DRAFT REPORT

Interim Analysis of the Estimated Potential Underclassification Rates of the Current Rabbit Test for Detecting Ocular Corrosives and Severe Irritants

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January 6, 2005

ABSTRACT

An analysis[1] was conducted to estimate the likelihood of underclassifying ocular corrosives or severe irritants when using the current sequential three animal *in vivo* rabbit eye test method based on existing protocol guidelines (e.g., OECD 2002) and the United Nations (UN) Globally Harmonized System (GHS) of Classification and Labeling of Chemicals (UN 2003). The analysis was based on a database of 128 substances classified as GHS Category 1 irritants (i.e., corrosives and severe irritants) based on 142 studies using a total of 661 rabbits. To conduct this analysis, individual rabbit responses were first classified according to the GHS classification system (UN 2003). The estimated underclassification rate was then calculated three ways, each using a different assumption. Calculation 1 assumed homogeneity of response for GHS Category 1 irritants; Calculation 2 assumed heterogeneity of response for GHS Category 1 irritants; and Calculation 3 assumed homogeneity of response for three subgroups of GHS Category 1 irritants. The three subgroups were: (1) strong responders, where all treated rabbits expressed a severe response; (2) moderate responders, where the majority but not all treated rabbits expressed a severe response; and (3) weak responders, where the majority of treated rabbits expressed a nonsevere irritant or nonirritant response.

Using the three calculation methods, the estimated underclassification rates for the total database were 4.95% for Calculation 1, 14.51% for Calculation 2, and 12.21% for Calculation 3. Substances were also separated into four GHS Category 1 subcategories based on the various injury response criteria. The lowest estimated underclassification rate (1.33% to 6.46%, depending on the calculation method used) was for criterion 2, which is based on a severe response (averaged across three days) in at least two of three rabbits. The highest estimated underclassification rate (8.48% to 18.24%) was for criterion 1, which is based on a persistent ocular lesion at 21 days post-treatment in at least one rabbit. A comparison of the underclassification rate for GHS Category 1 substances tested as solids or liquids/gels indicated that, regardless of which of the three calculation methods was used, the estimated rate for liquids/gels (6.08% to 15.91%) was higher than the rate for solids (3.43% to 11.11%). However, these differences were not statistically significant.

The small numbers of studies per chemical class made it difficult to assess whether or not heterogeneity was present within a given chemical class. Therefore, a single homogeneous calculation (Calculation 1) was conducted for the 13 chemical classes (formulations, organic salts, amines, aromatics, quaternary ammonium compounds, alcohols, esters, phenols, carboxylic acids, heterocyclics, alkanolamines, ethanolamines, acyl halides) judged to have sufficient data (≥20 rabbits) for a meaningful calculation. The estimated underclassification rates for six of the 13 chemical classes (formulations, aromatics, quaternary ammonium compounds, alcohols, carboxylic acids, heterocyclics) were similar to each other and within the range of potential underclassification rates estimated for the total database; these rates ranged from 4.39% for heterocyclics to 8.05% for carboxylic acids. Among the remaining seven chemical classes analyzed, the estimated underclassification rates for six of these classes were relatively low (0.00% for phenols, 0.25% for acyl halides, 0.66% for amines, 0.95% for alkanolamines, 0.95%

[1] Preliminary analysis presented at the October 20, 2004 meeting of the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) at the National Institutes of Environmental Health Sciences in Research Triangle Park, NC

for ethanolamines, 1.20% for esters) and the estimated underclassification rate for one class (organic salts at 18.85%) was relatively high. The low estimated underclassification rates suggests a greater consistency in responses among rabbits to GHS Category 1 substances for these chemical classes, while the high estimated underclassification rate for organic salts suggests a likelihood of greater variation in responses among rabbits to GHS Category 1 substances for this chemical class. These data suggest that the extent of inter-animal variation in ocular injury responses to substances capable of inducing ocular corrosion or severe irritation will differ depending on the chemical class of the test substance.

1.0 INTRODUCTION

1.1 Background

The Interagency Coordination Committee on the Validation of Alternative Methods is currently evaluating the validation status of four *in vitro* methods proposed for identifying ocular corrosives and severe ocular irritants. In support of this evaluation, the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) solicited and searched for data from *in vivo* animal and human studies that could be used to assess the accuracy of the *in vitro* methods. While it would also be desirable to have sufficient data to assess the reliability of the *in vivo* rabbit eye test and its accuracy for identifying substances that cause ocular corrosion and severe ocular irritation in humans, no data was found to allow such assessments. However, NICEATM was able to analyze available animal data to estimate the likelihood that ocular corrosives or severe irritants might be underclassified using current testing guidelines due to the variation in individual animal responses. This effort was facilitated by the fact that much of the data was generated with up to six rabbits, whereas current recommendations now only require one to three rabbits for identification of ocular corrosives and severe irritants. A preliminary analysis was presented at the October 20, 2004 meeting of the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM).). This report expands the original analysis and provides additional analyses for chemical classes and subcategories of severe ocular responses.

The analysis is based on the ocular irritancy classification system used in the United Nations (UN) Globally Harmonized System (GHS) of Classification and Labeling of Chemicals (UN 2003). Subsequent to the preliminary analysis, additional *in vivo* rabbit eye test results have been added to the database, and the expanded database along with various subsets of the database (liquids/gels versus solids, selected chemical classes, the four different GHS criteria used to identify a severe irritant or corrosive), have been analyzed using three different calculation methods to estimate the underclassification rates for GHS Category 1 substances (i.e., those classified as corrosive or severe irritants). We strongly encourage the submission of additional *in vivo* rabbit eye test data to NICEATM to facilitate the evaluation of alternative *in vitro* ocular

irritation test methods, to provide candidate substances for possible validation studies, and to expand the scope and usefulness of analyses such as those presented in this report.

