7	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (cyclic)	Industrial Chemical, Laboratory Chemical, Pharmaceutical Intermediate, Solvent	100%	0.1 mL	99%	107.2	?	?	4	?	?	?
nonirritant	Xylene	1330-20-7	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (cyclic)	Industrial Chemical, Laboratory Chemical, Pharmaceutical Intermediate, Solvent	100%	0.1 mL	99%	107.2	?	?	4	?	?	?

GHS Classification	Substance	Physical Form Tested	MMAS score	Corneal score	Irital score	Conjunctival score	NICEATM Category 1 SubClass.[2]	Tested in BCOP	Tested in HET-CAM	Tested in ICE	Tested in IRE	EPA Classification	EU Classification	FHSA Classification
nonirritant	**iso-Octylthioglycolate**	**liquid**	**4.0**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category IV**	**nonirritant**	**SCNM**
nonirritant	**2,4-Pentanediol**	**liquid**	**4.7**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category IV**	**nonirritant**	**SCNM**
nonirritant	**2,2-Dimethyl-3-pentanol**	**liquid**	**8.3**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category III**	**nonirritant**	**SCNM**
nonirritant	Perfluorotributylamine	liquid	0.0	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant
nonirritant	Phenothiazine	solid	0.0	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant
nonirritant	Phosphoric acid, tributyl ester	liquid	13.3	-	-	-	-	-	-	-	-	Category III	nonirritant	Insufficient Animal Data
nonirritant	Polyol 355 UCB	liquid	0.0	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM
nonirritant	Polyol XZ 95435.00	liquid	0.0	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM
nonirritant	Polyoxyethylene 23 lauryl ether (BRIJ-35)	liquid	0.0	-	-	-	-	-	X	-	-	Category IV	nonirritant	nonirritant
nonirritant	**Potassium tetrafluoroborate**	**solid**	**0.0**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category IV**	**nonirritant**	**SCNM**
nonirritant	**3-Methoxy-1,2-propanediol**	**liquid**	**0.0**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Category IV**	**nonirritant**	**SCNM**
nonirritant	(3-chloropropyl)trimethoxy-Silane	liquid	0.3	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant
nonirritant	(3-chloropropyl)trimethoxy-Silane	liquid	0.0	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant
nonirritant	**Sodium lauryl sulfate**	**liquid**	**7.3**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**X**	**Category III**	**nonirritant**	**irritant**
nonirritant	Styrene	liquid	6.8	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM
nonirritant	Thiodiglycol	liquid	5.3	-	-	-	-	-	-	-	-	Category III	nonirritant	SCNM
nonirritant	**Toluene**	**liquid**	**9.0**	**-**	**-**	**-**	**-**	**-**	**X**	**X**	**X**	**Category III**	**nonirritant**	**SCNM**
nonirritant	3-Ethyl toluene	liquid	2.3	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant
nonirritant	Triethyoxyoctylsilane	liquid	2.7	-	-	-	-	-	-	-	-	Category IV	nonirritant	nonirritant
nonirritant	Trifluoroethyl methacrylate	liquid	2.7	-	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM
nonirritant	**Triton X-100**	**liquid**	**1.7**	**-**	**-**	**-**	**-**	**X**	**-**	**-**	**-**	**Category II**	**R36**	**irritant**
nonirritant	Tween 20	liquid	40.0	-	-	-	-	X	X	X	X	Category III	nonirritant	SCNM
nonirritant	Xylene	liquid	1.5	-	-	-	-	X	-	-	-	Category IV	nonirritant	SCNM
nonirritant	Xylene	liquid	9.0	-	-	-	-	-	-	-	-	Category II	nonirritant	SCNM

GHS Classification	Substance	Human Exposure Summary	Animal Exposure Summary for Category 1(H) Substances	Notes
nonirritant	**iso-Octylthioglycolate**	**Human data not located**		
nonirritant	**2,4-Pentanediol**	**Human data not located**		
nonirritant	**2,2-Dimethyl-3-pentanol**	**Human data not located**		
nonirritant	Perfluorotributylamine	?	?	
nonirritant	Phenothiazine	?	?	
nonirritant	Phosphoric acid, tributyl ester	?	?	
nonirritant	Polyol 355 UCB	?	?	
nonirritant	Polyol XZ 95435.00	?	?	
nonirritant	Polyoxyethylene 23 lauryl ether (BRIJ-35)	?	?	
nonirritant	**Potassium tetrafluoroborate**	**Human data not located**		
nonirritant	**3-Methoxy-1,2-propanediol**	**Human data not located**		
nonirritant	(3-chloropropyl)trimethoxy-Silane	?	?	
nonirritant	(3-chloropropyl)trimethoxy-Silane	?	?	
nonirritant	**Sodium lauryl sulfate**	**Sodium lauryl sulfate is said to have been the commonest cause of eye irritation by commercial shampoos (10)**		
nonirritant	Styrene	?	?	
nonirritant	Thiodiglycol	?	?	
nonirritant	**Toluene**	**Vapors of toluene cause noticeable sensation of irritation to human eyes at 300-440 ppm in air, but even at 800 ppm, irritation is slight.** **Vapors irritate eyes and upper respiratory tract; liquid irritates eyes (10, 27).**		
nonirritant	3-Ethyl toluene	?	?	
nonirritant	Triethyoxyoctylsilane	?	?	
nonirritant	Trifluoroethyl methacrylate	?	?	
nonirritant	**Triton X-100**	**Human data not located**		
nonirritant	Tween 20	Human data not located		
nonirritant	Xylene	?	?	
nonirritant	Xylene	?	?	

Please see abbreviations and references in **Appendix V-A1**

APPENDIX V-B

LIST OF PROPOSED RERENENCE SUBSTANCES FOR VALIDATION STUDIES OF *IN VITRO* TEST METHODS FOR THE IDENTIFICATION OF OCULAR CORROSIVES/SEVERE IRRITANTS (SORTED BY GHS OCULAR HAZARD CLASSIFICATION CATEGORY AND SUBSTANCE NAME)

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Reference Substances (Sorted by GHS Classification and Substance Name)

GHS Classification	NICEATM Category 1 SubClass.[2]	Substance	CASRN	In Vivo Data Source	Substance Source	Commercial Availability	Chemical Class	Product Class	Conc. Tested	Amount Tested[1]	Purity	MW	pH	Dermal Corrosivity	# of Animals Tested	Water Solubility	Log Kow	Color	Physical Form Tested	MMAS score
Category 1	4	Acetic Acid	64-19-7	NIHS-Ohno	Japanese Cosmetic Industry Assn.	Sigma-Aldrich Corp.	Acid (organic) [carboxylic acid]	Industrial Chemical; Laboratory Agent, Solvent	10%	0.1 mL	n.a.	60.1	2.4	R35 (60%)	3	soluble	-0.17 (60%)	colorless	liquid	68.0
Category 1	4	Acid blue 40	6424-85-7	TSCA	Crompton and Knowles Corp.	Sigma-Aldrich Corp.	Amine, Quinone, Salt (organic)	Industrial Chemical	n.a.	100 mg	n.a.	473.4	8.0	noncorrosive	6	soluble (30 g/L@ 80C)	2.2	deep blue	solid	39.7
Category 1	4	Methoxyethyl acrylate	3121-61-7	ECETOC	Elf Atochem, Inc.	Sigma-Aldrich Corp.	Ester, Ether	Chemical Intermediate, Industrial Chemical, Laboratory Chemical	100%	0.1 mL	99.6%	130.1	n.a.	noncorrosive	3	Soluble	0.08	?	liquid	45.0
Category 1	4	Aluminum chloride	16603-84-2	TSCA	Monsanto Co.	Fisher Scientific International, Inc.	Salt (inorganic)	Chemical Intermediate, Dye, Industrial Chemical, Laboratory Chemical, Pesticide, Preservative	n.a.	0.1 mL	n.a.	98.9	?	?	6	?	?	light yellow-green	liquid	82.7
Category 1	4	gamma-Aminopropyltriethoxy silane	919-30-2	TSCA	Union Carbide Corp.	Sigma-Aldrich Corp.	Amine, Amidine, Organosilicon Compound	Industrial Chemical	100%	0.1 mL	99%	221.4	?	R34	6	?	?	?	liquid	78.7
Category 1	4	Antimony oxide	1309-64-4	TSCA	Monsanto Co.	Sigma-Aldrich Corp.	Salt (inorganic)	Flame Retardant, Industrial Chemical, Laboratory Chemical, Pharmaceutical Intermediate	100%	100 mg	83.5%	291.5	?	noncorrosive	6	?	?	white powder	solid	107.3
Category 1	3	Benzalkonium chloride	8001-54-5	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Onium Compound	Surfactant (cationic)	5%	0.1 mL	98%	471.5	3.1	R34 (50%)	4	soluble	n.a.	clear	liquid	4.8
Category 1	4	Benzenesulfonyl chloride	98-09-9	TSCA	n.a.	Fisher Scientific International, Inc.	Acyl Halide, Sulfur Compound (organic)	Chemical Intermediate, Pesticide	n.a.	0.1 mL	99.6%	176.6	?	R34	6	?	?	brown	liquid	80.7
Category 1	4	Benzethonium chloride	121-54-0	LNS	n.a.	Sigma-Aldrich Corp.	Amine, Onium Compound	Anti-Infective, Pharmaceutical, Veterinary Chemical	10%	0.1 mL	n.a.	448.1	?	?	3	?	?	?	liquid	76.3
Category 1	4	2-Benzyl-4-chlorophenol	120-32-1	TSCA	Monsanto Co.	Sigma-Aldrich Corp.	Phenol	Anti-Fungal, Anti-Infective, Herbicide	100%	100 mg	95%	218.7	?	?	6	?	?	light brown	solid	100.0
Category 1	1	2,2-Dimethyl butanoic acid	595-37-9	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Acid (organic) [carboxylic acid]	Pharmaceutical	100%	0.1 mL	96%	116.2	n.a.	R34	6	n.a.	n.a.	?	liquid	44.7
Category 1	4	n-Butanol	71-36-3	NIHS-Ohno	Japanese Cosmetic Industry Assn.	Sigma-Aldrich Corp.	Alcohol	Chemical Intermediate, Cosmetic Ingredient, Food Additive, Industrial Chemcial, Pesticide Intermediate, Pharmaceutical Intermediate, Solvent, Veterinary Chemical	10%	0.1 mL	n.a.	74.1	n.a.	noncorrosive	3	insoluble	0.88	colorless	liquid	34.0
Category 1	1	Butyl cellosolve	111-76-2	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Alcohol	Solvent	100%	0.1 mL	99%	118.2	n.a.	noncorrosive	3	soluble (5 g/L)	0.83	?	liquid	68.7
Category 1	4	4-tert-Butylcatechol	98-29-3	TSCA	n.a.	Sigma-Aldrich Corp.	Phenol	Chemical Intermediate, Laboratory Chemical	85%	0.1 mL	n.a.	166.2	?	?	6	?	?	?	liquid	83.7
Category 1	4	p-tert-Butylphenol	98-54-4	TSCA	Union Carbide Corp.	Sigma-Aldrich Corp.	Phenol	Chemical Intermediate, Perfume, Pesticide	100%	80 mg	n.a.	150.2	?	?	6	?	?	?	solid	71.3
Category 1	4	Captan 90-concentrate (solid)	133-06-2	ECETOC	US EPA	Gustafson, LLC	Heterocyclic Compound, Sulfur Compound (organic)	Pesticide	100%	100 mg	90%	300.6	8.0	noncorrosive	3	soluble (5.1 mg/L)	2.35	white	solid	83.0
Category 1	2	Cetylpyridinium bromide	140-72-7	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Onium Compound, Heterocyclic Compound	Anti-Infective; Laboratory Chemical; Surfactant (cationic)	6%	0.1 mL	99%	384.4	6.0-8.0 (0.5%)	noncorrosive	4	soluble (5 g/L)	1.83 (100%)	faintly beige	liquid	85.8
Category 1	4	Cetyltrimethylammonium bromide	57-09-0	NIHS-Ohno	Japanese Cosmetic Industry Assn.	Sigma-Aldrich Corp.	Onium Compound, Salt (organic)	Cosmetic Ingredient	10%	0.1 mL	n.a.	364.4	5.9	noncorrosive	3	soluble (30 g/L)	3.18/2.26	?	liquid	96.0
Category 1	4	Chlorhexidine	55-56-1	ECETOC	n.a.	Sigma-Aldrich Corp.	Amidine	Anti-Infective, Pharmaceutical	100%	100 mg	n.a.	505.5	?	?	3	?	n.a.	?	solid	82.3
Category 1	2	Cyclohexanol	108-93-0	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Alcohol	Solvent	100%	0.1 mL	97%	100.2	4.5	noncorrosive	4	soluble (3.6 mg/100 mL)	1.23	colorless	liquid	79.8
Category 1	1	3,4-Dichlorophenyl isocyanate	102-36-3	TSCA	Mobay Corp.	Fisher Scientific International, Inc.	Isocyanate	Chemical Intermediate, Industrial Chemical	100%	0.1 mL	n.a.	188.0	?	?	3	?	?	?	liquid	10.3

GHS Classification	NICEATM Category 1 SubClass.[2]	Substance	Corneal score	Irital score	Conjunctival score	Tested in BCOP	Tested in HET-CAM	Tested in ICE	Tested in IRE	EPA Classification	EU Classification	FHSA Classification	Human Exposure Summary
Category 1	4	Acetic Acid	n=2/3, CO=4	-	-	-	X	X	X	Category I	R41	SCNM	Has caused extreme eye and nasal irritation at concentrations in air in excess of 25 ppm. Has caused conjunctivitis at concentrations below 10 ppm. Concentrations of 200 ppm caused conjunctival hyerperemia. Glacial (100%) acetic acid has caused permanent corneal opacification. A splash of vinegar (4 to 10% acetic acid solution) in the eye causes immediate pain and conjunctival hyperemia, sometimes with injury of the corneal epithelium (2 patients). Accidental application of glacial acetic acid to the eyes followed very quickly by irrigation with water resulted in immediate corneal opacification. These corneas cleared sufficiently in a few days to reveal severe iritis and small pupils fixed by posterior synechiae. Regeneration of the epithelium took many months, but corneal anesthesia and opacity were permanent. In workers exposed to aerosol concentrations of 60 ppm for 7-12 years, with daily exposures as high as 100-200 ppm, investigators found conjunctivitis (in addition to bronchitis, pharyngitis, and erosion of exposed teeth) (1, 13,
Category 1	4	Acid blue 40	n=2/6, CO=4	-	-	-	-	-	-	SCNM	R36	irritant	Human data not located
Category 1	4	Methoxyethyl acrylate	n=2/3, CO=4	-	-	-	-	-	-	SCNM	R36	SCNM	Human data not located
Category 1	4	Aluminum chloride	n=5/6, CO=4	-	-	-	-	-	-	Category I	R41	irritant	Is caustic and irritating to the human eye, but in only 1 out of 55 instances of industrial corneal burns has healing been delayed beyond 2 days (10)
Category 1	4	gamma-Aminopropyltriethoxy silane	n=5/6, CO=4	-	-	-	-	-	-	SCNM	Review Data	irritant	Human data not located
Category 1	4	Antimony oxide	n=6/6, CO=4	n=6/6, IR=2 D14	n=6/6, CR=3, n=3/6, CC=4 D14	-	-	-	-	Category I	R41	irritant	Chronic exposure causes eye irritation (6, 53)
Category 1	3	Benzalkonium chloride	n=1/4, CO=4; n=2/4, CO=3; n=2/4, CO>0 D21	n=1/4, IR>1.5 D21	n=1/4, CR/CC>0 D21	X	X	X	X	Category I	R41	SCNM	A severe irritant to the human eye. Concentrations as low as 0.1 to 0.5% cause mild discomfort and conjunctival irritation. Slit lamp examination within 90 seconds of exposure to a single drop of 0.1% shows fine gray dots of keratitis epithelias in the corneal epithelium. Within 10 minutes of exposure, a gray haze may be seen in the corneal surface; superficial desquamation of the conjunctival epithelium may follow. These effects disappear in a day or less. (9, 17)
Category 1	4	Benzenesulfonyl chloride	n=5/6, CO=4	-	-	-	-	-	-	Category I	R41	irritant	Human data not located
Category 1	4	Benzethonium chloride	n=2/3, CO=4	-	-	-	-	-	-	Category I	R41	SCNM	Human data not located
Category 1	4	2-Benzyl-4-chlorophenol	n=6/6, CO=4	-	-	-	-	-	-	Category I	R41	irritant	Human data not located
Category 1	1	2,2-Dimethyl butanoic acid	n=1/6, CO=3 D14	n=1/6, IR=2 D14	-	X	X	X	X	Category I	R41	irritant	Human data not located
Category 1	4	n-Butanol	n=1/3, CO=4	-	-	-	X	-	-	SCNM	R41	SCNM	Is reported to cause irritation of the eyes from exposure to either vapor or liquid. Circumstantial evidence points to butyl alcohol vapor as cause of a special vacuolar keratopathy in some patients; the most severely affected it has been associated with pain & tearing, characteristically most marked on first opening eyes in morning. It can cause transient mild edema of conjunctiva of the eye. Vapor: Irritating to eyes. Considered a strong irritant of the eyes. (9, 11, 13, 27)
Category 1	1	Butyl cellosolve	-	-	n=2/3, CR>0, n=1/3, CC>0 D21	X	-	-	-	Category II	R36	SCNM	An irritant to the human eye. In several, single 8 hour exposures to concentrations of 100 to 200 ppm in air, participants reported discomfort and mild eye irritation. 7 workers exposed to aerosol concentrations of 200 to 300 ppm reported intense eye irritation, followed by recurrent ocular irritation after the initial exposure. (1, 14, 21, 24, 30)
Category 1	4	4-tert-Butylcatechol	n=6/6, CO=4	n=2/6, IR=2 D21	-	-	-	-	-	Category I	R41	irritant	Human data not located
Category 1	4	p-tert-Butylphenol	n=4/6, CO=4	-	-	-	-	-	-	Category I	R41	irritant	Human data not located
Category 1	4	Captan 90-concentrate (solid)	n=3/3, CO=4	n=1/3, IR>0 D21	n=2/3, CR/CC>0 D21	X	X	X	-	Category I	R41	SCNM	Has been reported to cause conjunctivitis (12)
Category 1	2	Cetylpyridinium bromide	-	n=3/4, I>1.5	-	X	-	X	X	Category II	R36	irritant	Human data not located
Category 1	4	Cetyltrimethylammonium bromide	n=3/3, CO=4	-	n=1/3, CR=3, n=3/3, CC=2 D14	-	-	-	-	Category I	R41	SCNM	In 179 patients treated with eye drops containing cetrimide (Cetyltrimethylammonium bromide) for 30 days, adverse effects were reported for 21 patients. The adverse events consisted of discomfort, blurred vision, hyperemia, burning and itching. Accidental application of cetrimide occurred during cataract surgery. This resulted in immediate corneal edema which in turn resulted in a bullous keratopathy. Four patients underwent a penetrating keratoplasty. In one patient the cornea was covered with a conjunctival flap. Light microscopy of the corneas included epithelial edema, loss of keratocytes, and a disrupted and sometimes absent endothelial cell layer. (3, 29)
Category 1	4	Chlorhexidine	n=1/3, CO=4	-	-	X	X	X	X	SCNM	R41	SCNM	Acutely toxic when applied to the eye. Irreversible corneal injuries and opacification attributed to Hibiclens (chlorhexidine gluconate, a 4% topical preparation), reported in 4 female patients, aged 9 months to 83 year, in whom the drug was accidentally introduced into the eye during surgical preparation. Inadvertently used as an intraocular irrigating solution in three patients undergoing surgery. In two of the three patients, corneal endothelium damage was so severe that penetrating keratoplasty had to be performed. Further effects included pronounced iris atrophy, anterior chamber applanation, and a retrocorneal membrane. (25, 28, 31)
Category 1	2	Cyclohexanol	n=3/4, CO=3	-	-	X	X	X	X	Category I	R41	SCNM	Irritation to the eyes of human subjects results at air concentrations of 100 ppm, and which occurs after 3 to 5 minutes exposure (13, 22)
Category 1	1	3,4-Dichlorophenyl isocyanate	n=3/3, CO>0 D21	-	-	-	-	-	-	Category I	R41	SCNM	An irritant to the human eye, causing lacrimation, and (rarely), conjunctivitis (13, 17)

GHS Classification	NICEATM Category 1 SubClass.[2]	Substance	Animal Exposure Summary for Category 1(II) Substances	Notes
Category 1	4	Acetic Acid		
Category 1	4	Acid blue 40		
Category 1	4	Methoxyethyl acrylate		
Category 1	4	Aluminum chloride		
Category 1	4	gamma-Aminopropyltriethoxy silane		
Category 1	4	Antimony oxide		
Category 1	3	Benzalkonium chloride		
Category 1	4	Benzenesulfonyl chloride		
Category 1	4	Benzethonium chloride		
Category 1	4	2-Benzyl-4-chlorophenol		
Category 1	1	2,2-Dimethyl butanoic acid		
Category 1	4	n-Butanol		
Category 1	1	Butyl cellosolve		
Category 1	4	4-tert-Butylcatechol		
Category 1	4	p-tert-Butylphenol		
Category 1	4	Captan 90-concentrate (solid)		
Category 1	2	Cetylpyridinium bromide		
Category 1	4	Cetyltrimethylammonium bromide		
Category 1	4	Chlorhexidine		
Category 1	2	Cyclohexanol		
Category 1	1	3,4-Dichlorophenyl isocyanate		