1.2 The GHS Classification System (UN 2003)

For the purpose of international harmonization of the classification of ocular irritants, the GHS classification system (UN 2003) includes two harmonized categories, one for irreversible effects on the eye/serious damage to the eye (Category 1), and one for reversible effects on the eye (Category 2). Reversible effects are further subclassified, based on the duration of persistence as Category 2A ("irritating to eyes") (reverses within 21 days) and Category 2B ("mildly irritating to eyes") (reverses within seven days). The GHS categories are based on severity of the lesions and/or the duration of persistence. Because the GHS classification system (UN 2003) has been internationally harmonized through the UN, and will be implemented globally in the near future, assessment of the *in vivo* rabbit eye test for identifying corrosives and severe irritants, as defined by this classification system, is the focus of this evaluation.

1.3 Accuracy of the Current Test for Identifying Potential Ocular Corrosives and Severe Irritants

Ideally, it would be desirable to determine the accuracy of the current *in vivo* rabbit eye test for identifying substances capable of producing ocular corrosion or severe irritation in humans. However, such a formal assessment of accuracy would require the availability of both human and rabbit eye data for corrosive and severely irritating substances. To the best of our knowledge, no such experimental data from humans is available. Nevertheless, accidental human exposure injury data involving severe or irreversible eye injuries could be used to assess if any substances or products causing these human injuries had not been identified in animal studies as having this potential. A comprehensive literature search and inquiries to Federal regulatory agencies did not identify any substances not found to be an ocular severe irritant or corrosive in the animal test that had caused severe ocular irritation or corrosion in humans from accidental exposures.

Several U.S. Federal agencies (Occupational Health and Safety Administration [OSHA], Consumer Product Safety Commission [CPSC], and the National Institute for Occupational

Safety and Health [NIOSH]) were contacted for accidental human exposure data. NIOSH estimated that there were approximately 39,200 chemical-related eye injuries in 1998, based on emergency department reports for work related eye-injuries (NIOSH 2004). Approximately 10,000 of these cases were attributed to an unidentified/unspecified chemical. Additional cases (<2500 each) were reported for injuries related to specific chemicals or chemical/product classes, which included acids (unspecified); adhesives/glues; cement/mortar mix; chlorine/chlorine bleach; cleaning/polishing agents; detergents/shampoos; disinfectants; drain/oven cleaners; gasoline/jet fuels/diesel fuel; hydrochloric acid; nonchlorine bleach; paint removers/thinners; paints, soaps; sodium hydroxide, potassium hydroxide, and potassium carbonate; solvents/degreasers; and sulfuric acid. However, for these product classes, specific information on which products were involved are not available, no human data were provided for any of these substances, and details of the types and severity of ocular injuries sustained were not described.

In addition, according to U.S. Bureau of Labor Statistics (BLS), 6303 lost workdays attributable to occupational eye injuries from chemical exposures were reported in 2002 (BLS 2004). These numbers may be underestimates of the actual incidence since not all employers are required to report such injuries. The specifics of the exposures were not provided.

Without more detail about the specific nature of the substances and exposure conditions, these accidental human exposure injury data are not useful for evaluating the accuracy of the *in vivo* rabbit eye test for predicting human severe ocular hazard.

1.4 Evaluation of the Reproducibility of the Current Rabbit Eye Test Method for Ocular Corrosives and Severe Irritants

Evaluating test method reproducibility requires the availability of data from repeat tests conducted on the same substances within and across multiple laboratories. Substances tested should represent the range of possible test outcomes as well as the range of physicochemical properties of the various substances for which the test method is proposed for use. However, sufficient data for such an evaluation for ocular corrosives and severe irritants could not be located. In an In an attempt to obtain such data, NICEATM searched the published literature and

published a Federal Register (*FR*) Notice (March 24, 2004; Volume 69, Number 57; Page 13859-13861) requesting high quality *in vivo* data from standardized ocular irritancy test methods using rabbits (e.g., EPA 1998; UN 2003). In addition, a request for relevant data as well as a copy of the *FR* notice was mailed to officers of 80 national and international organizations (e.g., animal welfare societies, professional organizations) with interest in this area. Data were sought from studies conducted to comply with Federal or other national/international testing requirements, but which may not be publicly available because: (1) the data were submitted to regulatory authorities, but are proprietary and cannot be released to the public by regulatory authorities or (2) there is no requirement to submit the data to regulatory authorities. In addition to requesting ocular irritation data from studies in rabbits, NICEATM also requested the submission of data from relevant human studies, including any human post-marketing or occupational exposure/surveillance data that might be available. However, no human data was received in response to the *FR* notice.

For *in vivo* rabbit eye test data to be useful for a direct evaluation of test method reproducibility, data for substances tested multiple times within and across laboratories were needed. Furthermore, to be useful for this analysis,

- the study had to have been conducted according to the *in vivo* rabbit eye test method protocol described in Draize et al. (1944), by U.S. Federal agencies (e.g., FHSA 1964, EPA 1998), and the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 405 (adopted in 1981 and first revised in 1987), and
- the data provided had to be sufficient for classifying the ocular irritancy of the test substance according to the GHS classification system (UN 2003) (i.e., individual rabbit data was needed at 1, 2, and 3 days post-treatment, as well as to 21 days post-treatment).

Based on the available published and submitted data, the numbers of substances tested multiple times are too few to conduct a direct evaluation of test method intra or inter-laboratory reproducibility.

2.0 MATERIALS AND METHODS

2.1 Database Development

Data compiled for these analyses are from corrosivity and irritation studies conducted using the *in vivo* rabbit eye test method described by Draize et al. (1994), U.S. Federal agencies (e.g., FHSA 1964, EPA 1998) and the OECD TG 405 (adopted in 1981 and first revised in 1987). Data used in these analyses were received from:

- the EPA
- the U.S. Food and Drug Administration (FDA)
- the Japanese National Institute of Health Sciences
- the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC)
- the Cosmetics, Toiletry, and Fragrance Association (CTFA)
- Access Business Group
- ExxonMobile Biomedical Sciences
- GlaxoSmithKline
- SC Johnson

The numbers of studies received from each source and the number of studies considered appropriate for this analysis are provided in **Table 1**. Not all studies received were considered appropriate for this analysis. Specifically, studies were excluded that did not follow the standard Draize test protocol or provide the individual rabbit data needed to classify the ocular irritancy of a test substance according to the GHS classification system (UN 2003). Examples of reasons for excluding studies include:

- The volume administered to the eye of a rabbit was not the standard 0.1 mL volume, unless a smaller volume was used and, based on the response obtained, the substance could be classified as a GHS ocular corrosive or severe irritant. This criterion was based on the expectation that a substance classified as a nonsevere irritant or nonirritant using a smaller than standard volume might be classified as a severe irritant if the standard volume had been used. In contrast, a substance classified as a corrosive or severe irritant would not be expected to result in a nonsevere or nonirritant classification when tested at the standard volume.

Table 1. Number of Studies from Various Data Sources

Data Source	Total Studies	Number of Acceptable Ocular Corrosives or Severe Irritant Studies	GLP-Compliant Studies
Access Business Group	14	7	Unknown
CTFA	56	17	Yes
ECETOC	149	31	Yes
EPA TSCA	152	28	Some studies
FDA	168	30	Unknown
GlaxoSmithKline	30	1	Unknown
ExxonMobil	13	3	Some studies
NIHS	62	20	Yes
SC Johnson	17	5	Unknown
Total	**661**	**142**	

Abbreviations: CTFA = Cosmetics, Toiletry, and Fragrance Association; ECETOC = European Centre for Ecotoxicology and Toxicology of Chemicals; EPA = U.S. Environmental Protection Agency; FDA = U.S. Food and Drug Administration; GLP = Good Laboratory Practice; NIHS = Japanese National Institute of Health Sciences; TSCA = Toxic Substances Control Act.

- The study was terminated prior to day 21 and a positive but noncorrosive response was present in one or more rabbits such that reversibility could not be assessed.
- Acceptable studies that resulted in the substance being classified as a nonsevere irritant or nonirritant were not considered for this analysis, which focuses on estimating the rate that a corrosive or severe irritant, according to the GHS classification system (UN 2003) would be underclassified as a nonsevere irritant or nonirritant.

The numbers of acceptable studies from each source used for this analysis are provided in **Table 1**. The complete dataset is provided in **Appendix A**. Information compiled for each study included:

- test substance name or unique identifier
- CASRN, if available
- source of data
- chemical class(es)
- number of rabbits tested
- amount of substance administered to the eye of each rabbit
- the ocular response of each rabbit at each time point evaluated

Several of the substances tested were commercial products, which were identified by a unique identifier and whose formulation and chemical composition were not provided.

2.2 Adequacy of In Vivo Rabbit Eye Test Data

Ideally, all of the *in vivo* rabbit eye tests should have been conducted in compliance with Good laboratory Practice (GLP) guidelines. These guidelines are nationally and internationally recognized rules designed to produce high-quality laboratory records (EPA 2003a, 2003b; FDA 2003). To the extent known, compliance with GLP guidelines in the conduct of the study is provided in **Table 1**.

2.3 Substance Classification Based on the GHS Classification System (UN 2003)

Prior to evaluating the estimated underclassification rate of the sequential three animal *in vivo* rabbit eye test method protocol for identifying a substance capable of inducing a corrosive or severe response, individual rabbit responses were classified according to the GHS classification system (UN 2003). As described in **Section 1.3**, this classification system delineates substances into three categories: Category 1, Category 2, or Nonirritant. Category 2 substances can be further subclassified as Category 2A or 2B, depending on the time required for reversal of any adverse effects.

For the purpose of this evaluation, Category 1 substances were classified into whether the classification was based on a single rabbit response (i.e., one of three rabbits with a corneal opacity score of 4 at any time or a positive response that is not expected to reverse or that does not fully reverse within 21 days [NICEATM Cat 1A]) or based on at least two of three rabbits having a mean corneal opacity score ≥3 and/or an iritis score ≥1.5 (scores for each rabbit are averaged across observations at days 1, 2, and 3 post-treatment) (NICEATM Cat 2A).

Based on this classification system, each rabbit tested in the database was assigned one of these irritancy categories, as described in **Table 2**.