GHS Classification	NICEATM Category 1 SubClass [2]	Substance	CASRN	In Vivo Data Source	Substance Source	Commercial Availability	Chemical Class	Product Class	Conc. Tested	Amount Tested [1]	Purity	MW	pH	Dermal Corrosivity	# of Animals Tested	Water Solubility	Log Kow	Color	Physical Form Tested	MMAS score
Category 1	4	Diethylaminopropionitrile	5351-04-2	ECETOC	Elf Atochem, Inc.	Fisher Scientific International, Inc.	Amine, Nitrile	Industrial Chemical	100%	0.1 mL	>98.8%	126.2	n.a.	noncorrosive	3	soluble	0.77	yellow	liquid	62.3
Category 1	4	Diethylethanolamine	100-37-8	TSCA	Union Carbide Corp.	Sigma-Aldrich Corp.	Alcohol, Amine	Chemical Intermediate, Pharmaceutical Intermediate	25%	0.1 mL	n.a.	117.2	?	?	6	?	?	colorless	liquid	94.7
Category 1	4	1,3-Diiminobenz (f)-isoindoline	65558-69-2	TSCA	Hoechst Celanese Corp.	Sigma-Aldrich Corp.	Amine, Heterocyclic Compound	Dye, Laboratory Chemical	100%	100 mg	n.a.	195.2	n.a.	?	3	?	?	?	solid	93.0
Category 1	1	2,5-Dimethylhexanediol	110-03-2	ECETOC	BASF	Sigma-Aldrich Corp.	Alcohol	Chemical Intermediate	100%	40 mg	99.5%	146.2	5.7	noncorrosive	3	soluble	n.a.	?	solid	28.3
Category 1	4	Bis-(3-aminopropyl) tetramethyl disiloxane	2469-55-8	TSCA	General Electric Co.	Sigma-Aldrich Corp.	Amine, Amidine, Organosilicon Compound	Industrial Chemical	100%	0.1 mL	n.a.	248.5	n.a.	R34	2	n.a.	n.a.	?	liquid	109.0
Category 1	4	Domiphen bromide	538-71-6	NIHS-Ohno	Japanese Cosmetic Industry Assn.	Sigma-Aldrich Corp.	Ether, Onium Compound, Salt (organic)	Anti-Infective, Pharmaceutical	10%	0.1 mL	n.a.	414.5	6.2	noncorrosive	3	n.a.	n.a.	?	liquid	96.3
Category 1	4	Granuform	30525-89-4	ZEBET	n.a.	Sigma-Aldrich Corp.	Aldehyde, Ether	Anti-Fungal, Anti-Infective, Industrial Chemical, Laboratory Chemical	n.a.	0.1 mL or 100 mg	n.a.	30.0	4.0	?	3	?	?	?	solid	75.3
Category 1	4	Hydroxyethyl acrylate	818-61-1	TSCA	n.a.	Dow Chemical Co. (Bulk)	Alcohol, Ester	Chemical Intermediate	100%	0.1 mL	n.a.	116.1	?	?	6	?	?	?	liquid	96.7
Category 1	2	2-Hydroxyisobutyric acid ethylester	80-55-7	ZEBET	n.a.	Sigma-Aldrich Corp.	Alcohol, Ester	Industrial Chemical	n.a.	0.1 mL or 100 mg	n.a.	132.2	?	?	3	?	?	?	solid	81.0
Category 1	4	2-Hydroxyisobutyric acid	594-61-6	ZEBET	n.a.	Sigma-Aldrich Corp.	Acid (organic) [carboxylic acid]	Industrial Chemical	n.a.	0.1 mL or 100 mg	n.a.	104.1	?	?	3	?	?	?	solid	98.7
Category 1	4	Imidazole	288-32-4	ECETOC	n.a.	Sigma-Aldrich Corp.	Heterocyclic Compound	Anti-Fungal	100%	100 mg	99%	68.1	10.3	R34	3	soluble (633 g/L)	n.a.	?	solid	59.3
Category 1	4	Cyclohexyl isocyanate	3173-53-3	TSCA	Mobay Corp.	Sigma-Aldrich Corp.	Isocyanate	Anesthetic, Chemical Intermediate, Cleaning Agent, Industrial Chemical, Pharmaceutical Intermediate, Solvent	100%	0.1 mL	Technical Grade	125.2	n.a.	R34	2	insoluble	6.11	?	liquid	101.0
Category 1	4	alpha-Ketoglutaric acid alpha	328-50-7	ZEBET	n.a.	Sigma-Aldrich Corp.	Acid (organic) [carboxylic acid]	Chemical Intermediate, Laboratory Chemical, Pharmaceutical,	n.a.	0.1 mL or 100 mg	n.a.	146.1	?	?	3	?	?	?	solid	93.0
Category 1	4	Lactic Acid	50-21-5	NIHS-Ohno	Japanese Cosmetic Industry Assn.	Sigma-Aldrich Corp.	Alcohol, Acid (organic) [carboxylic acid]	Cosmetic Ingredient	100%	0.1 mL	n.a.	90.1	1.9	R34	3	soluble	-0.72	colorless	liquid	102.7
Category 1	1	Lauric acid	143-07-7	ECETOC	Unichema International, Inc.	Sigma-Aldrich Corp.	Acid (organic) [carboxylic acid]	Surfactant (anionic)	100%	52 mg	>92%	200.3	4.2	noncorrosive	3	insoluble	4.20	colorless	solid	38.0
Category 1	4	4-Chloro-methanilic acid	98-36-2	ZEBET	n.a.	Fisher Scientific International, Inc.	Amine, Sulfur Compound (organic)	Chemical Intermediate, Laboratory Chemical	n.a.	0.1 mL or 100 mg	n.a.	207.6	?	?	1	?	?	?	solid	17.0
Category 1	4	*n*-Acetyl-methionine	1115-47-5	ZEBET	n.a.	Sigma-Aldrich Corp.	Amide, Amino Acid	Cosmetic Ingredient, Food Additive, Laboratory Chemical	n.a.	0.1 mL or 100 mg	n.a.	191.3	2.2	?	3	?	?	?	solid	57.3
Category 1	4	2-Methylbutyric acid	116-53-0	TSCA	Union Carbide Corp.	Sigma-Aldrich Corp.	Acid (organic) [carboxylic acid]	Chemical Intermediate, Cosmetic Ingredient, Solvent	100%	0.005 mL	97.9%	102.1	?	R34	6	?	1.18	?	liquid	38.3
Category 1	4	Methylpentynol	77-75-8	ZEBET	n.a.	Sigma-Aldrich Corp.	Alcohol	Pharmaceutical, Veterinary Chemical	n.a.	0.1 mL or 100 mg	n.a.	98.1	?	?	1	?	?	?	liquid	34.0
Category 1	4	Methylthioglycolate	2365-48-2	ECETOC	Elf Atochem, Inc.	Sigma-Aldrich Corp.	Ester, Sulfur Compound (organic)	Industrial Chemical	100%	0.1 mL	99.7%	106.1	pKa 8.22	noncorrosive	3	Soluble	0.65	?	liquid	53.0
Category 1	4	1-Naphthaleneacetic acid (solid)	86-87-3	ECETOC	US EPA	Sigma-Aldrich Corp.	Acid (organic) [carboxylic acid], Polycyclic Compound	Pesticide	100%	100 mg	96%	186.2	3.3	noncorrosive	6	insoluble (420 mg/L)	2.24	?	solid	46.7
Category 1	4	*n*-Octylamine	111-86-4	TSCA	Hoechst Celanese Corp.	Sigma-Aldrich Corp.	Amine	Chemical Intermediate, Laboratory Chemical	100%	0.1 mL	n.a.	129.2	?	?	4	?	?	?	liquid	79.5
Category 1	0 (likely 4)	tetra-N-Octylammonium bromide	14866-33-2	GSK	n.a.	Sigma-Aldrich Corp.	Onium Compound	Industrial Chemical, Laboratory Chemical	100%	0.1 mL or 100 mg	n.a.	546.8	?	?	1	?	?	?	solid	0.0
Category 1	1	Organofunctional Silane 45-49	82985-35-1	TSCA	Union Carbide Corp.	Sigma-Aldrich Corp.	Amine, Organosilicon Compound	Polish	100%	0.005 mL	n.a.	341.6	?	?	6	?	?	?	liquid	54.2
Category 1	2	4-(1,1,3,3-Tetramethylbutyl)phenol	140-66-9	TSCA	Rohm and Haas Co.	Sigma-Aldrich Corp.	Phenol	Chemical Intermediate	100%	100 mg	n.a.	206.3	?	?	6	?	?	?	solid	90.0
Category 1	4	Phosphorodicloridic acid, ethyl ester	1498-51-7	TSCA	Rhone-Poulenc, Inc.	Sigma-Aldrich Corp.	Ester, Organophosphorus Compound	Chemical Intermediate, Pesticide	100%	0.1 mL	96%	162.9	?	R34	6	?	?	?	liquid	100.0
Category 1	4	Polyethylene glycol nonylphenyl ether (Surfonic HDL-1)	9016-45-9	TSCA	Texaco, Inc.	Houghton Chemical Corp.	Alcohol, Ether	Cleaning Agent, Industrial Chemical, Pesticide, Surfactant (nonionic)	100%	0.1 mL	n.a.	308.5	?	?	6	?	?	?	liquid	52.3
Category 1	4	Potassium laurate	10124-65-9	NIHS-Ohno	Japanese Cosmetic Industry Assn.	Pfaltz & Bauer, Inc.	Acid (organic) [carboxylic acid], Salt (organic)	Cosmetic Ingredient, Pesticide	10%	0.1 mL	n.a.	238.4	?	?	3	?	?	?	liquid	33.7
Category 1	3	Promethazine hydrochloride	58-33-3	ECETOC	n.a.	Sigma-Aldrich Corp.	Amine, Amidine, Heterocyclic Compound, Sulfur Compound (organic)	Pharmaceutical	100%	100 mg	98%	320.9	?	?	3	n.a.	n.a.	white to faint yellow	solid	71.7
Category 1	1	Protectol PP	80-54-6	TSCA	BASF	Sigma-Aldrich Corp.	Aldehyde	Food Additive, Perfume	100%	0.1 mL	84.8%	204.3	n.a.	noncorrosive	3	n.a.	?	white powder	liquid	34.3
Category 1	4	Pyridine	110-86-1	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Heterocyclic Compound	Pesticide Intermediate, Pharmaceutical Intermediate, Solvent	100%	0.1 mL	99.9+%	79.1	9.9	noncorrosive	3	soluble	0.65	?	liquid	48.0
Category 1	3	Quinacrine	69-05-6	ECETOC	n.a.	Sigma-Aldrich Corp.	Amine, Heterocyclic Compound, Polycyclic Compound	Pharmaceutical	100%	100 mg	90%	472.9	?	noncorrosive	3	soluble (1 g/36 mL)	n.a.	?	solid	82.0
Category 1	4	beta-Resorcylic acid	89-86-1	ZEBET	n.a.	Sigma-Aldrich Corp.	Acid (organic) [carboxylic acid], Phenol	Chemical Intermediate, Dye	n.a.	0.1 mL or 100 mg	n.a.	154.1	?	?	1	?	?	?	solid	63.0

GHS Classification	NICEATM Category 1 SubClass [2]	Substance	Corneal score	Irital score	Conjunctival score	Tested in BCOP	Tested in HET-CAM	Tested in ICE	Tested in IRE	EPA Classification	EU Classification	FHSA Classification	Human Exposure Summary
Category 1	4	Diethylaminopropionitrile	n=3/3, CO=4	-	-	-	-	-	-	Category II	R41	SCNM	Human data not located
Category 1	4	Diethylethanolamine	n=6/6, CO=4	n=3/3, IR=2 D14	-	-	-	-	-	Category I	R41	irritant	A human eye irritant (18, 42, 43)
Category 1	4	1,3-Diiminobenz (f)-isoindoline	n=4/4, CO=4	-	-	-	-	-	-	SCNM	R41	SCNM	Human data not located
Category 1	1	2,5-Dimethylhexanediol	-	n=1/3, IR = 1 D21	n=1/3, CR=2 D21	X	X	X	-	Category I	R41	SCNM	Human data not located
Category 1	4	Bis-(3-aminopropyl) tetramethyl disiloxane	n=2/2, CO=4	n=2/2, IR=2	n=2/2, CR=3, CC=4	-	-	-	-	Category I	Review Data	SCNM	Human data not located
Category 1	4	Domiphen bromide	n=3/3, CO=4	-	-	-	X	-	-	Category I	R41	SCNM	Human data not located
Category 1	4	Granuform	n=1/3, CO=4	-	-	-	X	-	-	SCNM	Review Data	SCNM	A human eye irritant (27, 55)
Category 1	4	Hydroxyethyl acrylate	n=4/6, CO=4	n=6/6, IR=2 D14	-	-	-	-	-	Category I	R41	SCNM	Severe eye irritant (27)
Category 1	2	2-Hydroxyisobutyric acid ethylester	n=3/3, CO=3	-	-	-	-	-	-	SCNM	R41	SCNM	Human data not located
Category 1	4	2-Hydroxyisobutyric acid	n=3/3, CO=4	-	n=1/3, CR=3, n=3/3, CC=4	-	X	-	-	SCNM	R41	SCNM	Human data not located
Category 1	4	Imidazole	n=2/3, CO=4	n=2/3, I>1.5	-	X	X	X	X	Category I	R41	SCNM	Human data not located
Category 1	4	Cyclohexyl isocyanate	n=2/2, CO=4	-	-	-	-	X	-	Category I	R41	SCNM	Human data not located
Category 1	4	alpha-Ketoglutaric acid alpha	n=2/3, CO=4	-	-	-	-	-	-	SCNM	R41	SCNM	Human data not located
Category 1	4	Lactic Acid	n=3/3, CO=4	-	n=3/3, CR/CC=2 D14	-	X	-	-	Category I	R41	SCNM	Effect on the eye is similar to that of other acids of moderate strength, causing initial epithelial coagulation on the cornea and conjunctiva; more concentrated solutions can cause severe burns of the skin or eye (10, 20)
Category 1	1	Lauric acid	n=3/3, CO>1 D21	-	n=3/3, CR=1 D21	-	-	-	-	Category I	R41	SCNM	Human data not located
Category 1	4	4-Chloro-methanilic acid	n=1/1, CO=4	-	-	-	-	-	-	SCNM	Review Data	SCNM	Human data not located
Category 1	4	*n*-Acetyl-methionine	n=1/3, CO=4	-	-	-	X	-	-	SCNM	R41	SCNM	Human data not located
Category 1	4	2-Methylbutyric acid	n=2/6, CO=4	-	-	-	-	-	-	Category I	Review Data	SCNM	Human data not located
Category 1	4	Methylpentynol	n=1/1, CO=4	-	-	-	X	-	-	Category I	R41	SCNM	Human data not located
Category 1	4	Methylthioglycolate	n=1/3, CO=4	-	-	-	-	-	-	Category II	R36	SCNM	Human data not located
Category 1	4	1-Naphthaleneacetic acid (solid)	n=1/6, CO=4	-	-	X	X	X	-	Category I	R41	irritant	Has been reported to cause severe irritation to the human eye (17)
Category 1	4	*n*-Octylamine	n=4/4, CO=4	-	-	-	-	-	-	Category I	R41	SCNM	Human data not located
Category 1	0 (likely 4)	tetra-N-Octylammonium bromide	-	-	-	-	-	-	X	Category I	R41	SCNM	Human data not located
Category 1	1	Organofunctional Silane 45-49	n=2/6, CO>0 D21	n=2/6, IR>0 D21	n=2/6, CR>0 D21	-	-	-	-	Category I	R41	SCNM	Human data not located
Category 1	2	4-(1,1,3,3-Tetramethylbutyl)phenol	n=6/6, CO=3	n=6/6, IR=2	-	-	-	-	-	SCNM	R41	SCNM	A human eye irritant (23)
Category 1	4	Phosphorodicloridic acid, ethyl ester	n=6/6, CO=4	-	n=6/6, CR=3, CC=4 D21	-	-	-	-	Category I	R41	irritant	Vapor causes eye irritation; liquid causes sever burns to eye (27)
Category 1	4	Polyethylene glycol nonylphenyl ether (Surfonic HDL-1)	n=5/6, CO=4	-	-	-	-	-	-	Category I	R41	irritant	Human data not located
Category 1	4	Potassium laurate	n=1/3, CO=4 D14	-	-	-	-	-	-	Category I	R41	SCNM	Human data not located
Category 1	3	Promethazine hydrochloride	n=3/3, CO=3	n=3/3, IR=2	-	X	X	X	X	Category I	R41	SCNM	Severe eye irritant (17)
Category 1	1	Protectol PP	n=2/3, CO>0 D21	-	n=3/3, CR>0 D21	-	-	-	-	Category I	R41	SCNM	Severe eye irritant (17)
Category 1	4	Pyridine	n=1/3, CO=4	n=1/3, IR=2 D14	-	X	X	X	-	Category I	R41	SCNM	Causes irritation upon contact with the eyes (6, 20)
Category 1	3	Quinacrine	n=3/3, CO=3	n=3/3, IR=2	-	X	X	X	-	Category I	R41	SCNM	Direct contact with the eye causes yellow staining of the bulbar conjunctiva and cornea; in more severe reactions striate keratopathy or wrinkling of the posterior surface of cornea develops, presumably due to corneal edema (11)
Category 1	4	beta-Resorcylic acid	n=1/1, CO=4	-	-	-	-	-	-	SCNM	Review Data	SCNM	Human data not located

GHS Classification	NICEATM Category 1 SubClass [2]	Substance	Animal Exposure Summary for Category 1(H) Substances	Notes
Category 1	4	Diethylaminopropionitrile		
Category 1	4	Diethylethanolamine		
Category 1	4	1,3-Diiminobenz (f)-isoindoline		
Category 1	1	2,5-Dimethylhexanediol		
Category 1	4	Bis-(3-aminopropyl) tetramethyl disiloxane		
Category 1	4	Domiphen bromide		
Category 1	4	Granuform		
Category 1	4	Hydroxyethyl acrylate		
Category 1	2	2-Hydroxyisobutyric acid ethylester		
Category 1	4	2-Hydroxyisobutyric acid		
Category 1	4	Imidazole		
Category 1	4	Cyclohexyl isocyanate		
Category 1	4	alpha-Ketoglutaric acid alpha		
Category 1	4	Lactic Acid		
Category 1	1	Lauric acid		
Category 1	4	4-Chloro-methanilic acid		
Category 1	4	*n*-Acetyl-methionine		
Category 1	4	2-Methylbutyric acid		
Category 1	4	Methylpentynol		
Category 1	4	Methylthioglycolate		
Category 1	4	1-Naphthaleneacetic acid (solid)		
Category 1	4	*n*-Octylamine		
Category 1	0 (likely 4)	tetra-N-Octylammonium bromide		
Category 1	1	Organofunctional Silane 45-49		
Category 1	2	4-(1,1,3,3-Tetramethylbutyl)phenol		
Category 1	4	Phosphorodicloridic acid, ethyl ester		
Category 1	4	Polyethylene glycol nonylphenyl ether (Surfonic HDL-1)		
Category 1	4	Potassium laurate		
Category 1	3	Promethazine hydrochloride		
Category 1	1	Protectol PP		
Category 1	4	Pyridine		
Category 1	3	Quinacrine		
Category 1	4	beta-Resorcylic acid		

GHS Classification	NICEATM Category 1 SubClass [2]	Substance	CASRN	In Vivo Data Source	Substance Source	Commercial Availability	Chemical Class	Product Class	Conc. Tested	Amount Tested[1]	Purity	MW	pH	Dermal Corrosivity	# of Animals Tested	Water Solubility	Log Kow	Color	Physical Form Tested	MMAS score
Category 1	4	Sodium hydrogen sulfate	7681-38-1	ZEBET	n.a.	Sigma-Aldrich Corp.	Salt (inorganic)	Cleaning Agent, Laboratory Chemical, Pesticide	n.a.	0.1 mL or 100 mg	n.a.	120.1	?	?	1	?	?	?	solid	8.0
Category 1	4	Sodium hydroxide	1310-73-2	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Alkali	Caustic Agent, Chemical Intermediate, Industrial Chemical, Pharmaceutical Intermediate, Veterinary Chemical	10%	0.1 mL	Reagent Grade	40.0	12.7	R35 (5%)	1	soluble (1 g/0.9 mL)	"virtually 0"	?	liquid	108.0
Category 1	4	Sodium oxalate	62-76-0	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Acid (organic) [carboxylic acid]	Industrial Chemical, Laboratory Chemical	100%	100 mg	>99%	134.0	9.4	corrosive	3	soluble (37 g/L)	n.a.	?	solid	61.3
Category 1	1	Sodium perborate tetrahydrate	10486-00-7	ECETOC	Dupont Corp.	Sigma-Aldrich Corp.	Boron Compound, Salt (inorganic)	Cleaning Agent	100%	60 mg	98.6%	153.9	10.0	noncorrosive	6	n.a.	n.a.	?	solid	30.5
Category 1	4	Di(2-ethylhexyl) sodium sulfosuccinate	98-09-9	NIHS-Ohno	Japanese Cosmetic Industry Assn.	Sigma-Aldrich Corp.	Ester, Salt (organic), Sulfur Compound (organic)	Adjuvant, Cleaner, Solubilizer, Wetting Agent	10%	0.1 mL	n.a.	444.6	6.5	noncorrosive	3	soluble (15 g/L)	n.a.	?	liquid	57.0
Category 1	3	Dibenzoyl-L-tartaric acid	2743-38-6	ECETOC	n.a.	Sigma-Aldrich Corp.	Acid (organic) [carboxylic acid], Ester	Chemical Intermediate	100%	100 mg	98%	358.3	n.a.	noncorrosive	3	slightly soluble	n.a.	?	solid	36.7
Category 1	4	Tetraethylene glycol diacrylate	17831-71-9	TSCA	Rhone-Poulenc, Inc.	Sigma-Aldrich Corp.	Ether, Nitro Compound	Chemical Intermediate, Industrial Chemical	100%	0.1 mL	n.a.	302.3	?	?	6	?	?	?	liquid	103.3
Category 1	4	Tetrahydrofuran	109-99-9	TSCA	International Specialty Products Co.	Sigma-Aldrich Corp.	Ether, Heterocyclic Compound	Chemical Intermediate, Industrial Chemical, Pharmaceutical Intermediate, Solvent	100%	0.1 mL	n.a.	72.1	?	?	6	?	?	?	liquid	31.2
Category 1	4	N,N,N',N`-Tetramethylhexanediamine	111-18-2	TSCA	Union Carbide Corp.	Sigma-Aldrich Corp.	Amine	Anti-Infective, Industrial Chemical, Laboratory Chemical	100%	0.005 mL	n.a.	172.3	?	?	6	?	?	?	liquid	96.0
Category 1	0 (likely 4)	2-Nitro-4-thiocyanoaniline	54029-45-7	GSK	n.a.	Sigma-Aldrich Corp.	Amine, Nitro Compound, Sulfur Compound (organic)	Industrial Chemical	100%	0.1 mL or 100 mg	n.a.	195.2	?	?	1	?	?	?	solid	63.0
Category 1	1	TNO-35 (Propyl lactate)	616-09-1	TNO-Prinsen	n.a.	Cook Aromatics Ltd. (Bulk)	Alcohol, Ester	Cleaning Agent, Food Additive	n.a.	0.1 mL or 100 mg	n.a.	132.2	?	?	1	?	?	?	solid	63.0
Category 1	4	1,2,4-Triazole, sodium salt	41253-21-8	ECETOC	Elf Atochem, Inc.	Sigma-Aldrich Corp.	Heterocyclic Compound, Salt (organic)	Anti-Fungal	100%	100 mg	99%	91.1	n.a.	noncorrosive	1	soluble	n.a.	brown	solid	104.0
Category 1	4	Trichloroacetic acid	76-03-9	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Acid (organic) [carboxylic acid]	Caustic Agent, Herbicide	30%	0.1 mL	Reagent Grade	163.4	0.7	R34 (0.6N); R35 (undiluted)	1	soluble (10 g/mL)	1.33	?	liquid	106.0
Category 1	4	Trichloroacetyl chloride	76-02-8	TSCA	Rhone-Poulenc, Inc.	Sigma-Aldrich Corp.	Acyl Halide	Chemical Intermediate, Industrial Chemical	n.a.	0.1 mL	n.a.	163.4	?	?	4	?	?	?	liquid	91.0
Category 1	4	Triton X-100	9002-93-1	TSCA	Union Carbide Corp.	Sigma-Aldrich Corp.	Ether	Surfactant (nonionic)	100%	0.1 mL	n.a.	250.4	n.a.	noncorrosive	6	soluble	n.a.	colorless	liquid	65.8
Category 1(H)	-	Ammonia	7664-41-7	-	-	Sigma-Aldrich Corp.	Alkali	Anti-Fungal, Chemical Intermediate, Cleaning Agent, Fertilizer, Herbicide, Industrial Chemical, Refrigerant	-	-	-	17.0	-	-	-	n.a.	n.a.	?	Liquid	-
Category 1(H)	-	Chloroform	67-66-3	-	n.a.	Sigma-Aldrich Corp.	Hydrocarbon (acyclic)	Anesthetic, Chemical Intermediate, Cleaning Agent, Industrial Chemical, Pharmaceutical Intermediate, Solvent	-	-	-	119.4	-	-	-	n.a.	n.a.	?	liquid	-
Category 1(H)	-	Lime	1305-78-8	-	-	Sigma-Aldrich Corp.	Salt (inorganic)	Building Material, Chemical Intermediate, Cleaning Agent, Fertilizer, Industrial Chemical	-	-	-	56.1	-	-	-	n.a.	n.a.	white to grayish	solid	-
Category 1(H)	-	Magnesium hydroxide	12141-11-6	-	-	Sigma-Aldrich Corp.	Salt (inorganic)	Chemical Intermediate, Flame Retardant, Industrial Chemical, Pharmaceutical, Veterinary Agent	-	-	-	42.3	-	-	-	n.a.	n.a.	?	solid	-
Category 1(H)	-	Nitric acid	7697-37-2	-	-	Sigma-Aldrich Corp.	Acid, Salt (inorganic)	Chemical Intermediate, Industrial Chemical, Laboratory Reagent, Pharmaceutical Intermediate	-	-	-	63.0	-	-	-	n.a.	n.a.	colorless to yellow	liquid	-
Category 1(H)	-	Potassium hydroxide	1310-58-3	-	-	Sigma-Aldrich Corp.	Alkali, Salt (inorganic)	Chemical Intermediate, Cleaning Agent, Fertilizer, Food Additive, Industrial Chemical, Veterinary Chemical	-	-	-	56.1	-	-	-	n.a.	n.a.	?	solid	-

GHS Classification	NICEATM Category 1 SubClass [2]	Substance	Corneal score	Irital score	Conjunctival score	Tested in BCOP	Tested in HET-CAM	Tested in ICE	Tested in IRE	EPA Classification	EU Classification	FHSA Classification	Human Exposure Summary
Category 1	4	Sodium hydrogen sulfate	n=1/1, CO=4	-	-	-	-	-	-	SCNM	Review Data	SCNM	Human data not located
Category 1	4	Sodium hydroxide	n=1/1, CO=4	n=1/1, IR=2 D21	n=1/1, CR/CC=3 D21	X	X	X	X	Category I	R41	SCNM	Contact with the eyes causes disintegration and sloughing of conjunctival and corneal epithelia, corneal opacification, marked edema, and ulceration; after 7 to 13 days either gradual recovery begins, or there is progression of ulceration and corneal opacification. Opacification may be so severe that iris markings are not discernable. Complications of severe eye burns are symblepharon, with overgrowth of the cornea by a vascularized membrane, progressive or recurrent corneal ulceration, permanent corneal opacification, necrosis of the bulbar conjunctiva, blanched and necrotic corneal cul-de-sac, and blindness. Eye contact; Levels of toxic effect: (1) Irritation. (2) Conjunctivitis, corneal burns. (3) Photophobia. (4) Disintegration and sloughing of conjunctival and corneal epithelium. (5) Corneal edema, ulceration, and opacification. (6) Symblepharon. (7) Overgrowth of the cornea by a vascularized membrane. (8) Permanent corneal opacification. (11, 18)
Category 1	4	Sodium oxalate	n=1/3, CO=4	n=1/3, IR=2 D14	-	X	X	X	-	Category I	R41	SCNM	Human data not located
Category 1	1	Sodium perborate tetrahydrate	n=4/6, CO>1 D21	-	-	X	X	X	-	Category I	R41	SCNM	Very few cases of eye irritation were observed (26)
Category 1	4	Di(2-ethylhexyl) sodium sulfosuccinate	n=1/3, CO=4	-	-	-	-	-	-	SCNM	R41	SCNM	In ophthalmological formulations, concentrations of greater than 0.1% may cause conjunctival irritation; repeated use of such drugs may delay healing of corneal lesions. (7)
Category 1	3	Dibenzoyl-L-tartaric acid	n=3/3, CO=3	-	-	X	X	X	-	Category I	R41	SCNM	Human data not located
Category 1	4	Tetraethylene glycol diacrylate	n=5/6, CO=4	n=6/6, IR=2 D14	-	-	-	-	-	Category I	R41	irritant	Human data not located
Category 1	4	Tetrahydrofuran	n=2/6, CO=4	-	-	-	-	-	-	SCNM	Review Data	irritant	A human eye irritant (27)
Category 1	4	N,N,N',N`-Tetramethylhexanediamine	n=6/6, CO=4	-	-	-	-	-	-	Category I	R41	irritant	Human data not located
Category 1	0 (likely 4)	2-Nitro-4-thiocyanoaniline	-	-	-	-	-	-	X	Category I	R41	SCNM	Human data not located
Category 1	1	TNO-35 (Propyl lactate)	n=1/1, CO>0 D21	n=1/1, IR>0 D21	n=1/1, CC>0 D21	-	-	X	-	Category I	R41	SCNM	Human data not located
Category 1	4	1,2,4-Triazole, sodium salt	n=1/1, CO=4	n=1/1, IR=2	-	-	-	-	-	Category I	R41	SCNM	Human data not located
Category 1	4	Trichloroacetic acid	n=1/1, CO=4	n=1/1, IR=2 D21	n=1/1, CR/CC=2 D21	X	X	X	X	Category I	R41	SCNM	Reported to be irritating and very painful to the human eye (15, 19)
Category 1	4	Trichloroacetyl chloride	n=4/4, CO=4	-	-	-	-	-	-	Category I	R41	SCNM	Reported to be irritating and very painful to the human eye (15, 19)
Category 1	4	Triton X-100	n=2/6, CO=4	-	-	-	-	-	-	SCNM	Review Data	irritant	Human data not located
Category 1(H)	-	Ammonia	-	-	-	-	-	-	-	-	-	-	Ammonia vapors cause irritation of eyes, with high concentrations causing conjunctivitis. Corneal edema and semi-dilated, fixed pupils are typical. Ammonia has a greater tendency than other alkalies to penetrate and damage the iris, and to cause cataract. In severe burns, iritis may be accompanied by hypopyon or hemorrhages, extensive loss of pigment and severe glaucoma. Exposure to high gas concentrations of ammonia may cause temporary blindness and severe eye damage. Direct contact of the eyes with liquid anhydrous ammonia will produce serious eye burns. 2 cases of ocular injuries with a rise in intraocular pressure and cataract formation after ammonia of unknown concentration had been squirted into the victims' eyes during robberies were reported. In both cases, the more severely affected eyes showed marked injection and edema of the conjunctiva; diffuse corneal damage; semi-dilated, oval, and fixed pupils; and a marked increase of the intraocular pressure, which persisted and was controlled only with drugs. Glaucoma was observed to be associated with an open angle.
Category 1(H)	-	Chloroform	-	-	-	-	-	-	-	-	-	-	Splash of liquid chloroform in the eyes causes immediate burning pain, tearing and reddening of the conjunctiva. The corneal corneal epithelium corneal epithelium is usually injured and partially lost. Exposure to liquid or gaseous chloroform causes keratitis, corneal opacities, and ulceration (11, 37, 38, 39, 40, 41)
Category 1(H)	-	Lime	-	-	-	-	-	-	-	-	-	-	The major complaints of workers exposed to lime consist of eye and skin irritation. Calcium oxide dust irritates the eyes primarily because of its alkalinity. Exposure to lime has been reported to cause conjunctival necrosis, symblepharon, keratitis, corneal necrosis, corneal opacities, corneal scarring, corneal ulceration, corneal vascularization and iritis (1,5,44)
Category 1(H)	-	Magnesium hydroxide	-	-	-	-	-	-	-	-	-	-	Human ocular exposure to magnesium hydroxide produces combined thermal and alkali injury. Reported effects of exposure to magnesium hydroxide are conjunctival necrosis, symblepharon, keratitis, corneal necrosis, corneal opacities, corneal scarring, corneal ulceration, corneal vascularization and iritis (44, 45)
Category 1(H)	-	Nitric acid	-	-	-	-	-	-	-	-	-	-	Contact of nitric acid with the eye causes immediate opacification of the corneal and conjunctival epithelium. It also causes symblepharon, shrinkage of the globe, keratitis, corneal ulceration and corneal and conjunctival necrosis (11, 17, 46)
Category 1(H)	-	Potassium hydroxide	-	-	-	-	-	-	-	-	-	-	Eye contact with concentrated alkalis such as potassium hydroxide causes conjunctival edema and corneal destruction. Potassium hydroxide (caustic potash) is one of the strongest alkalies. It is extremely corrosive, and many reports have been made of devastating damage of the eye from contact with either the solid or solutions of potassium hydroxide. The type of injury is essentially the same as that produced by sodium hydroxide and other strong alkalies, and includes iritis, conjunctival necrosis, symblepharon, keratitis, corneal necrosis, opacities, scarring, ulceration and vascularization (1, 11, 27, 45, 47)

GHS Classification	NICEATM Category 1 SubClass [2]	Substance	Animal Exposure Summary for Category 1(H) Substances	Notes
Category 1	4	Sodium hydrogen sulfate		
Category 1	4	Sodium hydroxide		
Category 1	4	Sodium oxalate		
Category 1	1	Sodium perborate tetrahydrate		
Category 1	4	Di(2-ethylhexyl) sodium sulfosuccinate		
Category 1	3	Dibenzoyl-L-tartaric acid		
Category 1	4	Tetraethylene glycol diacrylate		
Category 1	4	Tetrahydrofuran		
Category 1	4	N,N,N',N`-Tetramethylhexanediamine		
Category 1	0 (likely 4)	2-Nitro-4-thiocyanoaniline		
Category 1	1	TNO-35 (Propyl lactate)		
Category 1	4	1,2,4-Triazole, sodium salt		
Category 1	4	Trichloroacetic acid		
Category 1	4	Trichloroacetyl chloride		
Category 1	4	Triton X-100		
Category 1(H)	-	Ammonia	Corneal opacity was observed in rabbits following continuous exposure to ammonia vapor (470 mg/M3). Swine exposed to ammonia for 2 to 6 weeks at 100 PPM in air developed conjunctival irritation. Continuous exposure of rabbits to 470 mg/cu m for several weeks produced opacities over ¼ to ½ of the cornea. Even fairly low airborne concentrations of ammonia produce rapid eye and nose irritation. Contact with concentrated ammonia solutions, such as some industrial cleaners, can cause serious corrosive injury (6, 11, 56).	
Category 1(H)	-	Chloroform	Liquid chloroform produced slight injury to the eyes which took over a week to heal. (62)	
Category 1(H)	-	Lime	Animal Data Not Located	
Category 1(H)	-	Magnesium hydroxide	Milk of magnesia applied to rabbit eyes twice a day for three or four days caused damage to the corneal epithelium, demonstrable by staining with fluorescein. After the applications were discontinued, the corneas returned to normal in two or three days. (10)	
Category 1(H)	-	Nitric acid	Animal Data Not Located	
Category 1(H)	-	Potassium hydroxide	Animal Data Not Located	

GHS Classification	NICEATM Category 1 SubClass [2]	Substance	CASRN	In Vivo Data Source	Substance Source	Commercial Availability	Chemical Class	Product Class	Conc. Tested	Amount Tested[1]	Purity	MW	pH	Dermal Corrosivity	# of Animals Tested	Water Solubility	Log Kow	Color	Physical Form Tested	MMAS score
Category 1(H)	-	Silver nitrate	7761-88-8	-	-	Sigma-Aldrich Corp.	Nitrate, Salt (inorganic)	Anti-Infective, Chemical Intermediate, Dye, Industrial Chemical, Laboratory Chemical, Pharmaceutical, Pharmaceutical Intermediate	-	-	-	169.9	-	-	-	n.a.	n.a.	white to grayish-black	liquid	-
Category 1(H)	-	Sodium hydrogen difluoride	1333-83-1	-	-	Sigma-Aldrich Corp.	Salt (inorganic)	Anti-Infective, Cleaning Agent, Industrial Chemical, Preservative	-	-	-	62.0	-	-	-	n.a.	n.a.	?	liquid	-
Category 1(H)	-	Sulfuric acid	7664-93-9	-	-	Sigma-Aldrich Corp.	Acid (inorganic), Sulfur Compound (inorganic)	Battery Acid, Chemical Intermediate, Cleaning Agent, Fertilizer, Food Additive, Industrial Chemical, Laboratory Chemical	-	-	-	98.1	-	-	-	n.a.	n.a.	?	liquid	-
Category 1(H)	-	Zinc chloride	7646-85-7	-	-	Sigma-Aldrich Corp.	Salt (inorganic)	Anti-Infective, Flame Retardant, Herbicide, Industrial Chemical. Pesticide, Preservative	-	-	-	136.3	-	-	-	n.a.	n.a.	?	solid	-
Category 2A	-	Methyl acetate	79-20-9	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Ester	Chemical Intermediate, Food Additive, Herbicide, Laboratory Chemical,Solvent	100%	0.1 mL	98%	74.1	n.a.	?	4	243 g/L	0.18	colorless	liquid	39.5
Category 2A	-	Acetone	67-64-1	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Ketone	Chemical Intermediate, Cleaning Agent, Industrial Chemical, Pharmaceutical Intermediate, Preservative, Solvent	100%	0.1 mL	99%	58.1	5.3	noncorrosive	4	soluble	-0.24	?	liquid	65.8
Category 2A	-	Benzotrichloride	98-07-7	TSCA	Velsicol Chemical Corp.	Sigma-Aldrich Corp.	Hydrocarbon (cyclic)	Chemical Intermediate	100%	0.1 mL	n.a.	195.5	?	?	6	?	?	?	liquid	11.7
Category 2A	-	gamma-Butyrolactone	96-48-0	ECETOC	Shell Oil Co. of California	Sigma-Aldrich Corp.	Heterocyclic Compound, Lactone	Solvent	100%	0.1 mL	>99%	86.1	4.5	noncorrosive	6	miscible	-0.57	colorless	liquid	43.0
Category 2A	-	4-Carboxybenzaldehyde	619-66-9	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Aldehyde, Acid (organic) [carboxylic acid]	Industrial Chemical	100%	0.1 mL	>95%	150.1	3.1	noncorrosive	3	Very soluble	n.a.	?	liquid	50.3
Category 2A	-	Cetylpyridinium bromide	140-72-7	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Onium Compound, Heterocyclic Compound	Anti-Infective; Laboratory Chemical; Surfactant (cationic)	1%	0.1 mL	99%	384.4	6.4	noncorrosive	6	soluble (5 g/L)	1.83 (100%)	faintly beige	liquid	36.0
Category 2A	-	Deoxycholic acid sodium salt	302-95-4	LNS	n.a.	Sigma-Aldrich Corp.	Alcohol, Acid (organic) [carboxylic acid], Polycyclic Compound, Salt (organic)	Anti-Infective, Laboratory Chemical, Solvent	10%	0.1 mL	n.a.	414.6	?	?	3	?	?	?	liquid	38.0
Category 2A	-	Dibenzyl phosphate	1623-08-1	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Ester, Organophosphorus Compound	Pesticide	100%	100 mg	99%	278.2	2.4	noncorrosive	3	n.a.	n.a.	?	solid	30.0
Category 2A	-	2,6-Dichlorobenzoyl chloride	4659-45-4	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Acyl Halide	Anti-Fungal, Anti-Infective	100%	0.1 mL	99%	209.5	2.5	R34	6	insoluble	2.57	slight yellow	liquid	23.8
Category 2A	-	2-Ethyl-1-hexanol	104-76-7	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Alcohol	Solvent	100%	0.1 mL	99%	130.2	4.8	noncorrosive	4	slightly soluble	2.82	?	liquid	51.3
Category 2A	-	*n*-Hexanol	111-27-3	ECETOC	Kodak Co.	Sigma-Aldrich Corp.	Alcohol	Solvent	100%	0.1 mL	98%	102.2	5.5	noncorrosive	4	soluble (5.8 g/L)	2.03	?	liquid	64.8
Category 2A	-	Methyl ethyl ketone	78-93-3	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Ketone	Solvent	100%	0.1 mL	99%	72.1	5.5	noncorrosive	4	soluble (353 g/L)	0.29	colorless	liquid	50.0
Category 2A	-	Methyl cyanoacetate	105-34-0	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Ester, Nitrile	Chemical Intermediate	100%	0.1 mL	99%	99.1	5.7	noncorrosive	3	soluble (54 g/L)	n.a.	light yellow	liquid	27.7
Category 2A	-	*n*-Octanol	111-87-5	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Alcohol	Solvent	100%	0.1 mL	>99%	130.2	6.1	noncorrosive	3	insoluble (540 mg/L)	3.00	?	liquid	41.0
Category 2A	-	Triton X-100	9002-93-1	ECETOC	n.a.	Sigma-Aldrich Corp.	Ether	Surfactant (nonionic)	5%	0.1 mL	98%	250.4	n.a.	noncorrosive	6	soluble	n.a.	colorless	liquid	33.8
Category 2B	-	Ethyl-2-methyl acetoacetate	609-14-3	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Ester, Ketone	Chemical Intermediate	100%	0.1 mL	97%	144.2	7.5	noncorrosive	3	Slightly soluble	n.a.	?	liquid	18.0
Category 2B	-	Ammonium nitrate	6484-52-2	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Onium Compound, Nitrate, Salt (organic)	Industrial Chemical	100%	100 mg	99.999%	80.0	4.8	noncorrosive	3	soluble (1920 g/L)	n.a.	white, hot concentrate	solid	18.3
Category 2B	-	Butyl Dipropasol Solvent	29911-27-1	TSCA	Union Carbide Corp.	Sigma-Aldrich Corp.	Alcohol, Ether	Solvent	100%	0.1 mL	99%	176.3	?	?	6	?	?	?	liquid	24.7
Category 2B	-	3-Chloropropionitrile	542-76-7	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Nitrile	Chemical Intermediate, Pharmaceutical Intermediate	100%	0.1 mL	99.9%	89.5	n.a.	noncorrosive	3	soluble (45 g/100 mL)	0.18	?	liquid	13.7
Category 2B	-	Cyclopentanol	96-41-3	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Alcohol	Pharmaceutical Intermediate	100%	0.1 mL	99%	86.1	n.a.	noncorrosive	3	slightly soluble	0.71	colorless	liquid	21.7
Category 2B	-	3,3-Dithiodipropionic acid	1119-62-6	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Acid (organic) [carboxylic acid], Organosilicon Compound	Chemical Intermediate, Laboratory Chemical	100%	100 mg	99%	210.3	pKa 3.94	R34	3	Very soluble	1.38	?	solid	31.7
Category 2B	-	Hexyl cinnamic aldehyde	101-86-0	TSCA	Confidential	International Flavors and Frangrances, Inc. (Bulk)	Aldehyde	Cosmetic Ingredient, Food Additive, Perfume	12.5% in Alcohol	0.1 mL	n.a.	216.3	?	?	3	?	?	?	liquid	21.3

GHS Classification	NICEATM Category 1 SubClass [2]	Substance	Corneal score	Irital score	Conjunctival score	Tested in BCOP	Tested in HET-CAM	Tested in ICE	Tested in IRE	EPA Classification	EU Classification	FHSA Classification	Human Exposure Summary
Category 1(H)	-	Silver nitrate	-	-	-	-	-	-	-	-	-	-	Solid silver nitrate, known as lunar caustic, can be very injurious to the eye. Particles of solid silver nitrate in the conjunctival sac have been known to cause severe inflammation with deep injury to surrounding tissues, scarring, and symblepharon. In a most unusual case of severe injury from solid nitrate the cornea became dark brown, and the lens became cataractous. Concentration solutions of silver nitrate from 5%-50% applied by mistake or accidentally splashed in the eye have caused severe injury, with permanent corneal opacification in some cases. Solutions of high concentration cause rapid appearance of edema of the conjunctiva and lids, with bloody purulent discharge from the conjunctival sac. Opacification of the cornea may result and may be permanent (5, 11, 13, 48, 49, 50)
Category 1(H)	-	Sodium hydrogen difluoride	-	-	-	-	-	-	-	-	-	-	Exposure to concentrated sodium hydrogen difluoride has caused corneal necrosis, opacification, scarring, ulceration, vascularization (11, 23)
Category 1(H)	-	Sulfuric acid	-	-	-	-	-	-	-	-	-	-	At aerosol concentrations of 1.1 to 2.1 mg/cu m, 40% of human subjects noticed irritation of the eyes. At 2.4 to 6.0 mg/cu m, all subjects experienced eye irritation. Contact of concentrated sulfuric acid with the eye may cause total loss of vision in addition to corneal necrosis, opacification, scarring, ulceration and vascularization. (1, 44, 51, 52)
Category 1(H)	-	Zinc chloride	-	-	-	-	-	-	-	-	-	-	An unstated concentration of zinc chloride solution splashed in 1 eye of a workman at first only caused redness and discomfort, but within 6 days grayish corneal opacities had developed, with irregularity of the overlying epithelium. A patient who had an eye burned with one drop of 50% zinc chloride solution there was immediate severe pain, erosion of the corneal epithelium, corneal vascularization, severe iritis and iridial hemorrhage (11, 27, 54)
Category 2A	-	Methyl acetate	-	-	-	X	X	X	X	Category II	R36	SCNM	Cases of slight poisoning under industrial conditions were manifested by eye burns and lacrimation. One case of blindness has been reported. (1, 13, 18)
Category 2A	-	Acetone	-	-	-	X	X	X	X	Category II	R36	SCNM	Acute exposures of humans to atmospheric concentrations have been reported to produce eye irritation. Exposure of15 minutes to aerosol concentrations of 1660 ppm also reportedly causes eye irritation. Direct contact with the eyes may produce irritation and corneal imjury. (14, 16, 30, 32)
Category 2A	-	Benzotrichloride	-	-	-	-	-	-	-	Category II	nonirritant	irritant	Human data not located
Category 2A	-	gamma-Butyrolactone	-	-	-	X	X	X	X	Category II	R36	irritant	Human data not located
Category 2A	-	4-Carboxybenzaldehyde	-	-	-	X	X	X	-	Category II	R36	SCNM	Human data not located
Category 2A	-	Cetylpyridinium bromide	-	-	-	-	X	-	X	SCNM	R41	SCNM	Human data not located
Category 2A	-	Deoxycholic acid sodium salt	-	-	-	X	-	-	-	Category II	R36	SCNM	Human data not located
Category 2A	-	Dibenzyl phosphate	-	-	-	X	-	X	-	Category II	R36	SCNM	Human data not located
Category 2A	-	2,6-Dichlorobenzoyl chloride	-	-	-	X	X	X	-	Category II	R36	irritant	Human data not located
Category 2A	-	2-Ethyl-1-hexanol	-	-	-	X	X	X	-	Category II	R36	SCNM	Irritation of eyes from vapor or liquid (8, 9)
Category 2A	-	*n*-Hexanol	-	-	-	X	X	X	X	Category II	R36	SCNM	Reported to cause eye burns (27)
Category 2A	-	Methyl ethyl ketone	-	-	-	X	X	X	X	Category III	R36	SCNM	High atmospheric concentrations are irritating to the eyes. May produce painful irritation and corneal injury if splashed in the eyes. Workers exposed to 33,000 and100,000 ppm in air reported intolerable irritation of the eyes. Implicated as the cause of retrobulbar neuritis in one patient. A workman splashed his eye accidentally with methyl ethyl ketone, but the next day had only slight conjunctival hyperemia and no residual corneal injury. (2, 5, 11, 20)
Category 2A	-	Methyl cyanoacetate	-	-	-	X	X	X	-	Category II	R36	SCNM	Human data not located
Category 2A	-	*n*-Octanol	-	-	-	X	X	X	X	Category II	R36	SCNM	Has caused injury of the corneal epithelium, with recovery in 48 hours (11)
Category 2A	-	Triton X-100	-	-	-	-	X	X	X	Category I	R41	SCNM	Human data not located
Category 2B	-	Ethyl-2-methyl acetoacetate	-	-	-	X	X	X	X	Category III	nonirritant	SCNM	Human data not located
Category 2B	-	Ammonium nitrate	-	-	-	X	X	X	X	Category III	R36	SCNM	Human data not located
Category 2B	-	Butyl Dipropasol Solvent	-	-	-	-	-	-	-	Category III	nonirritant	irritant	Human data not located
Category 2B	-	3-Chloropropionitrile	-	-	-	-	-	-	-	Category III	nonirritant	SCNM	Human data not located
Category 2B	-	Cyclopentanol	-	-	-	-	-	X	-	Category II	R36	SCNM	Human data not located
Category 2B	-	3,3-Dithiodipropionic acid	-	-	-	-	-	-	-	Category II	nonirritant	SCNM	Human data not located
Category 2B	-	Hexyl cinnamic aldehyde	-	-	-	-	-	-	-	Category III	nonirritant	SCNM	Human data not located

GHS Classification	NICEATM Category 1 SubClass [2]	Substance	Animal Exposure Summary for Category 1(H) Substances	Notes
Category 1(H)	-	Silver nitrate	Treatment of rat eyes with a single 3-drops 0.66% silver nitrate soln caused deposition of silver in the cornea, conjunctiva, subconjunctiva, Bowman's layer, reticular fibers of the corneal stroma, Descemete's membrane and the posterior corneal epithelium. Morphologic evolution of the early events of corneal vascularization in the rat cornea induced by silver nitrate cautery was followed by light and electron microscopy. An initial acute inflammatory response occurred within the first 6 hours after cautery as evidenced by vascular dilation, diapedesis of leukocytes, and an increased vascular permeability, as manifested by distended lymphatics and the presence of extravascular fibrin. At 33 hours after cautery, the first new vessels were observed as sprouts from the capillary arcade and postcapillary venules. Adult male Sprague-Dawley rats were anesthetized with halothane gas, and the centers of their right corneas treated with a silver nitrate applicator stick (75% silver nitrate, 25% potassium nitrate) to produce a discrete	
Category 1(H)	-	Sodium hydrogen difluoride	This substance causes the formation of hydrofluoric acid when exposed to mucous membranes. Ocular toxicity is caused by hydrofluoric acid. In inhalation studies in rabbits and guinea pigs, a concentration of 50 MG/CU M, hydrogen fluoride induced discharge from the eyes. Experimental splash burns of hydrofluoric acid into the eyes of rabbits have shown a 20% solution to cause immediate damage with total corneal opacification with conjunctival ischemia, and with corneal stromal edema within an hour, followed by necrosis of anterior ocular structures. An 8% solution produced ischemia and corneal stromal edema persisting for 40-65 days, accompanied by corneal vascularization. Even a 2% a solution caused mild persistent stromal edema and vascularization.. (6, 11)	
Category 1(H)	-	Sulfuric acid	Animals in the vicinity of potato fields sprayed with sulfuric acid during spraying, or gaining access to such fields soon after spraying, may develop eye burns from the spray. (63)	
Category 1(H)	-	Zinc chloride	10% zinc chloride was classified as a mild or non-irritant when test in the rabbit eye. A 50% solution of zinc chloride applied repeatedly during 1 day to 1 eye of an albino rabbit caused immediate corneal opacity. 6 days after exposure, the eye had become very hard, with extensive hemorrhage in the anterior segment, accompanied by infiltration with inflammatory cells, loss of corneal endothelium and clouding of the anterior portion of the lens. (11, 61)	
Category 2A	-	Methyl acetate		
Category 2A	-	Acetone		
Category 2A	-	Benzotrichloride		
Category 2A	-	gamma-Butyrolactone		
Category 2A	-	4-Carboxybenzaldehyde		
Category 2A	-	Cetylpyridinium bromide		
Category 2A	-	Deoxycholic acid sodium salt		
Category 2A	-	Dibenzyl phosphate		
Category 2A	-	2,6-Dichlorobenzoyl chloride		
Category 2A	-	2-Ethyl-1-hexanol		
Category 2A	-	*n*-Hexanol		
Category 2A	-	Methyl ethyl ketone		
Category 2A	-	Methyl cyanoacetate		
Category 2A	-	*n*-Octanol		
Category 2A	-	Triton X-100		
Category 2B	-	Ethyl-2-methyl acetoacetate		
Category 2B	-	Ammonium nitrate		
Category 2B	-	Butyl Dipropasol Solvent		
Category 2B	-	3-Chloropropionitrile		
Category 2B	-	Cyclopentanol		
Category 2B	-	3,3-Dithiodipropionic acid		
Category 2B	-	Hexyl cinnamic aldehyde		

GHS Classification	NICEATM Category 1 SubClass [2]	Substance	CASRN	In Vivo Data Source	Substance Source	Commercial Availability	Chemical Class	Product Class	Conc. Tested	Amount Tested[1]	Purity	MW	pH	Dermal Corrosivity	# of Animals Tested	Water Solubility	Log Kow	Color	Physical Form Tested	MMAS score
Category 2B	-	N-Laurylsarcosine sodium salt	137-16-6	LNS	n.a.	Sigma-Aldrich Corp.	Amide, Amine, Salt (organic)	Cleaning Agent, Detergent, Laboratory Chemical, Surfactant (anionic)	10%	0.1 mL	n.a.	293.4	?	?	3	?	?	?	liquid	31.0
Category 2B	-	Maneb (solid)	12427-38-2	ECETOC	US EPA	Sigma-Aldrich Corp.	Amine, Salt (organic), Urea	Pesticide	100%	100 mg	90% (approx)	265.3	8.4	noncorrosive	6	Moderately soluble	n.a.	?	solid	14.3
Category 2B	-	2-Methyl-1-pentanol	105-30-6	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Alcohol	Solvent	100%	0.1 mL	99%	102.2	n.a.	noncorrosive	3	soluble (6 g/L)	1.75	?	liquid	13.0
Category 2B	-	Propasol Solvent P	1569-01-3	TSCA	Union Carbide Corp.	Sigma-Aldrich Corp.	Alcohol	Solvent	100%	0.1 mL	n.a.	118.2	?	?	6	?	?	?	liquid	31.2
Category 2B	-	6-Methyl purine	2004-03-7	TSCA	Monsanto Co.	Sigma-Aldrich Corp.	Heterocyclic Compound	Laboratory Chemical, Pharmaceutical Intermediate	100%	0.1 mL	n.a.	134.1	-	-	6	?	?	?	liquid	48.7
Category 2B	-	2,6-Dichloro-5-fluoro-beta-oxo-3-pyridinepropanoate	96568-04-6	GSK	n.a.	Sigma-Aldrich Corp.	Ester, Heterocyclic Compound, Ketone	Industrial Chemical, Pharmaceutical Intermediate	100%	0.1 mL or 100 mg	n.a.	280.1	?	?	3	?	?	white	solid	21.3
Category 2B	-	Triton X-100	9002-93-1	ECETOC	n.a.	Sigma-Aldrich Corp.	Ether	Surfactant (nonionic)	5%	0.1 mL	98%	250.4	n.a.	noncorrosive	6	soluble	n.a.	colorless	liquid	33.8
nonirritant	-	iso-Octyl acrylate	29590-42-9	ECETOC	Elf Atochem, Inc.	Sigma-Aldrich Corp.	Ester	Building Material	100%	0.1 mL	>99%	184.3	n.a.	noncorrosive	3	n.a.	n.a.	?	liquid	5.3
nonirritant	-	tetra-Aminopyrimidine sulfate	5392-28-9	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Amine, Heterocyclic Compound, Salt (organic)	Chemical Intermediate	100%	100 mg	97%	238.2	n.a.	noncorrosive	3	slightly soluble	n.a.	?	solid	10.3
nonirritant	-	2,4-Difluoronitrobenzene	446-35-5	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Hydrocarbon (halogenated)	Pesticide, Pharmaceutical Intermediate	100%	0.1 mL	99%	159.1	n.a.	noncorrosive	6	n.a.	n.a.	n.a.	solid	4.7
nonirritant	-	n,n-Dimethylguanidine sulfate	598-65-2	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Amidine, Salt (organic)	Laboratory Chemical	100%	100 mg	>95%	272.3	n.a.	noncorrosive	3	n.a.	n.a.	n.a.	solid	6.7
nonirritant	-	2-(n-Dodecylthio)ethanol	1462-55-1	ECETOC	Elf Atochem, Inc.	Sigma-Aldrich Corp.	Alcohol, Ether, Sulfur Compound (organic)	Chemical Intermediate	100%	100 mg	>99%	206.3	?	?	3	?	?	white	solid	0.0
nonirritant	-	iso-Propyl bromide	75-26-3	ECETOC	Fluka, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (halogenated)	Chemical Intermediate, Pharmaceutical Intermediate	100%	0.1 mL	>99%	123.0	?	?	3	3 g/L	1.9	?	liquid	9.7
nonirritant	-	Di-iso-butyl ketone	108-83-8	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Ketone	Pharmaceutical Intermediate, Solvent	100%	0.1 mL	99%	142.2	n.a.	noncorrosive	3	0.05 g/ 100 mL	n.a.	?	liquid	7.3
nonirritant	-	iso-Octylthioglycolate	25103-09-7	ECETOC	Elf Atochem, Inc.	Sigma-Aldrich Corp.	Ester, Sulfur Compound (organic)	Industrial Chemical	100%	0.1 mL	99%	204.3	n.a.	noncorrosive	3	n.a.	n.a.	clear, water-white	liquid	4.0
nonirritant	-	2,4-Pentanediol	625-69-4	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Alcohol	Chemical Intermediate	100%	0.1 mL	98%	104.2	n.a.	?	3	?	?	?	liquid	4.7
nonirritant	-	2,2-Dimethyl-3-pentanol	3970-62-5	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Alcohol	Pharmaceutical	100%	0.1 mL	97%	116.2	n.a.	noncorrosive	3	insoluble	n.a.	colorless	liquid	8.3
nonirritant	-	Potassium tetrafluoroborate	14075-53-7	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Salt (inorganic)	Industrial Chemical, Pesticide	100%	100 mg	>99%	125.9	n.a.	R34	3	4.4 g/L	n.a.	n.a.	solid	0.0
nonirritant	-	3-Methoxy-1,2-propanediol	623-39-2	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Ether, Phenol	Laboratory Chemical	100%	0.1 mL	98%	106.1	?	?	3	soluble	?	?	liquid	0.0
nonirritant	-	Sodium lauryl sulfate	151-21-3	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Acid (organic) [carboxylic acid], Salt (organic)	Cleaning Agent, Cosmetic Ingredient, Food Additive, Laboratory Chemical, Pesticide Intermediate, Surfactant (anionic)	3%	0.1 mL	98 %	288.4	8.0-10.0 (1% aq.)	noncorrosive	6	1 g/10 mL	1.60 (100%)	?	liquid	7.3
nonirritant	-	Toluene	108-88-3	ECETOC	Fisher Scientific International, Inc.	Sigma-Aldrich Corp.	Hydrocarbon (cyclic)	Chemical Intermediate, Industrial Chemical, Laboratory Chemical	100%	0.1 mL	99%	92.1	?	?	4	?	?	colorless	liquid	9.0
nonirritant	-	Triton X-100	9002-93-1	ECETOC	Sigma-Aldrich Corp.	Sigma-Aldrich Corp.	Ether	Surfactant (nonionic)	1%	0.1 mL	98%	250.4	7.2	noncorrosive	6	soluble	n.a.	colorless	liquid	1.7