Table 2. Criteria Used for Classification of Rabbits According to the GHS Classification System (UN 2003)

Rabbit Category	Criteria for Classification
Category 1A (Cat 1A)	- Corneal opacity score of 4 at any time - Rabbit with effects not expected to reverse or that do not fully reverse within 21 days
Category 1B (Cat 1B)	- Rabbit with mean corneal opacity score ≥ 3 and/or iritis score > 1.5 (rabbit values are averaged across observation days 1, 2, and 3)
Category 2A (Cat 2A)	Rabbit with mean scores (rabbit values are averaged across observation days 1,2, and 3) for one of more of the following: Iritis ≥1 Corneal opacity ≥1 Redness ≥2 Chemosis ≥2 and the effects fully reverse within 21 days
Category 2B (Cat 2B)	When the effects listed for Category 2A fully reverse within 7 days
Nonirritant	Rabbit mean scores fall below threshold values for Category 1, 2A, and 2B

Each substance was then classified based upon the number of rabbits within each category and the following classification rules. Since the current classification system was applied retrospectively to some studies where more than three rabbits were tested, the decision criteria for substance classification were expanded to allow for classification of these substances. Substance classification, according to the GHS classification guidelines (UN 2003), depends on the proportion of rabbits that produce the same response. When more than three rabbits were tested, the proportionality needed to classify a substance was maintained (e.g., 1 of 3 or 2 of 6 positive rabbits were required for classification for most categories). However, in some cases, additional classification rules were necessary to include the available data. These additional rules are distinguished by italicized text.

GHS Category 1

1. At least 1 of 3 rabbits or 2 of 6 rabbits classified as Cat 1A.
2. *One of 6 rabbits classified as Cat 1A and another rabbit classified as Cat 1B.*
3. At least 2 of 3 rabbits or 4 of 6 rabbits classified as Cat 1B.

If none of the above options were fulfilled, then the following classifications were applied in sequential order:

GHS Category 2A

1. At least 2 of 3 rabbits or 4 of 6 rabbits classified as Cat 2A.
2. *One of 3 (2 of 6) rabbits classified as Cat 2A and 1 of 3 (2 of 6) rabbits classified as Cat 2B.*

GHS Category 2B

1. At least 2 of 3 rabbits or 4 of 6 rabbits classified as Cat 2B.

GHS Nonirritant

1. At least 2 of 3 rabbits or 4 of 6 rabbits classified as nonirritant.

2.4 Calculations Performed

The estimated underclassification rates were calculated for each possible classification category based on the decision rules and the observed distribution of specific rabbit responses among all rabbit responses for each subcategory evaluated. Rabbit responses were denoted by 1A, 1B, 2A, 2B, and N (for a Cat 1A, Cat 1B, Cat 2A, Cat 2B, or nonirritant response, respectively). Likewise, the probability that a rabbit would produce each of these responses is denoted by p1A, p1B, p2A, p2B and pN. The specific test outcomes for a sequential test protocol (up to three rabbits) are as follows:

GHS Category 2A

The following outcomes for a sequential test protocol (up to three rabbits) could lead to a test substance being classified as GHS Category 2A:

1. 2A-2A (testing stopped). This outcome sequence has a probability of (p2A)x(p2A).
2. 2A-(1B, 2B, or N)-2A, or (1B, 2B, or N)-2A-2A. This outcome sequence has a probability of 2x(p2A)x(p2A)x(p1B+p2B+pN).
3. 2A-2B-N (this outcome can occur in six different orders). This outcome sequence has a total probability of 6x(p2A)x(p2B)x(pN).

4. 2A-2B-Cat1B (this outcome can occur in six different orders). This outcome sequence has a total probability of 6x(p2A)x(p2B)x(p1B).

Summing these four probabilities gives the estimated rate for GHS Category 1 substances being underclassified as GHS Category 2A substances.

GHS Category 2B

A similar approach was used for the other classifications. The following outcomes could lead to a GHS Category 2B classification for a test substance:

1. 2B-2B (testing stopped). This outcome sequence has a probability of (p2B)x(p2B).
2. 2B-(2A or 1B or N)-2B (this outcome can occur in two different orders). This outcome sequence has a total probability of 2x(p2B)x(p2B)x(p2A+p1B+pN).

Summing these two probabilities gives the estimated rate for GHS Category 1 substances being under classified as GHS Category 2B substances.

GHS Nonirritant Category

Similarly, the following outcomes could lead to a nonirritant classification:

1. N-N (testing stopped). This outcome sequence has a probability of (pN)x(pN).
2. N-(1B or 2A or 2B)-N (this outcome can occur in two different orders). This outcome sequence has a total probability of 2x(pN)x(pN)x(p1B+p2A+p2B).

Summing these two probabilities gives the estimated rate for GHS Category 1 substances being underclassified as GHS nonirritants.

Variable Responder Category

Using this testing strategy, two different outcomes could lead to the inability to assign an unequivocal GHS classification. In these cases, based on the classification rules described above, a majority of the rabbits tested are not classified in the same manner. These outcomes were designated as “variable responders”. This classification could occur based on the following rabbit outcomes:

1. Cat1B-N-2A (this outcome can occur in six different orders). This outcome sequence has a total probability of 6x(p1B)x(pN)x(p2A).
2. Cat1B-N-2B (this outcome can occur in six different orders). This outcome sequence has a total probability of 6x(p1B)x(pN)x(p2B).