GHS Classification	NICEATM Category 1 SubClass [2]	Substance	Corneal score	Irital score	Conjunctival score	Tested in BCOP	Tested in HET-CAM	Tested in ICE	Tested in IRE	EPA Classification	EU Classification	FHSA Classification	Human Exposure Summary
Category 2B	-	N-Laurylsarcosine sodium salt	-	-	-	X	-	-	-	Category III	nonirritant	SCNM	Human data not located
Category 2B	-	Maneb (solid)	-	-	-	X	X	X	X	Category III	R36	irritant	Generally regarded as harmless, with no irritation, except for mild conjunctivitis (9)
Category 2B	-	2-Methyl-1-pentanol	-	-	-	-	-	-	-	Category III	nonirritant	SCNM	Human data not located
Category 2B	-	Propasol Solvent P	-	-	-	-	-	-	-	Category II	nonirritant	irritant	Human data not located
Category 2B	-	6-Methyl purine	-	-	-	-	-	-	-	Category IV	R36	irritant	Human data not located
Category 2B	-	2,6-Dichloro-5-fluoro-beta-oxo-3-pyridinepropanoate	-	-	-	-	-	-	-	Category III	nonirritant	SCNM	Human data not located
Category 2B	-	Triton X-100	-	-	-	-	X	X	X	Category I	R41	SCNM	Human data not located
nonirritant	-	iso-Octyl acrylate	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	Human data not located
nonirritant	-	tetra-Aminopyrimidine sulfate	-	-	-	X	X	X	-	Category III	nonirritant	SCNM	Human data not located
nonirritant	-	2,4-Difluoronitrobenzene	-	-	-	-	-	-	-	Category III	nonirritant	SCNM	Human data not located
nonirritant	-	n,n-Dimethylguanidine sulfate	-	-	-	-	-	-	-	Category III	nonirritant	SCNM	Human data not located
nonirritant	-	2-(n-Dodecylthio)ethanol	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	Human data not located
nonirritant	-	iso-Propyl bromide	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	Human data not located
nonirritant	-	Di-iso-butyl ketone	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	Causes minor irritation to the eye (4, 20)
nonirritant	-	iso-Octylthioglycolate	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	Human data not located
nonirritant	-	2,4-Pentanediol	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	Human data not located
nonirritant	-	2,2-Dimethyl-3-pentanol	-	-	-	-	-	-	-	Category III	nonirritant	SCNM	Human data not located
nonirritant	-	Potassium tetrafluoroborate	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	Human data not located
nonirritant	-	3-Methoxy-1,2-propanediol	-	-	-	-	-	-	-	Category IV	nonirritant	SCNM	Human data not located
nonirritant	-	Sodium lauryl sulfate	-	-	-	X	X	X	X	Category III	nonirritant	irritant	Sodium lauryl sulfate is said to have been the commonest cause of eye irritation by commercial shampoos (10)
nonirritant	-	Toluene	-	-	-	-	X	X	X	Category III	nonirritant	SCNM	Vapors of toluene cause noticeable sensation of irritation to human eyes at 300-440 ppm in air, but even at 800 ppm, irritation is slight. Vapors irritate eyes and upper respiratory tract; liquid irritates eyes (10, 27).
nonirritant	-	Triton X-100	-	-	-	X	-	-	-	Category II	R36	irritant	Human data not located

GHS Classification	NICEATM Category 1 SubClass [2]	Substance	Animal Exposure Summary for Category 1(H) Substances	Notes
Category 2B	-	N-Laurylsarcosine sodium salt		
Category 2B	-	Maneb (solid)		
Category 2B	-	2-Methyl-1-pentanol		
Category 2B	-	Propasol Solvent P		
Category 2B	-	6-Methyl purine		
Category 2B	-	2,6-Dichloro-5-fluoro-beta-oxo-3-pyridinepropanoate		
Category 2B	-	Triton X-100		
nonirritant	-	iso-Octyl acrylate		
nonirritant	-	tetra-Aminopyrimidine sulfate		
nonirritant	-	2,4-Difluoronitrobenzene		
nonirritant	-	n,n-Dimethylguanidine sulfate		
nonirritant	-	2-(n-Dodecylthio)ethanol		
nonirritant	-	iso-Propyl bromide		
nonirritant	-	Di-iso-butyl ketone		
nonirritant	-	iso-Octylthioglycolate		
nonirritant	-	2,4-Pentanediol		
nonirritant	-	2,2-Dimethyl-3-pentanol		
nonirritant	-	Potassium tetrafluoroborate		
nonirritant	-	3-Methoxy-1,2-propanediol		
nonirritant	-	Sodium lauryl sulfate		
nonirritant	-	Toluene		
nonirritant	-	Triton X-100		

Abbreviations: ? = Data has not been obtained at this time; - = not applicable; AG = Aktiengesellschaft (incorporated); Assn. = Association; BASF = Badische Anilin- & Soda Fabrik AG; BCOP = Bovine Corneal Opacity and Permeability; CASRN = Chemical Abstracts Service Registry Number; CC = Conjunctival Chemosis; Co. = Company; CO = Corneal Opacity; Conc. = concentration; Corp. = Corporation; CR = Conjunctival Redness; CTFA = Cosmetic, Toiletries and Fragrance Association; D = Day; ECETOC= European Center for Ecotoxicology and Toxicology of Chemicals; GmbH = Gesellschaft mit beschränkter Haftung (Inc.); GSK = Glaxo Smith-Kline; HET-CAM = Hen's Egg Test- Chorioallantoic Membrane; ICE = Isolated Chicken Eye; IRE = Isolated Rabbit Eye; ISOPA = European Diisocyanate and Polyol Producers Association; I = Iritis; Lab. = Laboratory; LNS= Laboratoire National de la Sante; Log Kow = octanol/water partition coefficient; Ltd. = Limited; LLC = Limited Liability Company; MeSH = Medical Subject Headings, information on chemical class criteria can be obtained at www.nlm.nih.gov/mesh; MG CU/ M = Milligrams Per Cubic Meter; MMAS = Modified Maximum Average Score; the highest (maximum) average of the individual animal weighted scores for observation times greater than or equal to 24 hours after test substance instillation.; MW = molecular weight; n = number of animals; n.a. = not available; noncorrosive = not classified as a dermal corrosive; NIHS-Ohno = National Institute of Health Sciences, Japan, Yasuo Ohno; PPM = Parts Per Million; R34 = causes burns; R35 = causes severe burns; SCNM = Study Criteria Not Met; (H) = classification based on inducing severe ocular damage in humans; TNO-Prinsen = Institute CIVO, Menk Prinsen; TSCA = Toxic Substances Control Act; ZEBET = German Center for Documentation and Evaluation of Alternative Methods to Animal Experiments; X = Where a substance has been tested in BCOP, HET-CAM, ICE, or IRE, the presence of an "X" indicates that the substance has been tested in the proposed version of this test method.

NICEATM Cat. 1 Subcat. = Category 1 subcategories = NICEATM-assigned subcategories for GHS Category 1 substances (ocular corrosives and severe irritants) were assigned based on the following: 0 = not classifiable; 1 = positive response based on a persistent lesion involving the cornea, iris, and/or conjunctiva through to day 21 in at least one of three rabbits and not on severity; 2 = positive response based on mean for first 3 days (corneal opacity [CO] score >3 and <4 or iritis [IR] score >1.5) in at least two of three rabbits but lesions do not persist through day 21; 3 = positive response based on mean for first 3 days (CO >3 and <4 or IR >1.5) in at least two of three rabbits and a persistent (>21 days) lesion in at least one rabbit; 4 = CO score of 4 at any time in at least one of three rabbits

“100 mg or 0.1 mL” indicates studies which were conducted according to Draize, but for which the amount tested was not provided in the study information provided or obtained.

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APPENDIX V-C

LIST OF PROPOSED REFERENCE SUBSTANCES FOR VALIDATION STUDIES OF *IN VITRO* TEST METHODS FOR THE IDENTIFICATION OF OCULAR CORROSIVES/SEVERE IRRITANTS (SORTED BY CHEMICAL CLASS, AND SUBSTANCE NAME)

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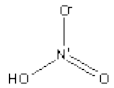
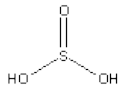
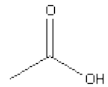
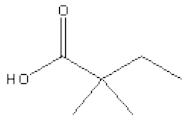
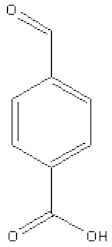
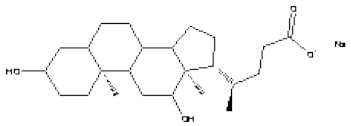
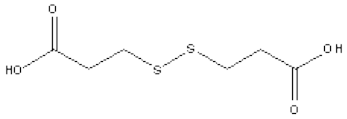
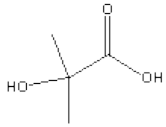
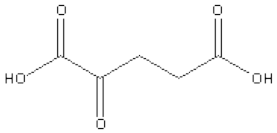
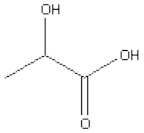
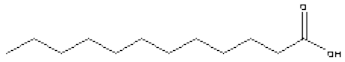
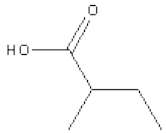
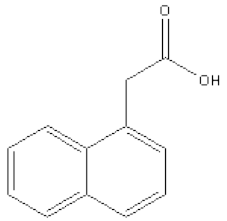
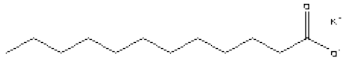
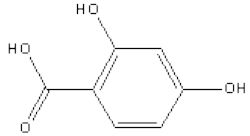
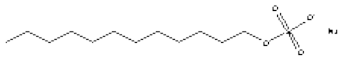
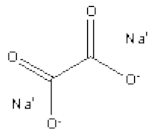
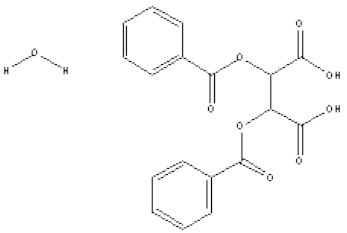
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Acid (inorganic)	1 (H)	-[7]	Nitric acid	7697-37-2		NO_3	63.0	Chemical Intermediate, Industrial Chemical, Laboratory Reagent, Pharmaceutical Intermediate	Solid
Acid (inorganic)	1 (H)	-	Sulfuric acid	7664-93-9		H_2O_4S	98.1	Battery Acid, Chemical Intermediate, Cleaning Agent, Fertilizer, Food Additive, Industrial Chemical, Laboratory Chemical	Solid
Acid (organic) [Carboxylic acid]	1	4	Acetic acid	64-19-7		$C_2H_4O_2$	60.1	Industrial Chemical; Laboratory Agent, Solvent	Liquid

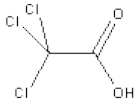
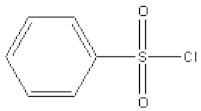
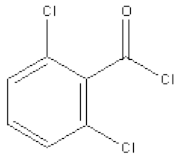
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Acid (organic) [Carboxylic acid]	1	1	2,2-Dimethyl butanoic acid	595-37-9		$C_6H_{12}O_2$	116.2	Pharmaceutical	Solid
Acid (organic) [Carboxylic acid]	2A	-	4-Carboxybenz-aldehyde	619-66-9		$C_8H_6O_3$	150.1	Industrial Chemical	Solid
Acid (organic) [Carboxylic acid]	2A	-	Deoxycholic acid sodium salt	302-95-4		$C_{24}H_{39}NaO_4$	414.6	Anti-Infective, Laboratory Chemical, Solvent	Solid

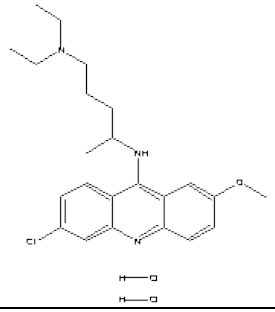
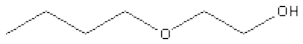
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Acid (organic) [Carboxylic acid]	2B	-	3,3-Dithiopropionic acid	1119-62-6		$C_6H_{10}O_4S_2$	210.3	Chemical Intermediate, Laboratory Chemical	Solid
Acid (organic) [Carboxylic acid]	1	4	2-Hydroxyiso-butyric acid	594-61-6		$C_4H_8O_3$	104.1	Industrial Chemical	Solid
Acid (organic) [Carboxylic acid]	1	4	alpha-Ketoglutaric acid	328-50-7		$C_5H_6O_5$	146.1	Chemical Intermediate, Laboratory Chemical, Pharmaceutical,	Solid

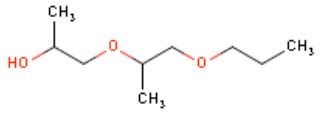
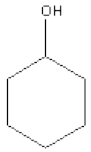
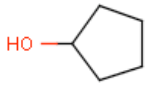
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Acid (organic) [Carboxylic acid]	1	4	Lactic acid	50-21-5		$C_3H_6O_3$	90.1	Cosmetic	Solid
Acid (organic) [Carboxylic acid]	1	1	Lauric acid	143-07-7		$C_{12}H_{24}O_2$	200.3	Surfactant (anionic)	Solid
Acid (organic) [Carboxylic acid]	1	4	2-Methylbutyric acid	116-53-0		$C_5H_{10}O_2$	102.1	Chemical Intermediate, Cosmetic Ingredient, Solvent	Solid

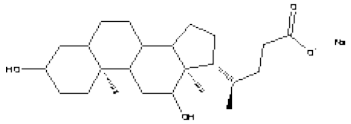
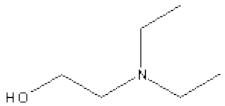
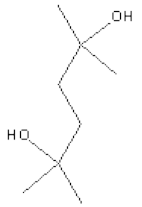
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Acid (organic) [Carboxylic acid]	1	4	1-Naphthalene acetic acid	86-87-3		$C_{12}H_{10}O_2$	186.2	Pesticide	Solid
Acid (organic) [Carboxylic acid]	1	4	Potassium laurate	10124-65-9		$C_{12}H_{23}KO_2$	238.4	Cosmetic Ingredient, Pesticide	Solid
Acid (organic) [Carboxylic acid]	1	4	beta-Resorcylic acid	89-86-1		$C_7H_6O_4$	154.1	Chemical Intermediate, Dye	Solid

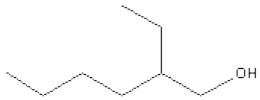
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Acid (organic) [Carboxylic acid]	NI	-	Sodium lauryl sulfate	151-21-3		$C_{12}H_{25}NaO_4S$	288.4	Surfactant (anionic)	Liquid
Acid (organic) [Carboxylic acid]	1	4	Sodium oxalate	62-76-0		C_2Na_2O	134	Industrial Chemical, Laboratory Chemical	Solid
Acid (organic) [Carboxylic acid]	1	3	Dibenzoyl-L-tartaric acid	2743-38-6		$C_{18}H_{16}O_9$	358.3	Chemical Intermediate	Solid

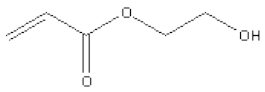
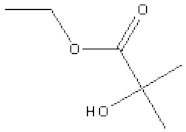
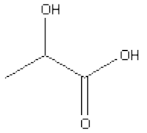
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Acid (organic) [Carboxylic acid]	1	4	Trichloroacetic acid	76-03-9		$C_2HCl_3O_2$	163.4	Caustic Agent, Herbicide	Liquid
Acyl Halide	1	4	Benzenesulfonyl chloride	98-09-9		$C_6H_5ClO_2S$	176.6	Chemical Intermediate, Pesticide	Solid
Acyl Halide	2A	-	2,6-Dichlorobenzoyl chloride	4659-45-4		$C_7H_3Cl_3O$	209.5	Anti-Fungal, Anti-Infective	Liquid

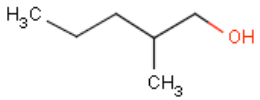
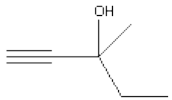
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Acyl Halide	1	4	Trichloroacetyl chloride	76-02-8		C_2Cl_4O	163.4	Chemical Intermediate, Industrial Chemical	Liquid
Alcohol	1	4	n-Butanol	71-36-3		$C_4H_{10}O$	74.1	Chemical Intermediate, Cosmetic Ingredient, Food Additive, Industrial Chemcial, Pesticide Intermediate, Pharmaceutical Intermediate, Solvent, Veterinary Chemical	Liquid
Alcohol	1	1	Butyl cellosolve	111-76-2		$C_6H_{14}O_2$	118.2	Solvent	Solid

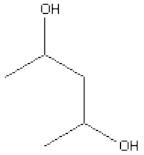
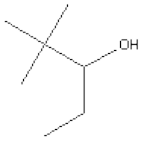
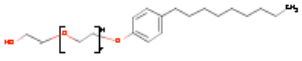
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Alcohol	2B	-	Butyl Dipropasol Solvent	29911-27-1		$C_9H_{20}O_3$	176.3	Solvent	Liquid
Alcohol	1	2	Cyclohexanol	108-93-0		$C_6H_{12}O$	100.2	Solvent	Solid
Alcohol	2B	-	Cyclopentanol	96-41-3		$C_5H_{10}O$	86.1	Pharmaceutical Intermediate	Liquid

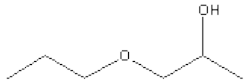
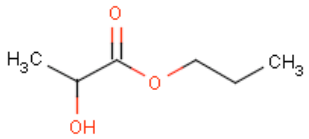
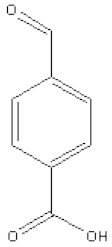
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Alcohol	2A	-	Deoxycholic acid sodium salt	302-95-4		$C_{24}H_{39}NaO_4$	414.6	Anti-Infective, Laboratory Chemical, Solvent	Solid
Alcohol	1	4	Diethylethanol-amine	100-37-8		$C_6H_{15}NO$	117.9	Chemical Intermediate, Pharmaceutical Intermediate	Solid
Alcohol	1	1	2,5-Dimethylhexane diol	110-03-2		$C_8H_{18}O_2$	146.2	Chemical Intermediate	Solid

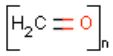
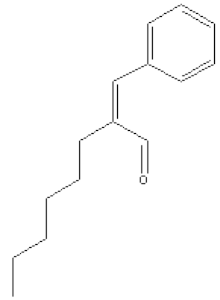
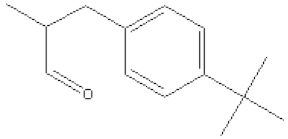
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Alcohol	NI	-	2-(n-Dodecylthio)-ethanol	1462-55-1		$C_{14}H_{30}OS$	206.3	Laboratory Chemical	Solid
Alcohol	2A	-	2-Ethyl-1-hexanol	104-76-7		$C_8H_{18}O$	130.2	Solvent	Liquid
Alcohol	2A	-	n-Hexanol	111-27-3		$C_6H_{14}O$	102.2	Solvent	Solid

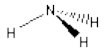
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Alcohol	1	4	Hydroxyethyl acrylate	818-61-1		$C_5H_8O_3$	116.1	Chemical Intermediate	Solid
Alcohol	1	2	2-Hydroxyiso-butyric acid ethylester	80-55-7		$C_6H_{12}O_3$	132.2	Industrial Chemical	Solid
Alcohol	1	4	Lactic acid	50-21-5		$C_3H_6O_3$	90.1	Cosmetic	Liquid

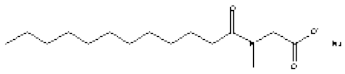
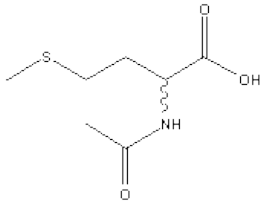
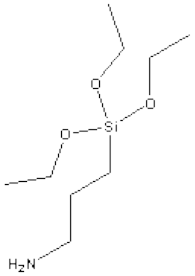
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Alcohol	2B	-	2-Methyl-1-pentanol	105-30-6		$C_6H_{14}O$	102.2	Solvent	Liquid
Alcohol	1	4	Methylpentynol	77-75-8		$C_6H_{10}O$	98.1	Pharmaceutical, Veterinary Chemical	Solid
Alcohol	2A	-Froggie	n-Octanol	111-87-5		$C_8H_{18}O$	130.2	Solvent	Liquid

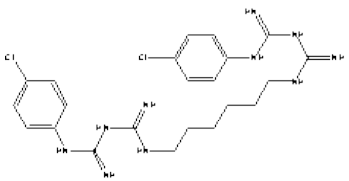
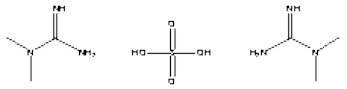
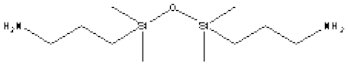
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Alcohol	NI	-	2,4-Pentanediol	625-69-4		$C_5H_{12}O_2$	104.2	Chemical Intermediate	Liquid
Alcohol	NI	-	2,2-Dimethyl-3-pentanol	3970-62-5		$C_7H_{16}O$	116.2	Pharmaceutical	Solid
Alcohol	1	4	Polyethylene glycol nonylphenyl ether (Surfonic HDL-1)	9016-45-9		C_{31}-H_{56}-O_9	308.5	Cleaning Agent, Industrial Chemical, Pesticide, Surfactant (nonionic)	Liquid

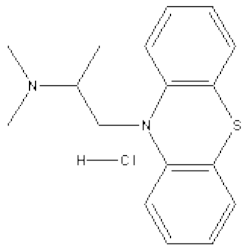
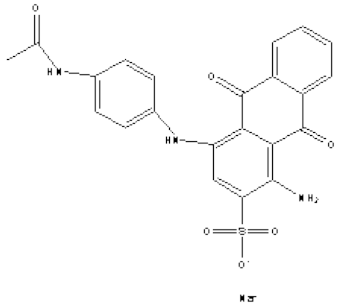
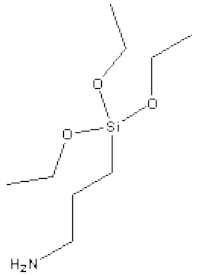
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Alcohol	2B	-	Propasol Solvent P	1569-01-3		$C_6H_{14}O_2$	118.2	Solvent	Liquid
Alcohol	1	1	Propyl lactate	616-09-1		$C_6H_{12}O_3$	132.2	Cleaning Agent, Food Additive	Liquid
Aldehyde	2A	-	4-Carboxybenz-aldehyde	619-66-9		$C_8H_6O_3$	150.1	Industrial Chemical	Liquid

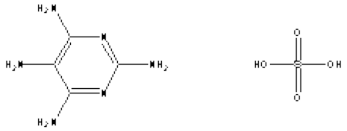
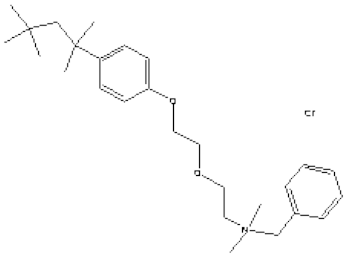
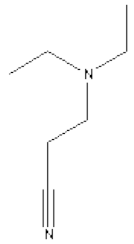
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Aldehyde	1	4	Granuform	30525-89-4		$(CH_2O)_n$[8]	30	Anti-Fungal, Anti-Infective, Industrial Chemical, Laboratory Chemical	Liquid
Aldehyde	2B	-	Hexyl cinnamic aldehyde	101-86-0		$C_{15}H_{20}O$	216.3	Cosmetic Ingredient, Food Additive, Perfume	Liquid
Aldehyde	1	1	Protectol PP	80-54-6		$C_{14}H_{20}O$	204.31	Food Additive, Perfume	Solid

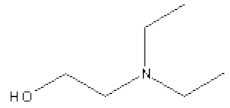
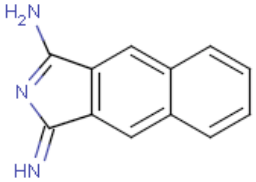
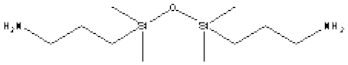
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Alkali	1 (H)	-	Ammonia	7664-41-7		NH_3	17	Anti-Fungal, Chemical Intermediate, Cleaning Agent, Fertilizer, Herbicide, Industrial Chemical, Refrigerant	Liquid
Alkali	1 (H)	-	Potassium hydroxide	1310-58-3		KOH	56.1	Chemical Intermediate, Cleaning Agent, Fertilizer, Food Additive, Industrial Chemical, Veterinary Chemical	Liquid
Alkali	1	4	Sodium hydroxide	1310-73-2		NaOH	40	Caustic Agent, Chemical Intermediate, Industrial Chemical, Pharmaceutical Intermediate, Veterinary Chemical	Liquid

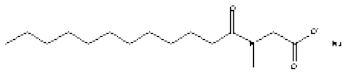
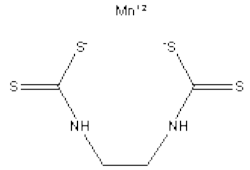
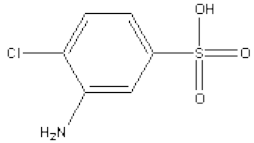
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Amide	2B	-	N-Laurylsarcosine sodium salt	137-16-6		$C_{15}H_{28}NNaO_3$	293.4	Cleaning Agent, Laboratory Chemical, Surfactant (anionic)	Solid
Amide	1	4	n-Acetyl-methionine	1115-47-5		$C_7H_{13}NO_3S$	191.3	Cosmetic Ingredient, Food Additive, Laboratory Chemical	Solid
Amidine	1	4	gamma-Aminopropyl-triethoxy silane	919-30-2		$C_9H_{23}NO_3Si$	221.4	Industrial Chemical	Liquid

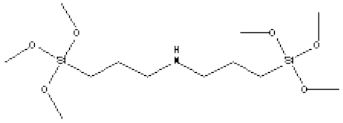
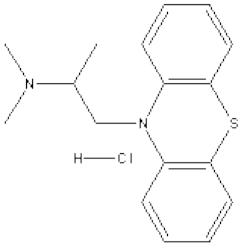
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Amidine	1	4	Chlorhexidine	55-56-1		$C_{22}H_{30}Cl_2N_{10}$	505.4	Pharmaceutical, Anti-Infective	Liquid
Amidine	NI	-	n,n-Dimethyl-guanidine sulfate	598-65-2		$C_6H_{20}N_6O_4S$	272.3	Laboratory Chemical	Liquid
Amidine	1	4	Bis-(3-aminopropyl) tetramethyl disiloxane	2469-55-8		$C_{10}H_{28}N_2OSi_2$	248.5	Industrial Chemical	Liquid

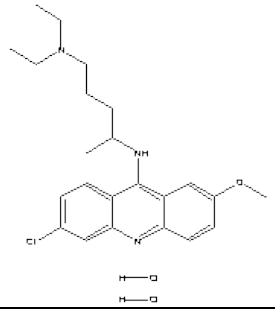
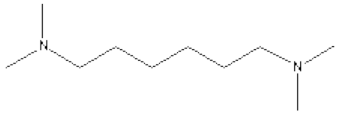
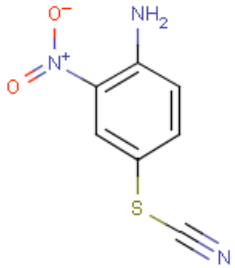
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Amidine	1	3	Promethazine hydrochloride	58-33-3		$C_{17}H_{21}ClN_2S$	320.9	Pharmaceutical	Liquid
Amine	1	4	Acid blue 40	6424-85-7		$C_{22}H_{16}N_3NaO_6S$	473.4	Industrial Chemical	Liquid
Amine	1	4	gamma-Aminopropyl-triethoxy silane	919-30-2		$C_9H_{23}NO_3Si$	221.4	Industrial Chemical	Solid

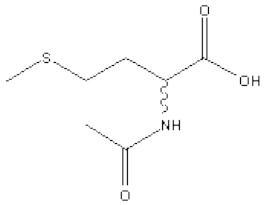
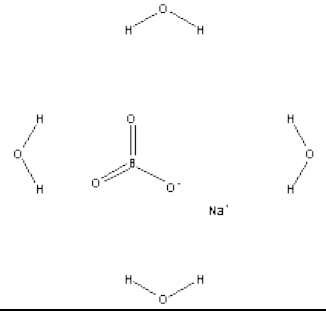
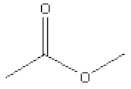
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Amine	NI	-	tetra-Amino-pyrimidine sulfate	5392-28-9		$C_4H_{10}N_6O_4S$	238.2	Chemical Intermediate	Liquid
Amine	1	4	Benzethonium chloride	121-54-0		$C_{27}H_{42}ClNO_2$	448.1	Anti-Infective, Pharmaceutical, Veterinary Chemical	**Solid**
Amine	1	4	Diethylamino-propionitrile	5351-04-2		$C_7H_{14}N_2$	126.2	Industrial Chemical	Liquid

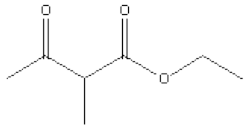
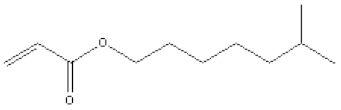
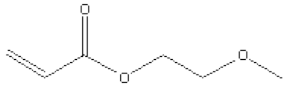
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Amine	1	4	Diethylethanol-amine	100-37-8		$C_6H_{15}NO$	117.9	Chemical Intermediate, Pharmaceutical Intermediate	Liquid
Amine	1	4	1,3-Diiminobenz (f)-isoindoline	65558-69-2		$C_{12}H_9N_3$	195.2	Dye, Laboratory Chemical	Liquid
Amine	1	4	Bis-(3-aminopropyl) tetramethyl disiloxane	2469-55-8		$C_{10}H_{28}N_2OSi_2$	248.5	Industrial Chemical	**Solid**

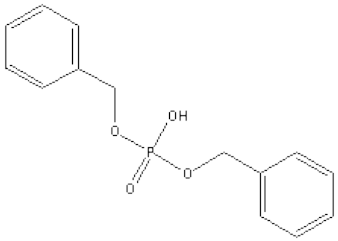
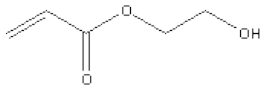
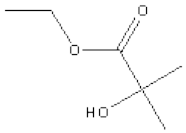
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Amine	2B	-	N-Laurylsarcosine sodium salt	137-16-6		$C_{15}H_{28}NNaO_3$	293.4	Cleaning Agent, Laboratory Chemical, Surfactant (anionic)	Liquid
Amine	2B	-	Maneb	12427-38-2		$C_4H_6MnN_2S_4$	265.3	Pesticide	Liquid
Amine	1	4	4-Chloro-methanilic acid	98-36-2		$C_6H_6ClNO_3S$	207.6	Chemical Intermediate, Industrial Chemical, Laboratory Chemical	Solid

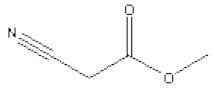
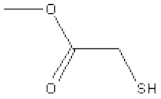
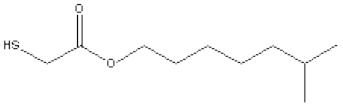
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Amine	1	4	n-Octylamine	111-86-4		$C_8H_{19}N$	129.2	Chemical Intermediate, Laboratory Chemical	Liquid
Amine	1	1	Organo functional Silane 45-49	82985-35-1		$C_{12}H_{31}NO_6Si_2$	341.6	Polish	Solid
Amine	1	3	Promethazine hydrochloride	58-33-3		$C_{17}H_{21}ClN_2S$	320.9	Pharmaceutical	Liquid

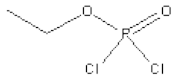
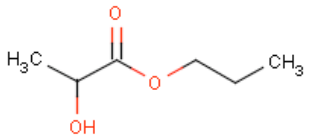
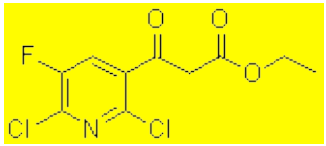
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Amine	1	3	Quinacrine	69-05-6		$C_{23}H_{32}Cl_3N_3O$	472.9	Pharmaceutical	Liquid
Amine	1	4	N,N,N`,N`-Tetramethyl hexanediamine	111-18-2		$C_{10}H_{24}N_2$	172.31	Anti-Infective, Industrial Chemical, Laboratory Chemical	Liquid
Amine	1	not classifiable (likely 4)	2-Nitro-4-thiocyanoaniline	54029-45-7		$C_7H_5N_3O_2S$	195.2	Industrial Chemical	Liquid

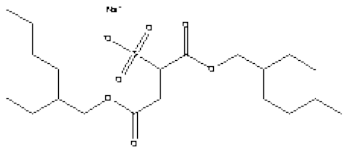
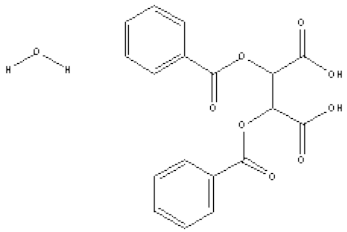
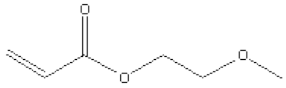
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Amino Acid	1	4	n-Acetyl-methionine	1115-47-5		$C_7H_{13}NO_3S$	191.3	Cosmetic Ingredient, Food Additive, Laboratory Chemical	Liquid
Boron Compound	1	1	Sodium perborate tetrahydrate	10486-00-7		BH_8NaO_7	153.9	Cleaning Agent	Solid
Ester	2A	-	Methyl acetate	79-20-9		$C_3H_6O_2$	74.1	Chemical Intermediate, Food Additive, Herbicide, Laboratory Chemical,Solvent	Liquid

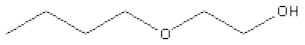
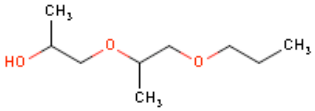
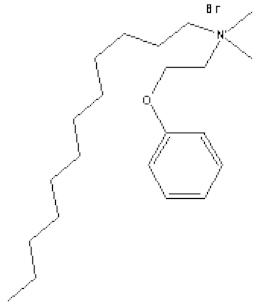
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Ester	2B	-	Ethyl-2-methyl acetoacetate	609-14-3		$C_7H_{12}O_3$	144.2	Chemical Intermediate	Solid
Ester	NI	-	Iso-octyl acrylate	29590-42-9		$C_{11}H_{20}O_2$	184.3	Building Material	Solid
Ester	1	4	Methoxyethyl acrylate	3121-61-7		$C_6H_{10}O_3$	130.1	Chemical Intermediate, Industrial Chemical, Laboratory Chemical	Liquid

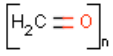
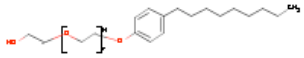
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Ester	2A	-	Dibenzyl phosphate	1623-08-1		$C_{14}H_{15}O_4P$	278.2	Pesticide	Liquid
Ester	1	4	Hydroxyethyl acrylate	818-61-1		$C_5H_8O_3$	116.1	Chemical Intermediate	Liquid
Ester	1	2	2-Hydroxyiso-butyric acid ethylester	80-55-7		$C_6H_{12}O_3$	132.2	Industrial Chemical	Solid

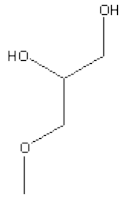
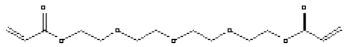
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Ester	2A	-	Methyl cyanoacetate	105-34-0		$C_4H_5NO_2$	99.1	Chemical Intermediate	Liquid
Ester	1	4	Methylthio-glycolate	2365-48-2		$C_3H_6O_2S$	106.1	Industrial Chemical	Liquid
Ester	NI	-	iso-Octylthio-glycolate	25103-09-7		$C_{10}H_{20}O_2S$	205.3	Industrial Chemical	Solid

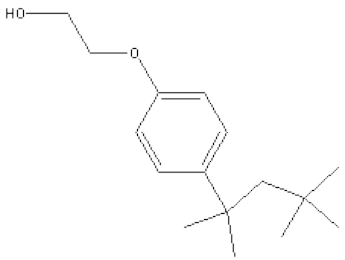
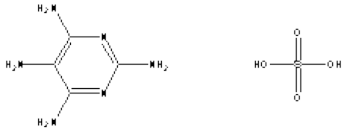
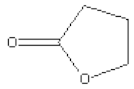
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Ester	1	4	Phosphoro-dicloridic acid, ethyl ester	1498-51-7		$C_2H_5Cl_2O_2P$	162.9	Chemical Intermediate, Pesticide	Liquid
Ester	1	1	Propyl lactate	616-09-1		$C_6H_{12}O_3$	132.2	Cleaning Agent, Food Additive	Liquid
Ester	2B	-	2,6-Dichloro-5-fluoro-beta-oxo-3-pyridine-propanoate	96568-04-6		$C_{10}H_8Cl_2FNO_3$	280.1	Industrial Chemical, Pharmaceutical Intermediate	Solid

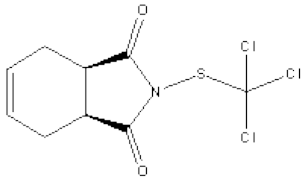
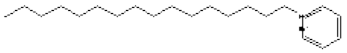
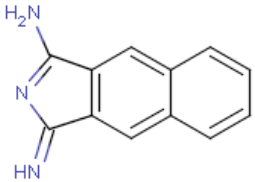
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Ester	1	4	Di(2-ethylhexyl) sodium sulfosuccinate	577-11-7		$C_{20}H_{37}NaO_7S$	444.6	Adjuvant, Cleaner, Solubilizer, Wetting Agent	Liquid
Ester	1	3	Dibenzoyl-L-tartaric acid	2743-38-6		$C_{18}H_{16}O_9$	358.3	Chemical Intermediate	Liquid
Ether	1	4	Methoxyethyl acrylate	3121-61-7		$C_6H_{10}O_3$	130.1	Chemical Intermediate, Industrial Chemical, Laboratory Chemical	Solid

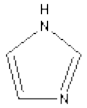
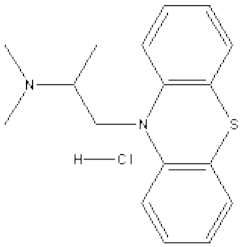
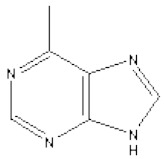
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Ether	1	1	Butyl cellosolve	111-76-2		$C_6H_{14}O_2$	118.2	Solvent	Solid
Ether	2B	-	Butyl Dipropasol Solvent	29911-27-1		$C_9H_{20}O_3$	176.3	Solvent	Solid
Ether	1	4	Domiphen bromide	538-71-6		$C_{22}H_{40}BrNO$	414.5	Anti-Infective, Pharmaceutical	Solid

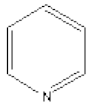
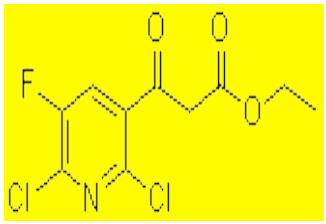
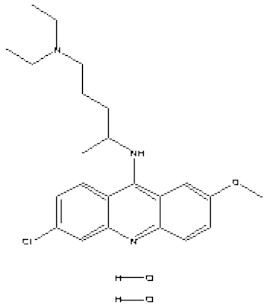
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Ether	NI	-	2-(n-Dodecylthio) ethanol	1462-55-1		$C_{14}H_{30}OS$	206.3	Laboratory Chemical	Liquid
Ether	1	4	Granuform	30525-89-4		$(CH_2O)_n$	30	Anti-Fungal, Anti-Infective, Industrial Chemical, Laboratory Chemical	Liquid
Ether	1	4	Polyethylene glycol nonylphenyl ether (Surfonic HDL-1)	9016-45-9		$C_{31}H_{56}O_9$	308.5	Cleaning Agent, Industrial Chemical, Pesticide, Surfactant (nonionic)	Liquid

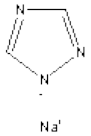
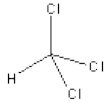
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Ether	NI	-	3-Methoxy-1,2-propanediol	623-39-2		$C_4H_{10}O_3$	106.1	Laboratory Chemical	Solid
Ether	1	4	Tetraethylene glycol diacrylate	17831-71-9		$C_{14}H_{22}O_7$	302.32	Chemical Intermediate, Industrial Chemical	Solid
Ether	**1**	4	Tetrahydrofuran	109-99-9		C_4H_8O	72.1	Chemical Intermediate, Industrial Chemical, Pharmaceutical Intermediate, Solvent	Solid

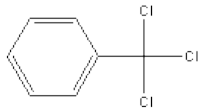
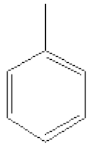
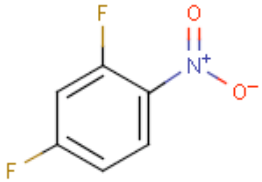
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Ether	1, 2A/2B, NI	-	Triton X-100	9002-93-1		$C_{16}H_{26}O_2$	250.4	Surfactant (non-ionic)	Solid
Hetero cyclic Compound	NI	-	tetra-Amino-pyrimidine sulfate	5392-28-9		$C_4H_{10}N_6O_4S$	238.2	Chemical Intermediate	Liquid
Hetero cyclic Compound	2A	-	gamma-Butyrolactone	96-48-0		$C_4H_6O_2$	86.1	Solvent	Solid

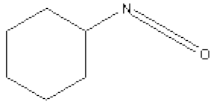
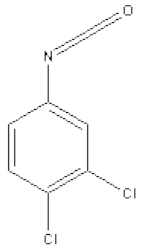
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Hetero cyclic Compound	1	4	Captan 90-concentrate (solid)	133-06-2		$C_9H_8Cl_3NO_2S$	300.6	Pesticide	Solid
Hetero cyclic Compound	1, 2A	-	Cetylpyridinium bromide	140-72-7		$C_{21}H_{38}BrN$	384.4	Anti-Infective; Laboratory Reagent; Surfactant (cationic)	Liquid
Hetero cyclic Compound	1	4	1,3-Diiminobenz (f)-isoindoline	65558-69-2		$C_{12}H_9N_3$	195.2	Dye, Laboratory Chemical	Solid

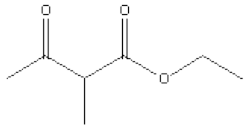
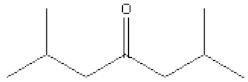
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Hetero cyclic Compound	1	4	Imidazole	288-32-4		$C_3H_4N_2$	68.1	Anti-Fungal	Liquid
Hetero cyclic Compound	1	3	Promethazine hydrochloride	58-33-3		$C_{17}H_{21}ClN_2S$	320.9	Pharmaceutical	Liquid
Hetero cyclic Compound	2B	-	6-Methyl purine	2004-03-7		$C_6H_6N_4$	134.1	Laboratory Chemical, Pharmaceutical Intermediate	Liquid

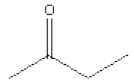
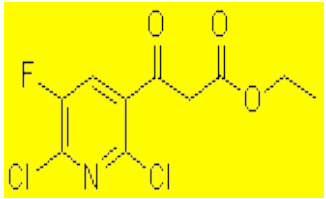
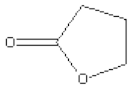
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Hetero cyclic Compound	1	4	Pyridine	110-86-1		C_5H_5N	79.1	Pesticide Intermediate, Pharmaceutical Intermediate, Solvent	Liquid
Hetero cyclic Compound	2B	-	2,6-Dichloro-5-fluoro-beta-oxo-3-pyridine-propanoate	96568-04-6		$C_{10}H_8Cl_2FNO_3$	280.1	Industrial Chemical, Pharmaceutical Intermediate	Solid
Hetero cyclic Compound	1	3	Quinacrine	69-05-6		$C_{23}H_{32}Cl_3N_3O$	472.9	Pharmaceutical	Liquid

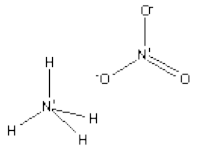
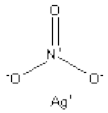
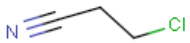
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Hetero cyclic Compound	**1**	4	Tetrahydrofuran	109-99-9		C_4H_8O	72.1	Chemical Intermediate, Industrial Chemical, Pharmaceutical Intermediate, Solvent	Liquid
Hetero cyclic Compound	1	4	1,2,4-Triazole, sodium salt	41253-21-8		$C_2H_2N_3N_a$	91.1	Anti-Fungal	Solid
Hydro carbon (acyclic)	1 (H)	-	Chloroform	67-66-3		$CHCl_3$	119.4	Anesthetic, Chemical Intermediate, Cleaning Agent, Industrial Chemical, Pharmaceutical Intermediate, Solvent	Solid

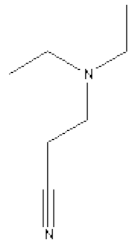
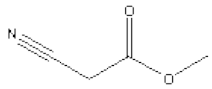
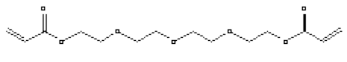
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Hydro carbon (cyclic)	2A	-	Benzotrichloride	98-07-7		$C_7H_5Cl_3$	195.5	Chemical Intermediate	Liquid
Hydro carbon (cyclic)	NI	-	Toluene	108-88-3		C_7H_8	92.1	Chemical Intermediate, Industrial Chemical, Laboratory Chemical	Liquid
Hydro carbon (halogen-ated)	NI	-	2,4-Difluoronitro benzene	446-35-5		$C_6H_3F_2NO_2$	159.1	Pesticide, Pharmaceutical Intermediate	Liquid

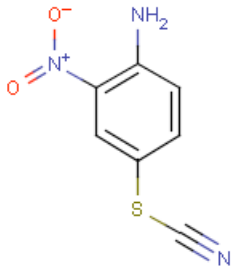
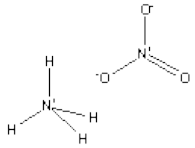
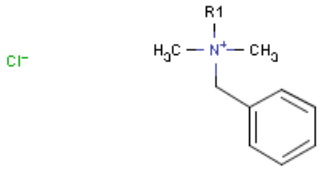
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Hydro carbon (halogen-ated)	NI	-	iso-Propyl bromide	75-26-3		C_3H_7Br	123.0	Chemical Intermediate, Pharmaceutical Intermediate	Liquid
Isocyanate	1	4	Cyclohexyl isocyanate	3173-53-3		$C_7H_{11}NO$	125.2	Anesthetic, Chemical Intermediate, Cleaning Agent, Industrial Chemical, Pharmaceutical Intermediate, Solvent	Solid
Isocyanate	1	1	3,4-Dichlorophenyl isocyanate	102-36-3		$C_6H_3Cl_2NO$	188.1	Chemical Intermediate, Industrial Chemical	Liquid

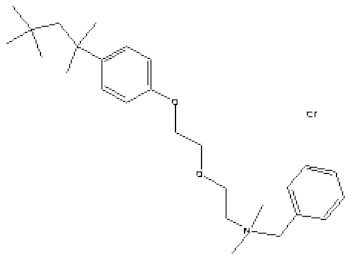
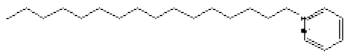
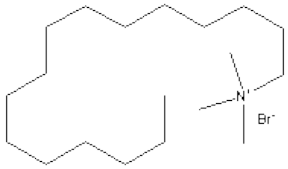
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Ketone	2B	-	Ethyl-2-methyl acetoacetate	609-14-3		$C_7H_{12}O_3$	144.2	Chemical Intermediate	Liquid
Ketone	2A	-	Acetone	67-64-1		C_3H_6O	58.1	Chemical Intermediate, Cleaning Agent, Industrical Chemical, Pharmaceutical Intermediate, Preservative, Solvent	Liquid
Ketone	NI	-	Di-iso-butyl ketone	108-83-8		$C_9H_{18}O$	142.2	Pharmaceutical Intermediate, Solvent	Liquid

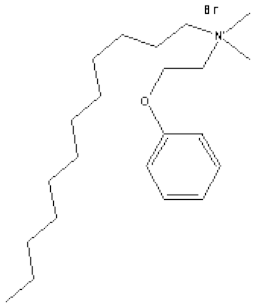
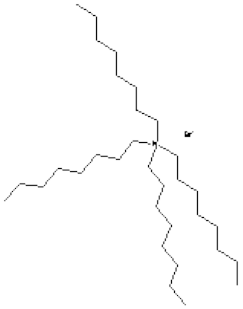
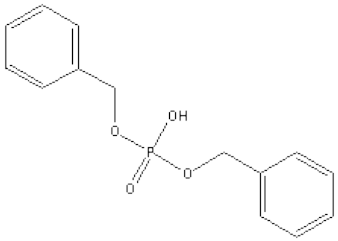
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Ketone	2A	-	Methyl ethyl ketone	78-93-3		C_4H_8O	72.1	Solvent	Liquid
Ketone	2B	-	2,6-Dichloro-5-fluoro-beta-oxo-3-pyridine-propanoate	96568-04-6		$C_{10}H_8Cl_2FNO_3$	280.1	Industrial Chemical, Pharmaceutical Intermediate	Liquid
Lactone	2A	-	gamma-Butyrolactone	96-48-0		$C_4H_6O_2$	86.1	Solvent	Liquid

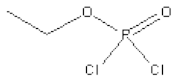
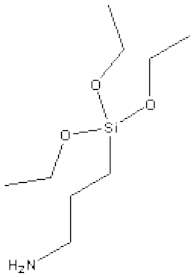
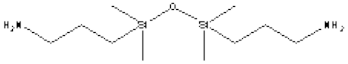
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Nitrate	2B	-	Ammonium nitrate	6484-52-2		$H_4N_2O_3$	80	Industrial Chemical	Liquid
Nitrate	1 (H)	-	Silver nitrate	7761-88-8		$AgNO_3$	169.9	Anti-Infective, Chemical Intermediate, Dye, Industrial Chemical, Laboratory Chemical, Pharmaceutical, Pharmaceutical Intermediate	Liquid
Nitrile	2B	-	3-Chloropropio nitrile	542-76-7		C_3H_4ClN	89.5	Chemical Intermediate, Pharmaceutical Intermediate	Liquid

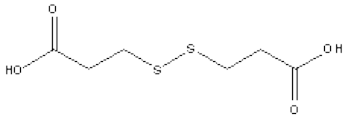
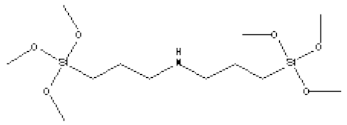
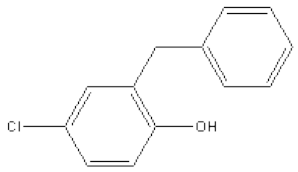
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Nitrile	1	4	Diethylamino propionitrile	5351-04-2		$C_7H_{14}N_2$	126.2	Industrial Chemical	Liquid
Nitrile	2A	-	Methyl cyanoacetate	105-34-0		$C_4H_5NO_2$	99.1	Chemical Intermediate	Liquid
Nitro Compound	1	4	Tetraethylene glycol diacrylate	17831-71-9		$C_{14}H_{22}O_7$	302.32	Chemical Intermediate, Industrial Chemical	Solid