The probabilities p1A, p1B, p2A, p2B, and pN were estimated from the observed distribution of rabbit responses within each analysis conducted. Summing these two probabilities gives the estimated rate for GHS Category 1 substances being underclassified as variable responders.

Due to the nature of the database (i.e., very few substances were tested multiple times within or across laboratories, the number of rabbits tested ranged from one to six), several different calculations were conducted to develop a range of estimated rates for underclassifying a corrosive or severe irritant as a nonsevere irritant or nonirritant.

2.4.1 Calculation 1: Homogeneity of response for GHS Category 1 substances

For this calculation, it was assumed that rabbits have the same (homogeneous) pattern of response for all substances within a given classification category. The advantage of this assumption is that only a single calculation is required to determine the likelihood for underclassifying a corrosive or severe irritant as a nonsevere irritant or nonirritant. However, since the normal variability in response among animals for different test substances is eliminated, the calculation likely will underestimate the overall underclassification rate.

2.4.2 Calculation 2: Heterogeneity of response for GHS Category 1 substances

For this calculation, it is assumed that rabbits have a different (heterogeneous) pattern of response for each study in the database, which is calculated and then pooled. One limitation of this approach is that the distribution of observed rabbit responses for each substance is based on a small number of rabbits. However, this approach takes into account variability of response among substances. As a result, this method leads to a higher estimated underclassification rate than Calculation 1.

2.4.3 Calculation 3: Homogeneity of response for three subgroups of GHS Category 1 substances

This calculation was based upon the observation that there were three subgroups of GHS Category 1 eye irritants that showed, internally, a relatively homogeneous response. These three groups are:

- *Strong responders.* These are GHS Category 1 substances that always produce either a Cat 1A or 1B response in all tested rabbits. In essence, these substances have an estimated underclassification rate of zero.
- *Moderate responders.* These are GHS Category 1 substances that produced a Cat 1 response in at least 50% but not 100% of the rabbits tested.
- *Weak responders.* These are GHS Category 1 substances that produced a nonsevere (i.e., Cat 2A, 2B) or nonirritant response in more than half of the rabbits tested.

Using this approach, the estimated underclassification rates are based on the pooled results from three subgroups rather than being based on a single computation (Calculation 1) or the pooled results across studies (Calculation 2). This approach, by taking into account the presence of subgroups of GHS Category 1 substances differing in the proportion of affected rabbits, should provide the most reasonable estimate of the underclassification rate.

To conduct these analyses using the calculation methods described above, sampling from data based on sequential testing and stopping rules as follows were used:

First Rabbit Sampled from Database

- If a rabbit is classified as Cat 1A, then stop test and the substance tested is classified as GHS Category 1.
- If not, record rabbit classification (e.g., Cat 2B) and then test second rabbit.

Second Rabbit Sampled from Database

- If second rabbit is classified as Cat 1A, then stop test and the substance tested is classified as GHS Category 1.

- If second rabbit has the same classification as the first rabbit, (e.g., Cat 2B) then stop test and the substance tested is classified according to the rabbit classifications.
- If rabbit responses are different, record rabbit classification and then test third rabbit.

Third Rabbit Sampled from Database

- If third rabbit is classified as Cat 1A, then stop test and the substance tested is classified as GHS Category 1.
- Otherwise, record classification of third rabbit.
- If two of the three rabbits have the same classification, then that classification is used for the substance tested.
- If one rabbit is classified as Cat 2B and at least one rabbit is classified as Cat 2A, then the substance tested is classified as GHS Category 2A.
- If all rabbits have different classification (e.g., Cat 1B, Cat 2A, and nonirritant), then the substance tested is identified as a "variable responder."

3.0 RESULTS

The estimated underclassification rate depends on (i) the distribution of rabbit responses for GHS Category 1 irritants; and (ii) the specific test procedure used to evaluate irritancy and to assign substances to irritancy categories. Based on the data, the distribution of rabbit responses for substances judged to be GHS Category 1 irritants is given below for the ECETOC studies, the non-ECETOC studies, and the total database (**Table 3**).

Table 3. Distribution of Rabbits in the Total, ECETOC, and Non-ECETOC Databases

	ECETOC	Non-ECETOC*	Total
Total Number of Studies	31	111	142
Total Number of Rabbits Classified as Cat 1A	54 (48%)	382 (72%)	436 (68%)
Total Number of Rabbits Classified as Cat 1B	20 (18%)	17 (3%)	37 (6%)
Total Number of Rabbits Classified as Cat 2A	19 (17%)	53 (10%)	72 (11%)
Total Number of Rabbits Classified as Cat 2B	18 (16%)	60 (11%)	78 (12%)
Total Number of Rabbits Classified as Nonirritant	1 (1%)	18 (3%)	19 (3%)
Total Number of Rabbits	**112**	**530**	**642**

Abbreviations: Cat = Category, ECETOC = European Centre for Ecotoxicology and Toxicology of Chemicals; total include both ECETOC and NON-ECETOC studies.
* data submitted in response to the *FR* notice (March 24, 2004; Volume 69, Number 57; Page 13859-13861) and provided by industry and U.S. Federal agencies.

Estimated underclassification rates were estimated for the ECETOC database, the total database, and for certain subsets of the total database (e.g., solids versus liquids/gels, selected chemical classes, the four different GHS criteria used to identify a severe irritant or corrosive).

3.1 Calculation 1: Homogeneity of Response for GHS Category 1 Substances

The calculations are illustrated using the values from the total database and the assignment probabilities described previously.