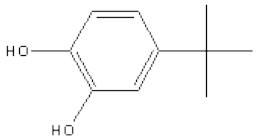
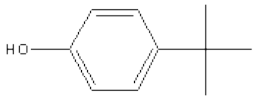
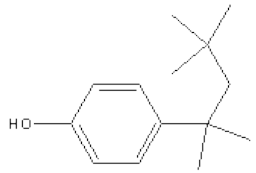
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Nitro Compound	1	not classifiable (likely 4)	2-Nitro-4-thiocyanoaniline	54029-45-7		$C_7H_5N_3O_2S$	195.2	Industrial Chemical	Solid
Onium Compound	2B	-	Ammonium nitrate	6484-52-2		$H_4N_2O_3$	80	Industrial Chemical	Liquid
Onium Compound	1	3	Benzalkonium chloride	8001-54-5		$C_9N_1H_{11}R1$[9]	471.5	Surfactant (cationic)	Liquid

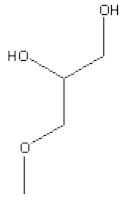
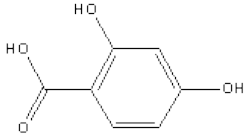
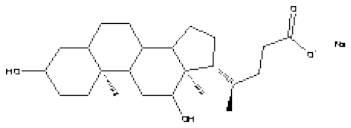
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Onium Compound	1	4	Benzethonium chloride	121-54-0		$C_{27}H_{42}ClNO_2$	448.1	Anti-Infective, Pharmaceutical, Veterinary Chemical	Solid
Onium Compound	1, 2A	-	Cetylpyridinium bromide	140-72-7		$C_{21}H_{38}BrN$	384.4	Anti-Infective; Laboratory Reagent; Surfactant (cationic)	Liquid
Onium Compound	1	4	Cetyltrimethyl ammonium bromide	57-09-0		$C_{19}H_{42}BrN$	364.4	Cosmetic	Liquid

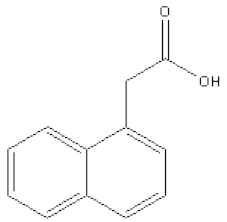
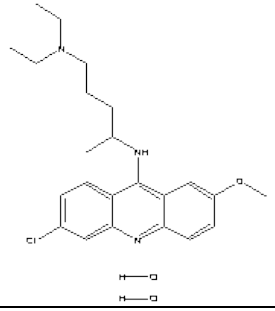
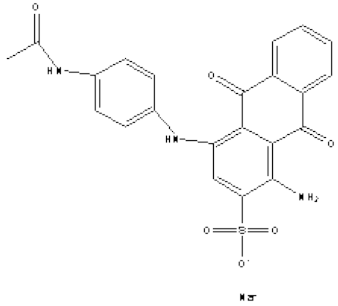
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Onium Compound	1	4	Domiphen bromide	538-71-6		$C_{22}H_{40}BrNO$	414.5	Anti-Infective, Pharmaceutical	Liquid
Onium Compound	1	not classifiable (likely 4)	tetra-N-Octylammonium bromide	14866-33-2		$C_{32}H_{68}BrN$	546.8	Industrial Chemical,Laboratory Chemical	Liquid
Organo-phosphorus Compound	2A	-	Dibenzyl phosphate	1623-08-1		$C_{14}H_{15}O_4P$	278.2	Pesticide	Liquid

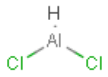
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Organo-phosphorus Compound	1	4	Phosphoro dicloridic acid, ethyl ester	1498-51-7		$C_2H_5Cl_2O_2P$	162.9	Chemical Intermediate, Pesticide	Liquid
Organo-silicon Compound	1	4	gamma-Aminopropyl triethoxy silane	919-30-2		$C_9H_{23}NO_3Si$	221.4	Industrial Chemical	Solid
Organo-silicon Compound	1	4	Bis-(3-aminopropyl) tetramethyl disiloxane	2469-55-8		$C_{10}H_{28}N_2OSi_2$	248.5	Industrial Chemical	Liquid

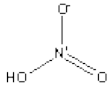
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Organo-silicon Compound	2B	-	3,3-Dithiopropionic acid	1119-62-6		$C_6H_{10}O_4S_2$	210.3	Chemical Intermediate, Laboratory Chemical	Solid
Organo-silicon Compound	1	1	Organo functional Silane 45-49	82985-35-1		$C_{12}H_{31}NO_6Si_2$	341.6	Polish	Solid
Phenol	1	4	2-Benzyl-4-chlorophenol	120-32-1		$C_{13}H_{11}ClO$	218.7	Anti-Fungal, Anti-Infective, Herbicide	Liquid

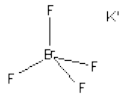
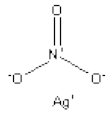
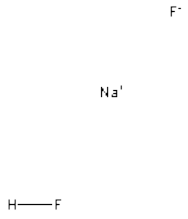
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Phenol	1	4	4-tert-Butylcatechol	98-29-3		$C_{10}H_{14}O_2$	166.2	Chemical Intermediate, Laboratory Chemical	Solid
Phenol	1	4	p-tert-Butylphenol	98-54-4		$C_{10}H_{14}O$	150.2	Chemical Intermediate, Perfume, Pesticide	Liquid
Phenol	1	2	4-(1,1,3,3-Tetramethyl butyl)phenol	140-66-9		$C_{14}H_{22}O$	206.3	Chemical Intermediate	Solid

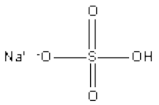
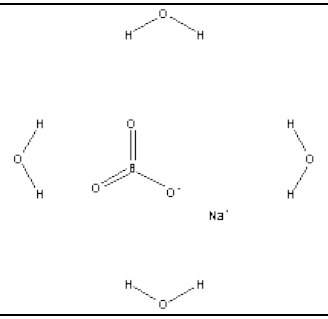
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Phenol	NI	-	3-Methoxy-1,2-propanediol	623-39-2		$C_4H_{10}O_3$	106.1	Laboratory Chemical	Solid
Phenol	1	4	beta-Resorcylic acid	89-86-1		$C_7H_6O_4$	154.1	Chemical Intermediate, Dye	Liquid
Polycyclic Compound	2A	-	Deoxycholic acid sodium salt	302-95-4		$C_{24}H_{39}NaO_4$	414.6	Anti-Infective, Laboratory Chemical, Solvent	Liquid

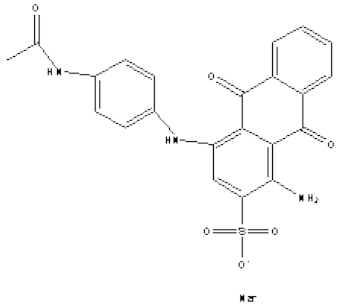
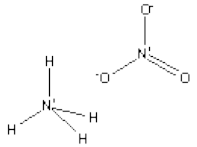
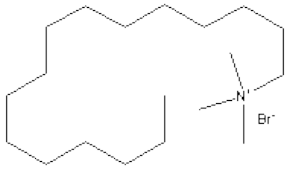
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Polycyclic Compound	1	4	1-Naphthalene acetic acid	86-87-3		$C_{12}H_{10}O_2$	186.2	Pesticide	Solid
Polycyclic Compound	1	3	Quinacrine	69-05-6		$C_{23}H_{32}Cl_3N_3O$	472.9	Pharmaceutical	Solid
Quinone	1	4	Acid blue 40	6424-85-7		$C_{22}H_{16}N_3NaO_6S$	473.4	Industrial Chemical	Liquid

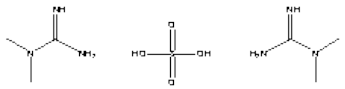
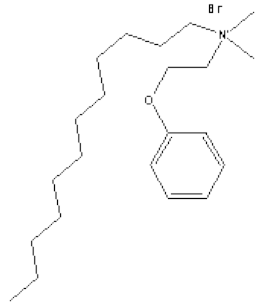
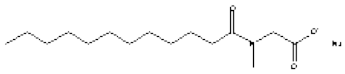
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Salt (inorganic)	1	4	Aluminum chloride	16603-84-2		$AlCl_2H$	98.9	Chemical Intermediate, Dye, Industrial Chemical, Laboratory Chemical, Pesticide, Preservative	Liquid
Salt (inorganic)	1	4	Antimony oxide	1309-64-4		Sb_2O_3	291.5	Flame Retardant, Industrial Chemical, Laboratory Chemical, Pharmaceutical Intermediate	Solid
Salt (inorganic)	1 (H)	-	Lime	1305-78-8		CaO	56.1	Building Material, Chemical Intermediate, Cleaning Agent, Fertilizer, Industrial Chemical	Solid

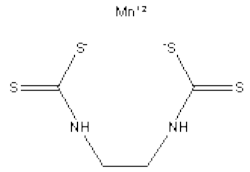
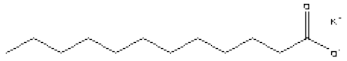
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Salt (inorganic)	1 (H)	-	Magnesium hydroxide	12141-11-6		MgOH	42.3	Chemical Intermediate, Flame Retardant, Industrial Chemical, Pharmaceutical, Veterinary Agent	Solid
Salt (inorganic)	1 (H)	-	Nitric acid	7697-37-2		NO_3	63	Chemical Intermediate, Industrial Chemical, Laboratory Reagent, Pharmaceutical Intermediate	Solid
Salt (inorganic)	1 (H)	-	Potassium hydroxide	1310-58-3		KOH	56.1	Chemical Intermediate, Cleaning Agent, Fertilizer, Food Additive, Industrial Chemical, Veterinary Chemical	Liquid

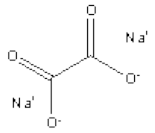
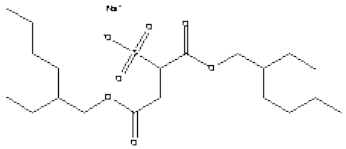
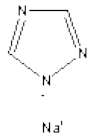
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Salt (inorganic)	NI	-	Potassium tetrafluoroborate	14075-53-7		BF_4K	125.9	Pesticide, Industrial Chemical	Liquid
Salt (inorganic)	1 (H)	-	Silver nitrate	7761-88-8		$AgNO_3$	169.9	Anti-Infective, Chemical Intermediate, Dye, Industrial Chemical, Laboratory Chemical, Pharmaceutical, Pharmaceutical Intermediate	Liquid
Salt (inorganic)	1 (H)	-	Sodium hydrogen difluoride	1333-83-1		F_2HNa	62	Anti-Infective, Cleaning Agent, Industrial Chemical, Preservative	Liquid

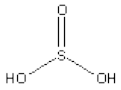
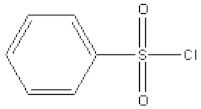
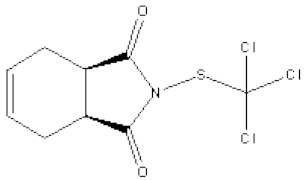
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Salt (inorganic)	1	4	Sodium hydrogen sulfate	7681-38-1		HN_aO_4S	120.1	Cleaning Agent, Laboratory Chemical, Pesticide	Liquid
Salt (inorganic)	1	1	Sodium perborate tetrahydrate	10486-00-7		BH_8NaO_7	153.9	Cleaning Agent	Liquid
Salt (inorganic)	1 (H)	-	Zinc chloride	7646-85-7		$C_{31}H_{56}0_9$	136.3	Anti-Infective, Flame Retardant, Herbicide, Industrial Chemical. Pesticide, Preservative	Liquid

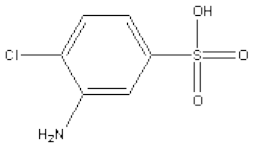
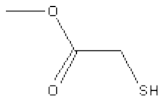
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Salt (organic)	1	4	Acid blue 40	6424-85-7		$C_{22}H_{16}N_3NaO_6S$	473.4	Industrial Chemical	Solid
Salt (organic)	2B	-	Ammonium nitrate	6484-52-2		$H_4N_2O_3$	80.0	Industrial Chemical	Liquid
Salt (organic)	1	4	Cetyltrimethyl ammonium bromide	57-09-0		$C_{19}H_{42}BrN$	364.4	Cosmetic	Solid

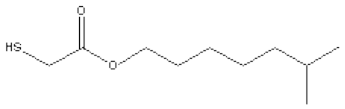
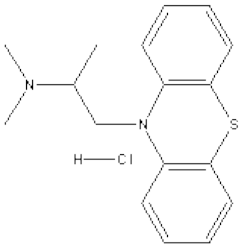
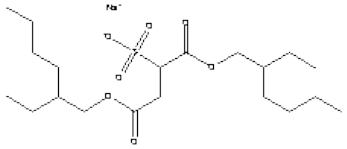
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Salt (organic)	NI	-	n,n-Dimethyl guanidine sulfate	598-65-2		$C_6H_{20}N_6O_4S$	272.3	Laboratory Chemical	Liquid
Salt (organic)	1	4	Domiphen bromide	538-71-6		$C_{22}H_{40}BrNO$	414.5	Anti-Infective, Pharmaceutical	Solid
Salt (organic)	2B	-	N-Laurylsarcosine sodium salt	137-16-6		$C_{15}H_{28}NNaO_3$	293.4	Cleaning Agent, Laboratory Chemical, Surfactant (anionic)	Liquid

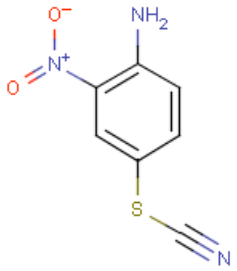
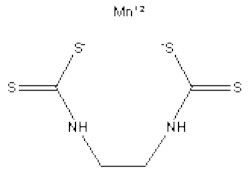
Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Salt (organic)	2B	-	Maneb	12427-38-2		$C_4H_6MnN_2S_4$	265.3	Pesticide	Liquid
Salt (organic)	1	4	Potassium laurate	10124-65-9		$C_{12}H_{23}KO_2$	238.4	Cosmetic Ingredient, Pesticide	Liquid
Salt (organic)	NI	-	Sodium lauryl sulfate	151-21-3		$C_{12}H_{25}NaO_4S$	288.4	Surfactant (anionic)	Liquid

Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Salt (organic)	1	4	Sodium oxalate	62-76-0		$C_2Na_2O_4$	134	Industrial Chemical, Laboratory Chemical	Liquid
Salt (organic)	1	4	Di(2-ethylhexyl) sodium sulfosuccinate	577-11-7		$C_{20}H_{37}NaO_7S$	444.6	Adjuvant, Cleaner, Solubilizer, Wetting Agent	Liquid
Salt (organic)	1	4	1,2,4-Triazole, sodium salt	41253-21-8		$C_2H_2N_3N_a$	91.1	Anti-Fungal	Solid

Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Sulfur Compound (inorganic)	1 (H)	-	Sulfuric acid	7664-93-9		H_2O_3S	98.1	Battery Acid, Chemical Intermediate, Cleaning Agent, Fertilizer, Food Additive, Industrial Chemical, Laboratory Chemical	Liquid
Sulfur Compound (organic)	1	4	Benzenesulfonyl chloride	98-09-9		$C_6H_5ClO_2S$	176.6	Chemical Intermediate, Pesticide	Liquid
Sulfur Compound (organic)	1	4	Captan 90-concentrate (solid)	133-06-2		$C_9H_8Cl_3NO_2S$	300.6	Pesticide	Liquid

Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Sulfur Compound (organic)	NI	-	2-(n-Dodecylthio) ethanol	1462-55-1		$C_{14}H_{30}OS$	206.3	Laboratory Chemical	Solid
Sulfur Compound (organic)	1	4	4-Chloro-methanilic acid	98-36-2		$C_6H_6ClNO_3S$	207.6	Chemical Intermediate, Industrial Chemical, Laboratory Chemical	Solid
Sulfur Compound (organic)	1	4	Methylthio-glycolate	2365-48-2		$C_3H_6O_2S$	106.1	Industrial Chemical	Solid

Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Sulfur Compound (organic)	NI	-	iso-Octylthio-glycolate	25103-09-7		$C_{10}H_{20}O_2S$	205.3	Industrial Chemical	Liquid
Sulfur Compound (organic)	1	3	Promethazine hydrochloride	58-33-3		$C_{17}H_{21}ClN_2S$	320.9	Pharmaceutical	Liquid
Sulfur Compound (organic)	1	4	Di(2-ethylhexyl) sodium sulfosuccinate	577-11-7		$C_{20}H_{37}NaO_7S$	444.6	Adjuvant, Cleaner, Solubilizer, Wetting Agent	Solid

Chemical Class[1]	GHS[2] Cat.[3]	NICEATM Cat. 1 Subcat[4]	Substance	CASRN[5]	Chemical Structure	Molecular Formula	MW[6]	Product Class	Physical Form Tested
Sulfur Compound (organic)	1	not classifiable (likely 4)	2-Nitro-4-thiocyanoaniline	54029-45-7		$C_7H_5N_3O_2S$	195.2	Industrial Chemical	Solid
Urea Compound	2B	-	Maneb	12427-38-2		$C_4H_6MnN_2S_4$	265.3	Pesticide	Liquid

[1]Chemical Class=Based on the MeSH Medical Subject Heading. Available http://www.nlm.nih.gov/mesh; substances may be assigned into one or more chemical classes (see **Appendix B**).
[2]GHS=Globally Harmonized System (UN [2003])
[3]Cat.=Category
[4]NICEATM Cat. 1 Subcat. = Category 1 subcategories = NICEATM-assigned subcategories for GHS Category 1 substances (ocular corrosives and severe irritants) were assigned based on the following: 0 = not classifiable; 1 = positive response based on a persistent lesion involving the cornea, iris, and/or conjunctiva through to day 21 in at least one of three rabbits and not on severity; 2 = positive response based on mean for first 3 days (corneal opacity [CO] score >3 and <4 or iritis [IR] score >1.5) in at least two of three rabbits but lesions do not persist through day 21; 3 = positive response based on mean for first 3 days (CO >3 and <4 or IR >1.5) in at least two of three rabbits and a persistent (>21 days) lesion in at least one rabbit ; 4 = CO score of 4 at any time in at least one of three rabbits.
[5]CASRN=Chemical Abstract Services Registry Number
[6]MW = molecular weight;
[7]"-" = not applicable
[8]'n' in molecular formula indicates that the polymer can be repeated multiple times;
[9]R1 in molecular formula indicates any alkyl sidechain

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APPENDIX V-D

LIST OF PROPOSED REFERENCE SUBSTANCES FOR VALIDATION STUDIES OF *IN VITRO* TEST METHODS FOR THE IDENTIFICATION OF OCULAR CORROSIVES/SEVERE IRRITANTS (SORTED BY PRODUCT CLASS, AND SUBSTANCE NAME)

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Product Class	GHS[1] Category	NICEATM Cat[2]. 1 Subcat[3]	Substance	CASRN[4]	MW[5]	Chemical Class[6]	Physical Form Tested
Adjuvant, Solubilier, Wetting Agent	2A	-[7]	Di(2-ethylhexyl)sodium sulfosuccinate	577-11-7	444.6	Ester, Organophosphorus Compound	Liquid
Anesthetics	1 (H)	-	Chloroform	67-66-3	119.4	Hydrocarbon (acyclic)	Liquid
Anesthetics	1	4	Cyclohexyl isocyanate	3173-53-3	125.2	Isocyanate	Liquid
Anti-Fungals	1 (H)	-	Ammonia	7664-41-7	17.0	Alkali	Liquid
Anti-Fungals	1	4	2-Benzyl-4-chlorophenol	120-32-1	218.7	Phenol	Solid
Anti-Fungals	2A	-	2,6-Dichlorobenzoyl chloride	4659-45-4	209.5	Acyl Halide	Liquid
Anti-Fungals	1	4	Granuform	30525-89-4	30.0	Aldehyde, Ether	Solid
Anti-Fungals	NI	-	Imidazole	288-32-4	68.1	Hydrocarbon (halogenated)	Solid
Anti-Fungals	1	4	1,2,4-Triazole, sodium salt	41253-21-8	91.1	Heterocyclic Compound, Salt (organic)	Solid
Anti-Infectives	1	4	Benzethonium chloride	121-54-0	448.1	Amine, Onium Compound	Liquid
Anti-Infectives	1	4	2-Benzyl-4-chlorophenol	120-32-1	218.7	Phenol	Solid
Anti-Infectives	1, 2A	2	Cetylpyridinium bromide	140-72-7	384.4	Onium Compound, Heterocyclic Compound	Liquid
Anti-Infectives	1	4	Chlorhexidine	55-56-1	505.4	Amidine	Solid
Anti-Infectives	2A	-	Deoxycholic acid sodium salt	302-95-4	414.6	Alcohol, Acid (organic) [carboxylic acid], Salt (organic), Polycyclic Compound	Liquid

Product Class	GHS[1] Category	NICEATM Cat[2]. 1 Subcat[3]	Substance	CASRN[4]	MW[5]	Chemical Class[6]	Physical Form Tested
Anti-Infectives	2A	-	2,6-Dichlorobenzoyl chloride	4659-45-4	209.5	Acyl Halide	Liquid
Anti-Infectives	1	4	Domiphen bromide	538-71-6	414.5	Ether, Onium Compound, Salt (organic)	Liquid
Anti-Infectives	1	4	Granuform	30525-89-4	30.0	Aldehyde, Ether	Solid
Anti-Infectives	1 (H)	-	Silver nitrate	7761-88-8	169.9	Nitrate, Salt (inorganic)	Liquid
Anti-Infectives	1 (H)	-	Sodium hydrogen difluoride	1333-83-1	62.0	Salt (inorganic)	Liquid
Anti-Infectives	1	4	N,N,N`,N`-Tetramethyl hexanediamine	111-18-2	172.3	Amine	Liquid
Anti-Infectives	1 (H)	-	Zinc chloride	7646-85-7	136.3	Salt (inorganic)	Solid
Battery Acid	1 (H)	-	Sulfuric acid	7664-93-9	98.1	Acid (inorganic), Sulfur Compound (inorganic)	Liquid
Building Materials	NI	-	Iso-octyl acrylate	29590-42-9	184.3	Ester	Liquid
Building Materials	1 (H)	-	Lime	1305-78-8	56.1	Salt (inorganic)	Solid
Caustic Agents	1	4	Sodium hydroxide	1310-73-2	40.0	Alkali	Liquid
Caustic Agents	1	4	Trichloroacetic acid	76-03-9	163.4	Acid (organic) [carboxylic acid]	Liquid
Chemical Intermediates	2A	-	Methyl acetate	79-20-9	74.1	Ester	Liquid
Chemical Intermediates	2B	-	Ethyl-2-methyl acetoacetate	609-14-3	144.2	Ester, Ketone	Solid
Chemical Intermediates	2A	-	Acetone	67-64-1	58.1	Ketone	Liquid-
Chemical Intermediates	1	4	Methoxyethyl acrylate	3121-61-7	130.1	Ester, Ether	Liquid

Product Class	GHS[1] Category	NICEATM Cat[2]. 1 Subcat[3]	Substance	CASRN[4]	MW[5]	Chemical Class[6]	Physical Form Tested
Chemical Intermediates	1	4	Aluminum chloride	16603-84-2	98.9	Salt (inorganic)	Liquid
Chemical Intermediates	NI	-	tetra-Aminopyrimidine sulfate	5392-28-9	238.2	Amine, Heterocyclic Compound, Salt (organic)	Solid
Chemical Intermediates	1 (H)	-	Ammonia	7664-41-7	17.0	Alkali	Liquid
Chemical Intermediates	1	4	Benzenesulfonyl chloride	98-09-9	176.6	Acyl Halide, Sulfur Compound (organic)	Liquid
Chemical Intermediates	2A	-	Benzotrichloride	98-07-7	195.5	Hydrocarbon (cyclic)	Liquid
Chemical Intermediates	1	4	n-Butanol	71-36-3	74.1	Alcohol	Liquid
Chemical Intermediates	1	4	4-tert-Butylcatechol	98-29-3	166.2	Phenol	Liquid
Chemical Intermediates	1	4	p-tert-Butylphenol	98-54-4	150.2	Phenol	Solid
Chemical Intermediates	1 (H)	-	Chloroform	67-66-3	119.4	Hydrocarbon (acyclic)	Liquid
Chemical Intermediates	2B	-	3-Chloropropionitrile	542-76-7	89.5	Nitrile	Liquid
Chemical Intermediates	1	4	Cyclohexyl isocyanate	3173-53-3	125.2	Isocyanate	Liquid
Chemical Intermediates	1	1	3,4-Dichlorophenyl isocyanate	102-36-3	188.1	Isocyanate	Liquid
Chemical Intermediates	1	4	Diethylethanolamine	100-37-8	117.9	Amine, Alcohol	Liquid
Chemical Intermediates	1	1	2,5-Dimethylhexanediol	110-03-2	146.2	Alcohol	Solid
Chemical Intermediates	2B	-	3,3-Dithiopropionic acid	1119-62-6	210.3	Acid (organic) [carboxylic acid], Organosilicon Compound	Solid

Product Class	GHS[1] Category	NICEATM Cat[2]. 1 Subcat[3]	Substance	CASRN[4]	MW[5]	Chemical Class[6]	Physical Form Tested
Chemical Intermediates	NI	-	2-(n-Dodecylthio)ethanol	1462-55-1	206.3	Alcohol, Ether, Sulfur Compound (organic)	Solid
Chemical Intermediates	1	4	Hydroxyethyl acrylate	818-61-1	116.1	Alcohol, Ester	Liquid
Chemical Intermediates	NI	-	iso-Propyl bromide	75-26-3	123.0	Hydrocarbon (halogenated)	Liquid
Chemical Intermediates	1	4	alpha-Ketoglutaric acid	328-50-7	146.1	Acid (organic) [carboxylic acid]	Solid
Chemical Intermediates	1 (H)	-	Lime	1305-78-8	56.1	Salt (inorganic)	Solid
Chemical Intermediates	1 (H)	-	Magnesium hydroxide	12141-11-6	42.3	Salt (inorganic)	Solid
Chemical Intermediates	1	4	4-Chloro-methanilic acid	98-36-2	207.6	Amine, Sulfur Compound (organic)	Solid
Chemical Intermediates	2A	-	Methyl cyanoacetate	105-34-0	99.1	Ester, Nitrile	Liquid
Chemical Intermediates	1	4	2-Methylbutyric acid	116-53-0	102.1	Acid (organic) [carboxylic acid]	Liquid
Chemical Intermediates	1 (H)	-	Nitric acid	7697-37-2	63.0	Acid, Salt (inorganic)	Liquid
Chemical Intermediates	1	4	n-Octylamine	111-86-4	129.2	Amine	Liquid
Chemical Intermediates	NI	-	2,4-Pentanediol	625-69-4	104.2	Alcohol	Liquid
Chemical Intermediates	1	2	4-(1,1,3,3-Tetramethylbutyl)phenol	140-66-9	206.3	Phenol	Solid
Chemical Intermediates	1	4	Phosphorodicloridic acid, ethyl ester	1498-51-7	162.9	Ester, Organophosphorus Compound	Liquid
Chemical Intermediates	1 (H)	-	Potassium hydroxide	1310-58-3	56.1	Alkali, Salt (inorganic)	Solid
Chemical Intermediates	1	4	beta-Resorcylic acid	89-86-1	154.1	Acid (organic) [carboxylic acid], Phenol	Solid

Product Class	GHS[1] Category	NICEATM Cat[2]. 1 Subcat[3]	Substance	CASRN[4]	MW[5]	Chemical Class[6]	Physical Form Tested
Chemical Intermediates	1 (H)	-	Silver nitrate	7761-88-8	169.9	Nitrate, Salt (inorganic)	Liquid
Chemical Intermediates	1	4	Sodium hydroxide	1310-73-2	40.0	Alkali	Liquid
Chemical Intermediates	1 (H)	-	Sulfuric acid	7664-93-9	98.1	Acid (inorganic), Sulfur Compound (inorganic)	Liquid
Chemical Intermediates	1	3	Dibenzoyl-L-tartaric acid	2743-38-6	358.3	Acid (organic) [Carboxylic Acid], Ester	Solid
Chemical Intermediates	1	4	Tetraethylene glycol diacrylate	17831-71-9	302.3	Ether, Nitro Compound	Liquid
Chemical Intermediates	1	4	Tetrahydrofuran	109-99-9	72.1	Ether, Heterocyclic Compound	Liquid
Chemical Intermediates	NI	-	Toluene	108-88-3	92.1	Hydrocarbon (cyclic)	Liquid
Chemical Intermediates	1	4	Trichloroacetyl chloride	76-02-8	163.4	Acyl Halide	Liquid
Cleaners or Cleaning Agents	2A	-	Acetone	67-64-1	58.1	Ketone	Liquid
Cleaners or Cleaning Agents	1 (H)	-	Ammonia	7664-41-7	17.0	Alkali	Liquid
Cleaners or Cleaning Agents	1 (H)	-	Chloroform	67-66-3	119.4	Hydrocarbon (acyclic)	Liquid
Cleaners or Cleaning Agents	1	4	Cyclohexyl isocyanate	3173-53-3	125.2	Isocyanate	Liquid
Cleaners or Cleaning Agents	2B	-	N-Laurylsarcosine sodium salt	137-16-6	293.4	Amide, Amine, Salt (organic)	Liquid
Cleaners or Cleaning Agents	1 (H)	-	Lime	1305-78-8	56.1	Salt (inorganic)	Solid
Cleaners or Cleaning Agents	1	4	Polyethylene glycol nonylphenyl ether (Surfonic HDL-1)	9016-45-9	308.5	Alcohol, Ether	Liquid

Product Class	GHS[1] Category	NICEATM Cat[2]. 1 Subcat[3]	Substance	CASRN[4]	MW[5]	Chemical Class[6]	Physical Form Tested
Cleaners or Cleaning Agents	1 (H)	-	Potassium hydroxide	1310-58-3	56.1	Alkali, Salt (inorganic)	Solid
Cleaners or Cleaning Agents	1	1	Propyl lactate	616-09-1	132.2	Ester, Alcohol	Solid
Cleaners or Cleaning Agents	1 (H)	-	Sodium hydrogen difluoride	1333-83-1	62.0	Salt (inorganic)	Liquid
Cleaners or Cleaning Agents	1	4	Sodium hydrogen sulfate	7681-38-1	120.1	Salt (inorganic)	Solid
Cleaners or Cleaning Agents	NI	-	Sodium lauryl sulfate	151-21-3	288.4	Acid (organic) [Carboxylic Acid], Salt (organic)	Liquid
Cleaners or Cleaning Agents	1	1	Sodium perborate tetrahydrate	10486-00-7	153.9	Boron Compound, Salt (inorganic)	Solid
Cleaners or Cleaning Agents	1	4	Di(2-ethylhexyl)sodium sulfosuccinate	577-11-7	444.6	Ester, Sulfur Compound (organic), Salt (organic)	Liquid
Cleaners or Cleaning Agents	1 (H)	-	Sulfuric acid	7664-93-9	98.1	Acid (inorganic), Sulfur Compound (inorganic)	Liquid
Cosmetics, Cosmetic Ingredients & Perfumes	1	4	n-Butanol	71-36-3	74.1	Alcohol	Liquid
Cosmetics, Cosmetic Ingredients & Perfumes	1	4	p-tert-Butylphenol	98-54-4	150.2	Phenol	Solid
Cosmetics, Cosmetic Ingredients & Perfumes	1	4	Cetyltrimethylammonium bromide	57-09-0	364.4	Onium Compound, Salt (organic)	Liquid
Cosmetics, Cosmetic Ingredients & Perfumes	2B	-	Hexyl cinnamic aldehyde	101-86-0	216.3	Aldehyde	Liquid

Product Class	GHS[1] Category	NICEATM Cat[2]. 1 Subcat[3]	Substance	CASRN[4]	MW[5]	Chemical Class[6]	Physical Form Tested
Cosmetics, Cosmetic Ingredients & Perfumes	1	4	Lactic acid	50-21-5	90.1	Acid (organic) [carboxylic acid], Alcohol	Liquid
Cosmetics, Cosmetic Ingredients & Perfumes	1	4	n-Acetyl-methionine	1115-47-5	191.3	Amide, Amino Acid	Solid
Cosmetics, Cosmetic Ingredients & Perfumes	1	4	2-Methylbutyric acid	116-53-0	102.1	Acid (organic) [carboxylic acid]	Liquid
Cosmetics, Cosmetic Ingredients & Perfumes	1	4	Potassium laurate	10124-65-9	238.4	Acid (organic) [carboxylic acid], Salt (organic)	Liquid
Cosmetics, Cosmetic Ingredients & Perfumes	1	1	Protectol PP	80-54-6	204.3	Aldehyde	Liquid
Cosmetics, Cosmetic Ingredients & Perfumes	NI	-	Sodium lauryl sulfate	151-21-3	288.4	Acid (organic) [Carboxylic Acid], Salt (organic)	Liquid
Fertilizers	1 (H)	-	Ammonia	7664-41-7	17.0	Alkali	Liquid
Fertilizers	1 (H)	-	Lime	1305-78-8	56.1	Salt (inorganic)	Solid
Fertilizers	1 (H)	-	Potassium hydroxide	1310-58-3	56.1	Alkali, Salt (inorganic)	Solid
Fertilizers	1 (H)	-	Sulfuric acid	7664-93-9	98.1	Acid (inorganic), Sulfur Compound (inorganic)	Liquid
Flame Retardants	1	4	Antimony oxide	1309-64-4	291.5	Salt (inorganic)	Solid

Product Class	GHS[1] Category	NICEATM Cat[2]. 1 Subcat[3]	Substance	CASRN[4]	MW[5]	Chemical Class[6]	Physical Form Tested
Flame Retardants	1 (H)	-	Magnesium hydroxide	12141-11-6	42.3	Salt (inorganic)	Solid
Flame Retardants	1 (H)	-	Zinc chloride	7646-85-7	136.3	Salt (inorganic)	Solid
Food Additives	2A	-	Methyl acetate	79-20-9	74.1	Ester	Liquid
Food Additives	1	4	n-Butanol	71-36-3	74.1	Alcohol	Liquid
Food Additives	2B	-	Hexyl cinnamic aldehyde	101-86-0	216.3	Aldehyde	Liquid
Food Additives	1	4	n-Acetyl-methionine	1115-47-5	191.3	Amide, Amino Acid	Solid
Food Additives	1 (H)	-	Potassium hydroxide	1310-58-3	56.1	Alkali, Salt (inorganic)	Solid
Food Additives	1	1	Propyl lactate	616-09-1	132.2	Ester, Alcohol	Solid
Food Additives	1	1	Protectol PP	80-54-6	204.3	Aldehyde	Liquid
Food Additives	NI	-	Sodium lauryl sulfate	151-21-3	288.4	Acid (organic) [Carboxylic Acid], Salt (organic)	Liquid
Food Additives	1 (H)	-	Sulfuric acid	7664-93-9	98.1	Acid (inorganic), Sulfur Compound (inorganic)	Liquid
Herbicides	2A	-	Methyl acetate	79-20-9	74.1	Ester	Liquid
Herbicides	1 (H)	-	Ammonia	7664-41-7	17.0	Alkali	Liquid
Herbicides	1	4	2-Benzyl-4-chlorophenol	120-32-1	218.7	Phenol	Solid
Herbicides	1	4	Trichloroacetic acid	76-03-9	163.4	Acid (organic) [carboxylic acid]	Liquid
Herbicides	1 (H)	-	Zinc chloride	7646-85-7	136.3	Salt (inorganic)	Solid

Product Class	GHS[1] Category	NICEATM Cat[2]. 1 Subcat[3]	Substance	CASRN[4]	MW[5]	Chemical Class[6]	Physical Form Tested
Industrial Chemicals & Dyes	1	4	Acetic acid	64-19-7	60.1	Acid (organic) [carboxylic acid]	Liquid
Industrial Chemicals & Dyes	2A	-	Acetone	67-64-1	58.1	Ketone	Liquid
Industrial Chemicals & Dyes	1	4	Acid blue 40	6424-85-7	473.4	Amine, Quinone, Salt (organic)	Solid
Industrial Chemicals & Dyes	1	4	Methoxyethyl acrylate	3121-61-7	130.1	Ester, Ether	Liquid
Industrial Chemicals & Dyes	1	4	Aluminum chloride	16603-84-2	98.9	Salt (inorganic)	Liquid
Industrial Chemicals & Dyes	1	4	gamma-Aminopropyltriethoxy silane	919-30-2	221.4	Amine, Amidine, Organosilicon Compound	Liquid
Industrial Chemicals & Dyes	1 (H)	-	Ammonia	7664-41-7	17.0	Alkali	Liquid
Industrial Chemicals & Dyes	2B	-	Ammonium nitrate	6484-52-2	80.0	Onium Compound, Nitrate, Salt (organic)	Solid
Industrial Chemicals & Dyes	1	4	Antimony oxide	1309-64-4	291.5	Salt (inorganic)	Solid
Industrial Chemicals & Dyes	1	4	n-Butanol	71-36-3	74.1	Alcohol	Liquid
Industrial Chemicals & Dyes	2A	-	4-Carboxybenzaldehyde	619-66-9	150.1	Acid (organic) [Carboxylic Acid], Aldehyde	Liquid
Industrial Chemicals & Dyes	1 (H)	-	Chloroform	67-66-3	119.4	Hydrocarbon (acyclic)	Liquid
Industrial Chemicals & Dyes	1	4	Cyclohexyl isocyanate	3173-53-3	125.2	Isocyanate	Liquid
Industrial Chemicals & Dyes	1	1	3,4-Dichlorophenyl isocyanate	102-36-3	188.1	Isocyanate	Liquid
Industrial Chemicals & Dyes	1	4	Diethylaminopropionitrile	5351-04-2	126.2	Amine, Nitrile	Liquid
Industrial Chemicals & Dyes	1	4	1,3-Diiminobenz (f)-isoindoline	65558-69-2	195.2	Amine, Heterocyclic Compound	Solid

Product Class	GHS[1] Category	NICEATM Cat[2]. 1 Subcat[3]	Substance	CASRN[4]	MW[5]	Chemical Class[6]	Physical Form Tested
Industrial Chemicals & Dyes	1	4	Bis-(3-aminopropyl) tetramethyl disiloxane	2469-55-8	248.5	Amine, Amidine, Organosilicon Compound	Liquid
Industrial Chemicals & Dyes	1	4	Granuform	30525-89-4	30.0	Aldehyde, Ether	Solid
Industrial Chemicals & Dyes	1	2	2-Hydroxyisobutyric acid ethylester	80-55-7	132.2	Alcohol, Ester	Solid
Industrial Chemicals & Dyes	1	4	2-Hydroxyisobutyric acid	594-61-6	104.1	Acid (organic) [Carboxylic Acid]	Solid
Industrial Chemicals & Dyes	1 (H)	-	Lime	1305-78-8	56.1	Salt (inorganic)	Solid
Industrial Chemicals & Dyes	1 (H)	-	Magnesium hydroxide	12141-11-6	42.3	Salt (inorganic)	Solid
Industrial Chemicals & Dyes	1	4	4-Chloro-methanilic acid	98-36-2	207.6	Amine, Sulfur Compound (organic)	Solid
Industrial Chemicals & Dyes	1	4	Methylthioglycolate	2365-48-2	106.1	Ester, Sulfur Compound (organic)	Liquid
Industrial Chemicals & Dyes	1 (H)	-	Nitric acid	7697-37-2	63.0	Acid, Salt (inorganic)	Liquid
Industrial Chemicals & Dyes	1	0 (likely 4)	tetra-N-Octylammonium bromide	14866-33-2	546.8	Onium Compound	Solid
Industrial Chemicals & Dyes	NI	-	iso-Octylthioglycolate	25103-09-7	205.3	Ester, Sulfur Compound (organic)	Liquid
Industrial Chemicals & Dyes	1	4	Polyethylene glycol nonylphenyl ether (Surfonic HDL-1)	9016-45-9	308.5	Alcohol, Ether	Liquid
Industrial Chemicals & Dyes	1 (H)	-	Potassium hydroxide	1310-58-3	56.1	Alkali, Salt (inorganic)	Solid
Industrial Chemicals & Dyes	NI	-	Potassium tetrafluoroborate	14075-53-7	125.9	Salt (inorganic)	Solid
Industrial Chemicals & Dyes	2B	-	2,6-Dichloro-5-fluoro-beta-oxo-3-pyridinepropanoate	96568-04-6	280.1	Ester, Heterocyclic Compound, Ketone	Solid

Product Class	GHS[1] Category	NICEATM Cat[2]. 1 Subcat[3]	Substance	CASRN[4]	MW[5]	Chemical Class[6]	Physical Form Tested
Industrial Chemicals & Dyes	1	4	beta-Resorcylic acid	89-86-1	154.1	Acid (organic) [carboxylic acid], Phenol	Solid
Industrial Chemicals & Dyes	1 (H)	-	Silver nitrate	7761-88-8	169.9	Nitrate, Salt (inorganic)	Liquid
Industrial Chemicals & Dyes	1 (H)	-	Sodium hydrogen difluoride	1333-83-1	62.0	Salt (inorganic)	Liquid
Industrial Chemicals & Dyes	1	4	Sodium hydroxide	1310-73-2	40.0	Alkali	Liquid
Industrial Chemicals & Dyes	1	4	Sodium oxalate	62-76-0	134.0	Acid (organic) [carboxylic acid], Salt (organic)	Solid
Industrial Chemicals & Dyes	1 (H)	-	Sulfuric acid	7664-93-9	98.1	Acid (inorganic), Sulfur Compound (inorganic)	Liquid
Industrial Chemicals & Dyes	1	4	Tetraethylene glycol diacrylate	17831-71-9	302.3	Ether, Nitro Compound	Liquid
Industrial Chemicals & Dyes	1	4	Tetrahydrofuran	109-99-9	72.1	Ether, Heterocyclic Compound	Liquid
Industrial Chemicals & Dyes	1	4	N,N,N`,N`-Tetramethyl hexanediamine	111-18-2	172.3	Amine	Liquid
Industrial Chemicals & Dyes	1	0 (likely 4)	2-Nitro-4-thiocyanoaniline	54029-45-7	195.2	Amine, Nitro Compound, Sulfur Compound (organic)	Solid
Industrial Chemicals & Dyes	NI	-	Toluene	108-88-3	92.1	Hydrocarbon (cyclic)	Liquid
Industrial Chemicals & Dyes	1	4	Trichloroacetyl chloride	76-02-8	163.4	Acyl Halide	Liquid
Industrial Chemicals & Dyes	1 (H)	-	Zinc chloride	7646-85-7	136.3	Salt (inorganic)	Solid
Laboratory Chemicals	2A	-	Methyl acetate	79-20-9	74.1	Ester	Liquid
Laboratory Chemicals	1	4	Acetic acid	64-19-7	60.1	Acid (organic) [carboxylic acid]	Liquid

Product Class	GHS[1] Category	NICEATM Cat[2]. 1 Subcat[3]	Substance	CASRN[4]	MW[5]	Chemical Class[6]	Physical Form Tested
Laboratory Chemicals	1	4	Methoxyethyl acrylate	3121-61-7	130.1	Ester, Ether	Liquid
Laboratory Chemicals	1	4	Aluminum chloride	16603-84-2	98.9	Salt (inorganic)	Liquid
Laboratory Chemicals	1	4	Antimony oxide	1309-64-4	291.5	Salt (inorganic)	Solid
Laboratory Chemicals	1	4	4-tert-Butylcatechol	98-29-3	166.2	Phenol	Liquid
Laboratory Chemicals	1, 2A	2	Cetylpyridinium bromide	140-72-7	384.4	Onium Compound, Heterocyclic Compound	Liquid
Laboratory Chemicals	2A	-	Deoxycholic acid sodium salt	302-95-4	414.6	Alcohol, Acid (organic) [carboxylic acid], Salt (organic), Polycyclic Compound	Liquid
Laboratory Chemicals	1	4	1,3-Diiminobenz (f)-isoindoline	65558-69-2	195.2	Amine, Heterocyclic Compound	Solid
Laboratory Chemicals	NI	-	N,n-Dimethylguanidine sulfate	598-65-2	272.3	Amidine, Salt (organic)	Solid
Laboratory Chemicals	2B	-	3,3-Dithiopropionic acid	1119-62-6	210.3	Acid (organic) [carboxylic acid], Organosilicon Compound	Solid
Laboratory Chemicals	1	4	Granuform	30525-89-4	30.0	Aldehyde, Ether	Solid
Laboratory Chemicals	1	4	alpha-Ketoglutaric acid	328-50-7	146.1	Acid (organic) [carboxylic acid]	Solid
Laboratory Chemicals	2B	-	N-Laurylsarcosine sodium salt	137-16-6	293.4	Amide, Amine, Salt (organic)	Liquid
Laboratory Chemicals	1	4	4-Chloro-methanilic acid	98-36-2	207.6	Amine, Sulfur Compound (organic)	Solid
Laboratory Chemicals	1	4	n-Acetyl-methionine	1115-47-5	191.3	Amide, Amino Acid	Solid

Product Class	GHS[1] Category	NICEATM Cat[2]. 1 Subcat[3]	Substance	CASRN[4]	MW[5]	Chemical Class[6]	Physical Form Tested
Laboratory Chemicals	1 (H)	-	Nitric acid	7697-37-2	63.0	Acid (inorganic), Salt (inorganic)	Liquid
Laboratory Chemicals	1	4	n-Octylamine	111-86-4	129.2	Amine	Liquid
Laboratory Chemicals	1	0 (likely 4)	tetra-N-Octylammonium bromide	14866-33-2	546.8	Onium Compound	Solid
Laboratory Chemicals	NI	-	3-Methoxy-1,2-propanediol	623-39-2	106.1	Phenol, Ether	Liquid
Laboratory Chemicals	2B	-	6-Methyl purine	2004-03-7	134.1	Heterocyclic Compound	Liquid
Laboratory Chemicals	1 (H)	-	Silver nitrate	7761-88-8	169.9	Nitrate, Salt (inorganic)	Liquid
Laboratory Chemicals	1	4	Sodium hydrogen sulfate	7681-38-1	120.1	Salt (inorganic)	Solid
Laboratory Chemicals	NI	-	Sodium lauryl sulfate	151-21-3	288.4	Acid (organic) [Carboxylic Acid], Salt (organic)	Liquid
Laboratory Chemicals	1	4	Sodium oxalate	62-76-0	134.0	Acid (organic) [carboxylic acid], Salt (organic)	Solid
Laboratory Chemicals	1 (H)	-	Sulfuric acid	7664-93-9	98.1	Acid (inorganic), Sulfur Compound (inorganic)	Liquid
Laboratory Chemicals	1	4	N,N,N`,N`-Tetramethyl hexanediamine	111-18-2	172.3	Amine	Liquid
Laboratory Chemicals	NI	-	Toluene	108-88-3	92.1	Hydrocarbon (cyclic)	Liquid
Pesticide & Pesticide Intermediates	1	4	Aluminum chloride	16603-84-2	98.9	Salt (inorganic)	Liquid4
Pesticide & Pesticide Intermediates	1	4	Benzenesulfonyl chloride	98-09-9	176.6	Acyl Halide, Sulfur Compound (organic)	Liquid
Pesticide & Pesticide Intermediates	1	4	n-Butanol	71-36-3	74.1	Alcohol	Liquid

Product Class	GHS[1] Category	NICEATM Cat[2]. 1 Subcat[3]	Substance	CASRN[4]	MW[5]	Chemical Class[6]	Physical Form Tested
Pesticide & Pesticide Intermediates	1	4	p-tert-Butylphenol	98-54-4	150.2	Phenol	Solid
Pesticide & Pesticide Intermediates	1	4	Captan 90-concentrate (solid)	133-06-2	300.6	Heterocyclic Compound, Sulfur Compound (organic)	Solid
Pesticide & Pesticide Intermediates	2A	-	Dibenzyl phosphate	1623-08-1	278.2	Ester, Organophosphorus Compound	Solid
Pesticide & Pesticide Intermediates	NI	-	2,4-Difluoronitrobenzene	446-35-5	159.1	Hydrocarbon (halogenated)	Solid
Pesticide & Pesticide Intermediates	2B	-	Maneb	12427-38-2	265.3	Amine, Salt (organic), Urea Compound	Solid
Pesticide & Pesticide Intermediates	1	4	1-Naphthalene acetic acid	86-87-3	186.2	Acid (organic) [carboxylic acid], Polycyclic Compound	Solid
Pesticide & Pesticide Intermediates	1	4	Phosphorodicloridic acid, ethyl ester	1498-51-7	162.9	Ester, Organophosphorus Compound	Liquid
Pesticide & Pesticide Intermediates	1	4	Polyethylene glycol nonylphenyl ether (Surfonic HDL-1)	9016-45-9	308.5	Alcohol, Ether	Liquid
Pesticide & Pesticide Intermediates	1	4	Potassium laurate	10124-65-9	238.4	Acid (organic) [carboxylic acid], Salt (organic)	Liquid
Pesticide & Pesticide Intermediates	NI	-	Potassium tetrafluoroborate	14075-53-7	125.9	Salt (inorganic)	Solid
Pesticide & Pesticide Intermediates	1	4	Pyridine	110-86-1	79.1	Heterocyclic Compound	Liquid
Pesticide & Pesticide Intermediates	1	4	Sodium hydrogen sulfate	7681-38-1	120.1	Salt (inorganic)	Solid
Pesticide & Pesticide Intermediates	NI	-	Sodium lauryl sulfate	151-21-3	288.4	Acid (organic) [Carboxylic Acid], Salt (organic)	Liquid

Product Class	GHS[1] Category	NICEATM Cat[2]. 1 Subcat[3]	Substance	CASRN[4]	MW[5]	Chemical Class[6]	Physical Form Tested
Pesticide & Pesticide Intermediates	1 (H)	-	Zinc chloride	7646-85-7	136.3	Salt (inorganic)	Solid
Pharmaceuticals & Pharmaceutical Intermediates	2A	-	Acetone	67-64-1	58.1	Ketone	Liquid-
Pharmaceuticals & Pharmaceutical Intermediates	1	4	Antimony oxide	1309-64-4	291.5	Salt (inorganic)	Solid
Pharmaceuticals & Pharmaceutical Intermediates	1	4	Benzethonium chloride	121-54-0	448.1	Amine, Onium Compound	Liquid
Pharmaceuticals & Pharmaceutical Intermediates	1	1	2,2-Dimethyl butanoic acid	595-37-9	116.2	Acid (organic) [carboxylic acid]	Liquid
Pharmaceuticals & Pharmaceutical Intermediates	1	4	n-Butanol	71-36-3	74.1	Alcohol	Liquid
Pharmaceuticals & Pharmaceutical Intermediates	1	4	Chlorhexidine	55-56-1	505.4	Amidine	Solid
Pharmaceuticals & Pharmaceutical Intermediates	1 (H)	-	Chloroform	67-66-3	119.4	Hydrocarbon (acyclic)	Liquid
Pharmaceuticals & Pharmaceutical Intermediates	2B	-	3-Chloropropionitrile	542-76-7	89.5	Nitrile	Liquid
Pharmaceuticals & Pharmaceutical Intermediates	1	4	Cyclohexyl isocyanate	3173-53-3	125.2	Isocyanate	Solid
Pharmaceuticals & Pharmaceutical Intermediates	2B	-	Cyclopentanol	96-41-3	86.1	Alcohol	Liquid
Pharmaceuticals & Pharmaceutical Intermediates	1	4	Diethylethanolamine	100-37-8	117.9	Amine, Alcohol	Liquid

Product Class	GHS[1] Category	NICEATM Cat[2]. 1 Subcat[3]	Substance	CASRN[4]	MW[5]	Chemical Class[6]	Physical Form Tested
Pharmaceuticals & Pharmaceutical Intermediates	NI	-	2,4-Difluoronitrobenzene	446-35-5	159.1	Hydrocarbon (halogenated)	Solid
Pharmaceuticals & Pharmaceutical Intermediates	1	4	Domiphen bromide	538-71-6	414.5	Ether, Onium Compound, Salt (organic)	Liquid
Pharmaceuticals & Pharmaceutical Intermediates	NI	-	iso-Propyl bromide	75-26-3	123.0	Hydrocarbon (halogenated)	Liquid
Pharmaceuticals & Pharmaceutical Intermediates	1	4	alpha-Ketoglutaric acid	328-50-7	146.1	Acid (organic) [carboxylic acid]	Solid
Pharmaceuticals & Pharmaceutical Intermediates	NI	-	Di-iso-butyl ketone	108-83-8	142.2	Ketone	Liquid
Pharmaceuticals & Pharmaceutical Intermediates	1 (H)	-	Magnesium hydroxide	12141-11-6	42.3	Salt (inorganic)	Solid
Pharmaceuticals & Pharmaceutical Intermediates	1	4	Methylpentynol	77-75-8	98.1	Alcohol	Liquid
Pharmaceuticals & Pharmaceutical Intermediates	1 (H)	-	Nitric acid	7697-37-2	63.0	Acid (inorganic), Salt (inorganic)	Liquid
Pharmaceuticals & Pharmaceutical Intermediates	NI	-	2,2-Dimethyl-3-pentanol	3970-62-5	116.2	Alcohol	Liquid
Pharmaceuticals & Pharmaceutical Intermediates	1	3	Promethazine hydrochloride	58-33-3	320.9	Amine, Amidine, Heterocyclic Compound, Sulfur Compound (organic)	Solid
Pharmaceuticals & Pharmaceutical Intermediates	2B	-	6-Methyl purine	2004-03-7	134.1	Heterocyclic Compound	Liquid