GHS Category 2A

The likelihood of a GHS Category 1 substance being underclassified as a GHS Category 2A substance is the sum of the following four probabilities, which is 0.0250:

1. (72/642)x(72/642) = 0.01258
2. 2x(72/642)x(134/642)x(72/642) = 0.00525
3. 6x(72/642)x(78/642)x(19/642) = 0.00242
4. 6x(72/642)x(78/642)x(37/642) = 0.00471

GHS Category 2B

The estimated underclassification rate of a GHS Category 1 substance being underclassified as a Category 2B substance is the sum of the following two probabilities, which is 0.0207:

1. (78/642)x(78/642) = 0.01476
2. 2x(78/642)x(78/642)x(128/642) = 0.00589

GHS Nonirritant

The estimated underclassification rate of a GHS Category 1 substance being underclassified as a GHS nonirritant is the sum of the following two probabilities, which is 0.0014:

1. (19/642)x(19/642) = 0.00088
2. 2x(19/642)x(187/642)x(19/642) = 0.00051

Variable Responder

Finally, the likelihood of a GHS Category 1 substance being underclassified as a "variable responder" is the sum of the following two probabilities, which is 0.0024:

1. 6x(37/642)x(19/642)x(72/642) = 0.00115
2. 6x(37/642)x(19/642)x(78/642) = 0.00124

Adding these summed probabilities for these four categories yields 0.0495 as the overall estimated underclassification rate for GHS Category 1 substances, based on the total database and assuming homogeneity of response for GHS Category 1 substances (**Table 4**). The results of a similar analysis based only on the ECETOC database are provided also in this table.

Table 4. Estimated Underclassification Rates for GHS Category 1 Substances Using Calculation 1 (Assumes Homogeneity of Response)

Category	ECETOC (31 Studies)	Total Database (142 Studies)
GHS Category 2A	0.0795	0.0250
GHS Category 2B	0.0442	0.0207
GHS Nonirritants	0.0002	0.0014
Variable Responders	0.0031	0.0024
Total	**0.1270 (12.70%)**	**0.0495 (4.95%)**

Abbreviation: ECETOC = European Centre for Ecotoxicology and Toxicology of Chemicals

3.2 Calculation 2: Heterogeneity of Response for GHS Category 1 Substances

The pattern of rabbit responses (i.e., Cat 1A, Cat 1B, Cat 2A, Cat 2B, nonirritant) observed for the individual GHS Category 1 studies in the total database is provided in **Table 5**. The last five rows represent data for substances that were classified as a GHS Category 1 irritant at one concentration but as a nonsevere irritant (GHS Categories 2A or 2B) at a higher concentration. The impact of such data on the estimated underclassification rate is discussed in **Section 4.0**.

Based on these probabilities, the estimated underclassification rate can be calculated for the heterogeneity assumption. Similar to the Calculation 1 method, the likelihood of a substance being underclassified is calculated for each outcome listed in **Table 5** (See columns labeled "Likelihood of Classification"). For each irritancy class, the classification probabilities are then averaged across substances to obtain the overall estimated underclassification rate (**Table 6**).

Table 5. Distribution of Rabbit Response Patterns for GHS Category 1 Substances in the Total and ECETOC Databases and the Corresponding Likelihood of Classification

Distribution of Rabbit Outcomes					Number of Studies		Likelihood of GHS Classification				
Cat 1A	***Cat 1B***	***Cat 2A***	***Cat 2B***	***NI***	***Total***	***ECETOC***	***1***	***2A***	***2B***	***NI***	***VR***
4	0	0	0	0	2	0	1.0000	0	0	0	0
5	0	0	0	0	1	0	1.0000	0	0	0	0
1	4	0	0	0	1	0	1.0000	0	0	0	0
3	0	0	0	0	25	5	1.0000	0	0	0	0
0	3	0	0	0	1	1	1.0000	0	0	0	0

Distribution of Rabbit Outcomes					Number of Studies		Likelihood of GHS Classification				
Cat 1A	***Cat 1B***	***Cat 2A***	***Cat 2B***	***NI***	***Total***	***ECETOC***	***1***	***2A***	***2B***	***NI***	***VR***
2	1	0	0	0	1	1	1.0000	0	0	0	0
0	6	0	0	0	1	0	1.0000	0	0	0	0
6	0	0	0	0	24	1	1.0000	0	0	0	0
5	1	0	0	0	2	1	1.0000	0	0	0	0
4	2	0	0	0	1	0	1.0000	0	0	0	0
2	0	0	0	0	2	0	1.0000	0	0	0	0
2	2	0	0	0	1	1	1.0000	0	0	0	0
1	0	0	0	0	6	5	1.0000	0	0	0	0
5	0	1	0	0	7	0	0.9723	0.0278	0	0	0
4	1	1	0	0	1	0	0.9630	0.0370	0	0	0
4	0	1	1	0	3	0	0.9259	0.0370	0.0370	0	0
2	0	0	0	1	1	0	0.8889	0	0	0.1111	0
4	0	0	2	0	2	0	0.8889	0	0.1111	0	0
3	0	0	3	0	2	0	0.7500	0	0.2500	0	0
5	0	0	1	0	2	0	0.9723	0	0.0278	0	0
4	0	2	0	0	5	2	0.8889	0.1111	0	0	0
2	2	2	0	0	1	0	0.8148	0.1852	0	0	0
3	0	3	0	0	1	0	0.7500	0.2500	0	0	0
2	0	0	1	0	4	1	0.8889	0	0.1111	0	0
0	2	0	1	0	1	1	0.7407	0	0.2593	0	0
2	1	3	0	0	2	1	0.6667	0.3333	0	0	0
4	0	1	0	1	3	0	0.9259	0.0370	0	0.0370	0
2	0	1	0	0	2	0	0.8889	0.1111	0	0	0
1	1	1	0	0	1	1	0.8148	0.1852	0	0	0
0	3	1	0	0	2	2	0.8437	0.1563	0	0	0
3	0	1	2	0	1	0	0.8056	0.0463	0.1481	0	0
2	0	2	2	0	6	0	0.6296	0.1852	0.1852	0	0
1	1	2	2	0	1	1	0.4444	0.3333	0.2222	0	0
2	0	3	1	0	1	0	0.6111	0.3333	0.0556	0	0
1	1	3	1	0	1	1	0.4352	0.5000	0.0648	0	0
2	0	0	3	1	2	0	0.6111	0	0.3333	0.0556	0
2	0	0	4	0	2	0	0.5556	0	0.4444	0	0
2	0	0	0	4	1	0	0.5556	0	0	0.4444	0
1	0	0	2	0	4	2	0.5556	0	0.4444	0	0
1	0	1	1	0	3	0	0.6296	0.1852	0.1852	0	0
1	0	2	0	0	2	1	0.5556	0.4444	0	0	0
1	0	0	1	1	3	0	0.6296	0	0.1852	0.1852	0
1	0	0	0	2	1	0	0.5556	0	0	0.4444	0
1	0	1	0	1	1	0	0.6296	0.1852	0	0.1852	0
0	0	1	1	1	1	0	0	0.4815	0.2593	0.2593	0
0	1	0	5	0	1	1	0.0741	0	0.9259	0	0
0	0	0	2	1	1	0	0	0	0.7407	0.2593	0
0	0	2	2	0	1	1	0	0.5000	0.5000	0	0
1	0	0	2	1	1	1	0.5000	0	0.3750	0.1250	0

Abbreviations: Cat = Category, NI = Nonirritant, VR = variable responder.

Table 6. Estimated Underclassification Rates for GHS Category 1 Substances Using Calculation 2 (Assumes Heterogeneity of Response)

Category	ECETOC (31 Studies)	Total Database (142 Studies)
GHS Category 2A	0.0913	0.0547
GHS Category 2B	0.1080	0.0720
GHS Nonirritants	0.0040	0.0184
Variable Reponders	0.0000	0.0000
Total	**0.2033 (20.33%)**	**0.1451 (14.51%)**

Abbreviation: ECETOC = European Centre for Ecotoxicology and Toxicology of Chemicals

3.3 Calculation 3: Homogeneity of Response for Three Subgroups of GHS Category 1 Substances Identified by Distribution of Rabbit Responses within Studies

To combine the attributes of the first two calculation methods (Calculation 1 and 2), an approach using homogeneity of response for each of three subgroups of GHS Category 1 substances was considered. Based on the three subgroups defined in **Section 2.0**, the distribution of response in each subgroup is summarized below for both the total and ECETOC databases (**Tables 7** and **8**).

Table 7. Distribution of Rabbits Among Three Subgroups of GHS Category 1 Substances for the Total Database

	All Data	Strong Responders	Moderate Responders	Weak Responders
Number of Studies	142	68	41	33
Total Number of Rabbits	642	281	215	146
Cat 1A	436	261	134	41
Cat 1B	37	20	14	3
Cat 2A	72	0	41	31
Cat 2B	78	0	22	56
Nonirritant	19	0	4	15

Abbreviation: Cat = Category
Strong responders are GHS Category 1 substances that produced either a Cat 1A or 1B response in all tested rabbits; Moderate responders are GHS Category 1 substances that produced a Cat 1 response in at least 50% but not 100% of the rabbits tested; Weak responders are GHS Category 1 substances that produced a nonsevere irritant (i.e., Cat 2A or 2B) or nonirritant response in more than half of the rabbits tested.

Table 8. Distribution of Rabbits Among Three Subgroups of GHS Category 1 Substances for the ECETOC Database

	All data	Strong Responders	Moderate Responders	Weak Responders
Number of Studies	31	15	8	8
Total Number of Rabbits	112	42	35	35
Cat 1A	54	35	13	6
Cat 1B	20	7	10	3
Cat 2A	19	0	10	9
Cat 2B	18	0	2	16
Nonirritant	1	0	0	1

Abbreviations: Cat = Category; ECETOC = European Centre for Ecotoxicology and Toxicology of Chemicals

Strong responders are GHS Category 1 substances that produced either a Cat 1A or 1B response in all tested rabbits; Moderate responders are GHS Category 1 substances that produced a Cat 1 response in at least 50% but not 100% of the rabbits tested; Weak responders are GHS Category 1 substances that produced a nonsevere irritant (i.e., Cat 2A or 2B) or nonirritant response in more than half of the rabbits tested.

Based on the observed distribution of responses in **Tables 7** and **8**, the estimated underclassification rate can be calculated as previously described; these probabilities are summarized in **Tables 9** and **10**.