Product Class	GHS[1] Category	NICEATM Cat[2]. 1 Subcat[3]	Substance	CASRN[4]	MW[5]	Chemical Class[6]	Physical Form Tested
Pharmaceuticals & Pharmaceutical Intermediates	2B	-	2,6-Dichloro-5-fluoro-beta-oxo-3-pyridinepropanoate	96568-04-6	280.1	Ester, Heterocyclic Compound, Ketone	Solid
Pharmaceuticals & Pharmaceutical Intermediates	1	4	Pyridine	110-86-1	79.1	Heterocyclic Compound	Liquid
Pharmaceuticals & Pharmaceutical Intermediates	1	3	Quinacrine	69-05-6	472.9	Amine, Heterocyclic Compound, Polycyclic Compound	Solid
Pharmaceuticals & Pharmaceutical Intermediates	1 (H)	-	Silver nitrate	7761-88-8	169.9	Nitrate, Salt (inorganic)	Liquid
Pharmaceuticals & Pharmaceutical Intermediates	1	4	Sodium hydroxide	1310-73-2	40.0	Alkali	Liquid
Pharmaceuticals & Pharmaceutical Intermediates	1	4	Tetrahydrofuran	109-99-9	72.1	Ether, Heterocyclic Compound	Liquid
Polish	1	1	Organofunctional Silane 45-49	82985-35-1	341.6	Amine, Organosilicon Compound	Liquid
Preservatives	2A	-	Acetone	67-64-1	58.1	Ketone	Liquid
Preservatives	1	4	Aluminum chloride	16603-84-2	98.9	Salt (inorganic)	Liquid
Preservatives	1 (H)	-	Sodium hydrogen difluoride	1333-83-1	62.0	Salt (inorganic)	Liquid
Preservatives	1 (H)	-	Zinc chloride	7646-85-7	136.3	Salt (inorganic)	Solid
Refrigerant	1 (H)	-	Ammonia	7664-41-7	17.0	Alkali	Liquid
Solvents	2A	-	Methyl acetate	79-20-9	74.1	Ester	Liquid
Solvents	1	4	Acetic acid	64-19-7	60.1	Acid (organic) [carboxylic acid]	Liquid

Product Class	GHS[1] Category	NICEATM Cat[2]. 1 Subcat[3]	Substance	CASRN[4]	MW[5]	Chemical Class[6]	Physical Form Tested
Solvents	2A	-	Acetone	67-64-1	58.1	Ketone	Liquid
Solvents	1	4	n-Butanol	71-36-3	74.1	Alcohol	Liquid
Solvents	1	1	Butyl cellosolve	111-76-2	118.2	Alcohol, Ether	Liquid
Solvents	2B	-	Butyl dipropasol solvent	29911-27-1	176.3	Alcohol, Ether	Liquid
Solvents	2A	-	gamma-Butyrolactone	96-48-0	86.1	Heterocyclic Compound, Lactone	Liquid
Solvents	1 (H)	-	Chloroform	67-66-3	119.4	Hydrocarbon (acyclic)	Liquid
Solvents	1	2	Cyclohexanol	108-93-0	100.2	Alcohol	Liquid
Solvents	1	4	Cyclohexyl isocyanate	3173-53-3	125.2	Isocyanate	Liquid
Solvents	2A	-	Deoxycholic acid sodium salt	302-95-4	414.6	Alcohol, Acid (organic) [carboxylic acid], Salt (organic), Polycyclic Compound	Liquid
Solvents	2A	-	2-Ethyl-1-hexanol	104-76-7	130.2	Alcohol	Liquid
Solvents	2A	-	*n*-Hexanol	111-27-3	102.2	Alcohol	Liquid
Solvents	NI	-	Di-iso-butyl ketone	108-83-8	142.2	Ketone	Liquid
Solvents	2A	-	Methyl ethyl ketone	78-93-3	72.1	Ketone	Liquid
Solvents	2B	-	2-Methyl-1-pentanol	105-30-6	102.2	Alcohol	Liquid
Solvents	1	4	2-Methylbutyric acid	116-53-0	102.1	Acid (organic) [carboxylic acid]	Liquid
Solvents	2A	-	*n*-Octanol	111-87-5	130.2	Alcohol	Liquid

Product Class	GHS[1] Category	NICEATM Cat[2]. 1 Subcat[3]	Substance	CASRN[4]	MW[5]	Chemical Class[6]	Physical Form Tested
Solvents	2B	-	Propasol Solvent P	1569-01-3	118.2	Alcohol	Liquid
Solvents	1	4	Pyridine	110-86-1	79.1	Heterocyclic Compound	Liquid
Solvents	1	4	Tetrahydrofuran	109-99-9	72.1	Ether, Heterocyclic Compound	Liquid
Surfactant (anionic)	1	1	Lauric acid	143-07-7	200.3	Acid (organic) [Carboxylic Acid]	Solid
Surfactant (anionic)	2B	-	N-Laurylsarcosine sodium salt	137-16-6	293.4	Amide, Amine, Salt (organic)	Liquid
Surfactant (anionic)	NI	-	Sodium lauryl sulfate	151-21-3	288.4	Acid (organic) [Carboxylic Acid], Salt (organic)	Liquid
Surfactants (cationic)	1	3	Benzalkonium chloride	8001-54-5	471.5	Onium Compound	Liquid
Surfactants (cationic)	1, 2A	2	Cetylpyridinium bromide	140-72-7	384.4	Onium Compound, Heterocyclic Compound	Liquid
Surfactants (nonionic)	1	4	Polyethylene glycol nonylphenyl ether (Surfonic HDL-1)	9016-45-9	308.5	Alcohol, Ether	Liquid
Surfactants (nonionic)	1, 2A/2B, NI	4	Triton X-100	9002-93-1	250.4	Ether	Liquid
Veterinary Agents	1	4	Benzethonium chloride	121-54-0	448.1	Amine, Onium Compound	Liquid
Veterinary Agents	1	4	n-Butanol	71-36-3	74.1	Alcohol	Liquid
Veterinary Agents	1 (H)	-	Magnesium hydroxide	12141-11-6	42.3	Salt (inorganic)	Solid
Veterinary Agents	1	4	Methylpentynol	77-75-8	98.1	Alcohol	Liquid
Veterinary Agents	1 (H)	-	Potassium hydroxide	1310-58-3	56.1	Alkali, Salt (inorganic)	Solid

Product Class	GHS[1] Category	NICEATM Cat[2]. 1 Subcat[3]	Substance	CASRN[4]	MW[5]	Chemical Class[6]	Physical Form Tested
Veterinary Agents	1	4	Sodium hydroxide	1310-73-2	40.0	Alkali	Liquid

[1]GHS=Globally Harmonized System (UN [2003]).
[2]Cat. = Category.
[3]NICEATM Cat. 1 Subcat. = Category 1 subcategories = NICEATM-assigned subcategories for GHS Category 1 substances (ocular corrosives and severe irritants) were assigned based on the following: 0 = not classifiable; 1 = positive response based on a persistent lesion involving the cornea, iris, and/or conjunctiva through to day 21 in at least one of three rabbits and not on severity; 2 = positive response based on mean for first 3 days (corneal opacity [CO] score >3 and <4 or iritis [IR] score >1.5) in at least two of three rabbits but lesions do not persist through day 21; 3 = positive response based on mean for first 3 days (CO >3 and <4 or IR >1.5) in at least two of three rabbits and a persistent (>21 days) lesion in at least one rabbit ; 4 = CO score of 4 at any time in at least one of three rabbits.
[4]CASRN = Chemical Abstract Services Registry Number.
[5]MW = molecular weight.
[6]Chemical Class=Based on the MeSH Medical Subject Heading. Available http://www.nlm.nih.gov/mesh; substances may be assigned into one or more chemical classes (see **Appendix B**).
[7]"-" = not applicable.

APPENDIX A

NICEATM-DEFINED RETROSPECTIVE *IN VIVO* OCULAR IRRITANCY CLASSIFICATION RULES

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NICEATM-Defined Retrospective *In Vivo* Ocular Irritancy Classification Rules

Regulatory Agency	Number of Rabbits	Observation Times (after treatment)	Mean Score Used?	Basis for a Positive Response	Classification Categories
EPA	Tests could be based on a single rabbit (if marked effects were expected), otherwise 3 to 6 rabbits	1 hour, and 1, 2, 3, 7, 14, and 21 days; if no irritation after 3 days study may be ended	No	Opacity or Iritis ≥ 1 or Redness or Chemosis ≥ 2	At least 1 positive rabbit needed for classification: **I** = Corrosive, corneal involvement, or irritation persisting more than 21 days **II**= Corneal involvement or irritation clearing* in 8-21 days **III** = Corneal involvement or irritation clearing* in 7 days or less **IV** = Minimal effects clearing* in less than 24 hours *Clearing: Opacity and Iritis = 0; Redness and Chemosis is 0 or 1
European Union	Single rabbit if marked effects expected; Sequential testing of rabbits until response is confirmed (typically, up to 3 rabbits)	Minimum observation times of 1, 2, and 3 days; Additional observation times may be performed at 7, 14, and 21; If no irritation after 3 days study may be ended.	Yes	**More than 3 rabbits:** Averaged score of all animals tested for each endpoint over Days 1, 2, and 3 **Three rabbits:** Individual rabbit endpoint scores averaged over Days 1, 2, and 3	**Classification is sequential (i.e., first determine if meets R41 criteria, then R36 criteria, any substance remaining is classified as nonirritant if test adequate)** **R41 Classification (follow rules sequentially)** (1) When more than 3 rabbits tested, where mean study value for Opacity ≥ 3 and/or Iritis > 1.5 (2) When 3 rabbits tested, when 2 rabbits have individual animal mean values where Opacity ≥ 3 and/or Iritis = 2 ***Regardless of the number of rabbits tested*** (3) At least 1 of 3 (or 2 of 6) rabbits on Day 21 where effects have not reversed to 0 (4) If study ends on or after Day 14 and before Day 21, at least 1 of 3 (2 of 4, 5, 6) rabbits where Opacity ≥ 3 and/or Iritis = 2 (5) At least one rabbit where study is terminated early and there is (a) corneal perforation or significant corneal ulceration including staphyloma, (b) blood in the anterior chamber of the eye, (c) Opacity = 4 which persists for 48 hours, (d) absence of light reflex (Iritis = 2) which persists for 72 hours, (e) ulceration of the conjunctival membrane, (f) necrosis of the conjunctivae or nictitating membrane, or (g) sloughing. (Notes should be clear that early termination was due to one of these effects) **R36 Classification (follow rules sequentially)** (1) When more than 3 rabbits tested, where mean study values are: ≥ 2 Opacity < 3, ≥ 1 Iritis < 1.5, Redness ≥ 2.5, and/or Chemosis ≥ 2 (2) When 3 rabbits tested, if 2 rabbits have individual animal mean values where ≥ 2 Opacity < 3, ≥ 1 Iritis < 2, Redness ≥ 2.5, and/or Chemosis ≥ 2

Regulatory Agency	Number of Rabbits	Observation Times (after treatment)	Mean Score Used?	Basis for a Positive Response	Classification Categories
					Nonirritant (1) When a substance cannot be classified as R41 or R36 and the test is adequate
GHS	Sequential testing of rabbits until response is confirmed (typically, up to 3 rabbits)	1, 2, 3 days (if effects induced, observation until reversal or Day 21, whichever comes first)	Yes	Individual rabbit values averaged over Days 1, 2, and 3	**Classification is sequential (i.e., first determine if meets Category 1 criteria, then Category 2 criteria, any substance remaining is classified as nonirritant if test adequate)** **Category 1 (Irreversible Eye Effects) (follow rules sequentially)** (1) At least 2 of 3 (or 4 of 6; 3 of 4; 4 of 5) rabbits have individual animal mean values where Opacity ≥ 3 and/or Iritis > 1.5 (2) At least 1 of 3 (2 of 4, 5, 6) rabbits where Opacity, Chemosis, Redness, and/or Iritis > 0 on Day 21 (3) 1 of 6 rabbits has an animal mean value where Opacity ≥ 3 and/or Iritis > 1.5 and 1 of 6 rabbits (a different rabbit) where Opacity, Chemosis, Redness, and/or Iritis > 0 on Day 21 (4) At least 1 of 3 (2 of 4, 5, 6) rabbits with an Opacity = 4 at any time (5) If study ends on or after Day 14, at least 1 rabbit where Opacity = 3 and/or Iritis = 2 (6) At least 1 rabbit where study is terminated early and there is (a) corneal perforation or significant corneal ulceration including staphyloma, (b) blood in the anterior chamber of the eye, (c) absence of light reflex (Iritis =2) which persists for 72 hours, (d) ulceration of the conjunctival membrane, (e) necrosis of the conjunctivae or nictitating membrane, or (f) sloughing. (Notes should be clear that early termination was due to one of these effects) **Category 2 (Reversible Eye Effects) (follow rules sequentially)** (1) Eye Irritant Category 2A - At least 2 of 3 (or 4 of 6; 3 of 4; 4 of 5) rabbits have individual animal mean values where ≥ 1 Opacity <3, ≥ 1 Iritis ≥ 1.5, Redness ≥ 2, and/or Chemosis ≥ 2 and the effect reverses > 7 days but < 21 days. (2) Eye Irritant Category 2B - At least 2 of 3 (or 4 of 6; 3 of 4; 4 of 5) rabbits have individual animal mean values where ≥ 1 Opacity <3, ≥ 1 Iritis ≥ 1.5, Redness ≥ 2, and/or Chemosis ≥ 2 and the effect reverses by 7 days **Nonirritant (follow rules sequentially)** (1) When a substance cannot be classified as Category 1 or 2 and the test is adequate

Regulatory Agency	Number of Rabbits	Observation Times (after treatment)	Mean Score Used?	Basis for a Positive Response	Classification Categories
					Study Criteria Not Met (1) When 1 of 6 animals falls into Category 1 rule (1) or (4) and other 5 animals are nonirritant (2) When no more than 3 animals fall into Category 1 rule (2) and other animals are nonirritant or Category 2

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APPENDIX B

Glossary of NICEATM-Defined Chemical Classes

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Glossary of NICEATM-Defined Chemical Classes,

Based on the National Library of Medicine Medical Subject Headings

Chemical Class	Definition
Inorganic Chemicals	
Acids	Chemical compounds which yield hydrogen ions or protons when dissolved in water, whose hydrogen can be replaced by metals or basic radicals, or which react with bases to form salts and water (neutralization).
Alkalis	Usually a hydroxide of lithium, sodium, potassium, rubidium or cesium, but also the carbonates of these metals, ammonia, and the amines.
Aluminum Compounds	Inorganic compounds that contain aluminum as an integral part of the molecule.
Arsenicals	Inorganic or organic compounds that contain arsenic.
Barium Compounds	Inorganic compounds that contain barium as an integral part of the molecule.
Boron Compounds	Inorganic or organic compounds that contain boron as an integral part of the molecule.
Bromine Compounds	Inorganic compounds that contain bromine as an integral part of the molecule.
Cadmium Compounds	Inorganic compounds that contain cadmium as an integral part of the molecule.
Calcium Compounds	Inorganic compounds that contain calcium as an integral part of the molecule.
Carbon Compounds, Inorganic	Inorganic compounds that contain carbon as an integral part of the molecule but are not derived from hydrocarbons.
Chlorine Compounds	Inorganic compounds that contain chlorine as an integral part of the molecule.
Chromium Compounds	Inorganic compounds that contain chromium as an integral part of the molecule.
Electrolytes	Substances that dissociate into two or more ions, to some extent, in water. Solutions of electrolytes thus conduct an electric current and can be decomposed by it (electrolysis).
Elements	Substances that comprise all matter. Each element is made up of atoms that are identical in number of electrons and protons and in nuclear charge, but may differ in mass or number of neutrons.
Fluorine Compounds	Inorganic compounds that contain fluorine as an integral part of the molecule.
Free Radicals	Highly reactive molecules with an unsatisfied electron valence pair.
Gases	The vapor state of matter; nonelastic fluids in which the molecules are in free movement and their mean positions far apart.

Chemical Class	Definition
Gold Compounds	Inorganic compounds that contain gold as an integral part of the molecule.
Hydrogen	Hydrogen. The first chemical element in the periodic table. It has the atomic symbol H, atomic number 1, and atomic weight 1. It exists, under normal conditions, as a colorless, odorless, tasteless, diatomic gas.
Hydroxides	Inorganic compounds that contain the -OH group.
Iodine Compounds	Inorganic compounds that contain iodine as an integral part of the molecule.
Iron Compounds	Inorganic compounds that contain iron as an integral part of the molecule.
Isotopes	Atomic species differing in mass number but having the same atomic number.
Lithium Compounds	Inorganic compounds that contain lithium as an integral part of the molecule.
Magnesium Compounds	Inorganic compounds that contain magnesium as an integral part of the molecule.
Manganese Compounds	Inorganic chemicals that contain manganese as an integral part of the molecule.
Mercury Compounds	Inorganic compounds that contain mercury as an integral part of the molecule.
Metals	Electropositive chemical elements characterized by ductility, malleability, luster, and conductance of heat and electricity. They can replace the hydrogen of an acid and form bases with hydroxyl radicals.
Minerals	Native, inorganic or fossilized organic substances having a definite chemical composition and formed by inorganic reactions. They may occur as individual crystals or may be disseminated in some other mineral or rock.
Nitrogen Compounds	Inorganic compounds that contain nitrogen as an integral part of the molecule.
Osmium Compounds	Inorganic compounds that contain osmium as an integral part of the molecule.
Oxygen Compounds	Inorganic compounds that contain oxygen as an integral part of the molecule.
Phosphorus Compounds	Inorganic compounds that contain phosphorus as an integral part of the molecule.
Platinum Compounds	Inorganic compounds which contain platinum as the central atom.
Potassium Compounds	Inorganic compounds that contain potassium as an integral part of the molecule.
Ruthenium Compounds	Inorganic compounds that contain ruthenium as an integral part of the molecule.
Salts	Substances produced from the reaction between acids and bases; compounds consisting of a metal (positive) and nonmetal (negative) radical.

Chemical Class	Definition
Selenium Compounds	Inorganic compounds that contain selenium as an integral part of the molecule.
Silicon Compounds	Inorganic compounds that contain silicon as an integral part of the molecule.
Silver Compounds	Inorganic compounds that contain silver as an integral part of the molecule.
Sodium Compounds	Inorganic compounds that contain sodium as an integral part of the molecule.
Sulfur Compounds	Inorganic compounds that contain sulfur as an integral part of the molecule.
Technetium Compounds	Inorganic compounds that contain technetium as an integral part of the molecule.
Thorium Compounds	Inorganic compounds that contain thorium as an integral part of the molecule.
Tin Compounds	Inorganic compounds that contain tin as an integral part of the molecule.
Tungsten Compounds	Inorganic compounds that contain tungsten as an integral part of the molecule.
Uranium Compounds	Inorganic compounds that contain uranium as an integral part of the molecule.
Vanadium Compounds	Inorganic compounds that contain vanadium as an integral part of the molecule.
Zinc Compounds	Inorganic compounds that contain zinc as an integral part of the molecule.
Organic Chemicals	
Alcohols	Alkyl compounds containing a hydroxyl group. They are classified according to relation of the carbon atom: primary alcohols, R-CH_2OH; secondary alcohols, R_2-CHOH; tertiary alcohols, R_3-COH.
Aldehydes	Organic compounds containing a carbonyl group in the form -CHO.
Amides	Organic compounds containing the -CO-NH_2 radical. Amides are derived from acids by replacement of -OH by -NH_2 or from ammonia by the replacement of H by an acyl group.
Amidines	Monovalent radical having the formula —C(NH)-NH_2
Amines	A group of compounds derived from ammonia by substituting organic radicals for the hydrogens.
Amino Acids, Peptides, and Proteins	Amino acids and chains of amino acids connected by peptide linkages.
Anhydrides	Chemical compounds derived from acids by the elimination of a molecule of water.
Aza Compounds	Structurally modified purine/pyrimidine bases and nucleosides/nucleotides.
Azides	Organic or inorganic compounds that contain the -N_3 group.

Chemical Class	Definition
Azo Compounds	Generally, organic or inorganic compounds that contain the -N=N group.
Boron Compounds	Inorganic or organic compounds that contain boron as an integral part of the molecule.
Carbohydrates	Carbohydrates are composed of carbon, hydrogen, and oxygen in a ratio of $C_n(H_2O)_n$.
Carboxylic Acids	Organic compounds containing the carboxy group (-COOH). This group of compounds includes amino acids and fatty acids. Carboxylic acids can be saturated, unsaturated, or aromatic.
Catenanes	Complex compounds where two cyclic molecules are interlaced together as links in a chain.
Cyanates	Organic salts of cyanic acid containing the -OCN radical.
Esters	Organic compound formed by reaction between an acid and an alcohol with elimination of water.
Ethers	Organic compounds characterized by an oxygen atom attached to two carbon atoms.
Free Radicals	Highly reactive molecules with an unsatisfied electron valence pair. Free radicals are produced in both normal and pathological processes.
Glycosylation End Products, Advanced	Products derived from the nonenzymatic reaction of glucose and proteins in vivo that exhibit a yellow-brown pigmentation and an ability to participate in protein-protein cross-linking.
Heterocyclic Compounds	Ring compounds having atoms other than carbon in their nuclei.
Hormones, Hormone Substitutes, and Hormone Antagonists	Chemical substances having a specific regulatory effect on the activity of a certain organ or organs.
Hydrazines	Organic molecules containing a diamine group: $H_2N\text{-}NH_2$.
Hydrocarbons	Molecules essentially derived from carbon and hydrogen
Hydrocarbons, Acyclic	Organic compounds composed exclusively of carbon and hydrogen where no carbon atoms join to form a ring structure.
Hydrocarbons, Cyclic	Organic compounds composed exclusively of carbon and hydrogen forming a closed ring that may be either alicyclic or aromatic.
Hydrocarbons, Halogenated	Organic compounds composed of carbon, hydrogen, and at least one halogen (e.g., Cl, Br, F)
Hydrocarbons, Other	Organic compound composed of carbon and halogen which does not fit into the groups of (a) Hydrocarbon, acyclic; (b) Hydrocarbon, cyclic; and (c) Hydrocarbon, halogenated.
Imides	Organic compounds that contain the divalent radical –C(O)NHCO-.
Imines	Organic or inorganic compound containing the -NH group or its substituted form -NR that is derived from ammonia by replacement of two hydrogen atoms by a hydrocarbon group or other nonacid organic group.
Isocyanates	Organic compounds that contain the -NCO radical.

Chemical Class	Definition
Ketones	Organic compounds having a carbonyl group linked to a carbon atom in each of two hydrocarbon radicals.
Lactones	Organic compounds, regarded as anhydrides of certain hydroxy acids
Lipids	Fats that are insoluble in water and include many natural oils, waxes, and steroids.
Nitrates	Inorganic or organic salts and esters of nitric acid. These compounds contain the NO_3- radical.
Nitriles	Organic compounds containing the -CN radical (not inorganic cyanides with –CN).
Nitrites	Salts of nitrous acid or compounds containing the group NO_2-. The inorganic nitrites of the type MNO_2 (where M=metal) are all insoluble, except the alkali nitrites. The organic nitrites may be isomeric, but not identical with the corresponding nitro compounds.
Nitro Compounds	Organic compounds containing a nitro group.
Nitroso Compounds	Generally, organic compounds containing the –NO radical.
Nucleic Acids, Nucleotides, and Nucleosides	High molecular weight polymers containing a mixture of purine and pyrimidine nucleotides chained together by ribose or deoxyribose linkages.
Onium Compounds	Ions with the suffix -onium, indicating cations with coordination number 4 of the type RxA+ which are analogous to ammonium compounds (H_4N+). Ions include phosphonium R_4P+, oxonium R_3O+, sulfonium R_3S+, chloronium R_2Cl+.
Organometallic Compounds	A class of compounds of the type R-M, where a C atom is joined directly to any other element except H, C, N, O, F, Cl, Br, I, or At.
Organophosphorus Compounds	Organic compounds that contain phosphorus as an integral part of the molecule.
Organoselenium Compounds	Organic compounds which contain selenium as an integral part of the molecule.
Organosilicon Compounds	Organic compounds that contain silicon as an integral part of the molecule.
Peroxides	A group of compounds that contain a bivalent O-O group, i.e., the oxygen atoms are univalent. They can either be inorganic or organic in nature. Such compounds release atomic (nascent) oxygen readily. Thus they are strong oxidizing agents and fire hazards when in contact with combustible materials, especially under high-temperature conditions.
Phenols	Weakly acidic organic compounds; molecule contains one or more hydroxyl groups.
Polycyclic Compounds	Compounds consisting of two or more fused ring structures.
Quinones	Hydrocarbon rings that contain two ketone moieties in any position. They can be substituted in any position except at the ketone groups.

Chemical Class	Definition
Rotaxanes	Complex compounds in which a dumbbell shaped molecule is encircled by a macrocycle. They are named after rota (wheel) and axis (axle). Notation with a prefix is used to indicate the number of interlocked components.
Semicarbazides[2]	Organic compounds in which the amide group of urea is replaced by a single rather than double hydrazine residue as in carbazide.
Sulfur Compounds	Organic compounds that contain sulfur as an integral part of the molecule.
Triazenes	Compounds with three contiguous nitrogen atoms in linear format, H_2N-N=NH, and hydrocarbyl derivatives.
Urea	A compound formed in the liver from ammonia produced by the deamination of amino acids.
Macromolecular Substances	Compounds and molecular complexes that consist of very large numbers of atoms and are generally over 500 kD in size.