Table 9. Estimated Underclassification Rates for Three Subgroups of GHS Category 1 Substances using Calculation 1 (Assumes Homogeneity of Response) for the Total Database

Category	Strong Responders	Moderate Responders	Weak Responders	Total Database
GHS Category 2A	0.0000	0.0597	0.1510	0.0523
GHS Category 2B	0.0000	0.0162	0.2459	0.0618
GHS Nonirritants	0.0000	0.0005	0.0236	0.0056
Variable Responders	0.0000	0.0021	0.0076	0.0024
Total	**0.0000 (0.00%)**	**0.0785 (7.85%)**	**0.4281 (42.81%)**	**0.1221 (12.21%)**

Strong responders are GHS Category 1 substances that produced either a Cat 1A or 1B response in all tested rabbits; Moderate responders are GHS Category 1 substances that produced a Cat 1 response in at least 50% but not 100% of the rabbits tested; Weak responders are GHS Category 1 substances that produced a nonsevere irritant (i.e., Cat 2A or 2B) or nonirritant response in more than half of the rabbits tested.

Table 10. Estimated Underclassification Rates for Three Subgroups of GHS Category 1 Substances using Calculation 1 (Assumes Homogeneity of Response) for the ECETOC Database

Category	Strong Responders	Moderate Responders	Weak Responders	Total Database
GHS Category 2A	0.0000	0.1656	0.2224	0.1001
GHS Category 2B	0.0000	0.0070	0.3642	0.0958
GHS Nonirritants	0.0000	0.0000	0.0021	0.0005
Variable Responders	0.0000	0.0000	0.0105	0.0027
Total	**0.0000 (0.00%)**	**0.1726 (17.26%)**	**0.5992 (59.92%)**	**0.1991 (19.91%)**

Abbreviation: ECETOC = European Centre for Ecotoxicology and Toxicology of Chemicals
Strong responders are GHS Category 1 substances that produced either a Cat 1A or 1B response in all tested rabbits; Moderate responders are GHS Category 1 substances that produced a Cat 1 response in at least 50% but not 100% of the rabbits tested; Weak responders are GHS Category 1 substances that produced in more than half of the rabbits tested responding with a Cat 2A, 2B, or nonirritant response.

3.4 Subsets of GHS Category 1 Substances

Estimated underclassification rates were calculated for various subsets of GHS Category 1 substances in the database (e.g., the four different GHS criteria used to identify a severe irritant or corrosive, liquids/gels versus solids, selected chemical classes). Because the number of substances in the ECETOC database is relatively few, these analyses were limited to the entire database.

3.4.1 GHS Criteria used to Identify Corrosives and Severe Irritants

One set of analyses compared the four subgroups that were created for GHS Category 1 substances, based on the type of response observed in the rabbits that led to classification of the test substance as a corrosive or severe irritant according to the GHS classification system (UN 2003). These criteria (1 through 4) are:

- *Criterion 1*: Positive response not based on severity but on persistent lesion involving cornea, iris, and/or conjunctiva through to day 21 in at least one of three rabbits
- *Criterion 2*: Positive response based on mean score for first three days (corneal opacity ≥3 and < 4 or iritis ≥1.5) in at least two of three rabbits but lesions do not persist through day 21

- *Criterion 3*: Positive response based on mean for first three days (corneal opacity ≥3 and < 4 or iritis ≥1.5) in at least two of three rabbits and lesions in at least one of three rabbits that persist through day 21
- *Criterion 4*: Corneal opacity equal to 4 at any time in at least one of three rabbits

The estimated underclassification rates for GHS Category 1 substances classified according to each of the four GHS criteria, using the three calculation methods described in **Section 2.0** are provided in **Tables 11**, **12**, and **13**.

Table 11. Distribution of GHS Category 1 Substances and Rabbits into the Four GHS Criteria for Classifying a Test Substance as a Corrosive or Severe Irritant

	Criterion			
	1	**2**	**3**	**4**
Number of Studies	52	7	6	72
Total Number of Rabbits	234	34	27	327
Cat 1A	148	12	17	258
Cat 1B	4	19	4	9
Cat 2A	37	2	2	28
Cat 2B	41	1	3	21
Nonirritant	4	0	1	11

Abbreviation: Cat = Category
Criterion 1: Positive response based not on severity but on persistent lesion involving cornea, iris, and/or conjunctiva through to day 21 in at least one of three rabbits; Criterion 2: Positive response based on mean for first three days (corneal opacity ≥3 and < 4 or iritis ≥1.5) in at least two of three rabbits but lesions do not persist through day 21; Criterion 3: Positive response based on mean for first three days (corneal opacity ≥3 and < 4 or iritis ≥1.5) in at least two of three rabbits and lesions in at least one of three rabbits that persist through day 21; Criterion 4: Corneal opacity equal to 4 at any time in at least one of three rabbits.

Using the three calculation methods described in **Section 2.0**, a range of estimated underclassification rates were calculated for each GHS Category 1 criterion (**Table 14**). Based on these analyses, the GHS Category 1 criterion with the lowest estimated underclassification rate was for substances that were classified as corrosives or severe irritants based on criterion 2 (positive response based on mean for first three days [corneal opacity ≥3 and < 4 or iritis ≥1.5]

Table 12. Distribution of Studies and Rabbits (Total and by Responder Classification) for GHS Category 1 Substances Categorized into the Four GHS Criteria for Classifying a Test Substance as a Corrosive or Severe Irritant

	Criterion 1				Criterion 2				Criterion 3				Criterion 4			
	Total	**Strong**	**Mod.**	**Weak**	**Total**	**Strong**	**Mod.**	**Weak**	**Total**	**Strong**	**Mod.**	**Weak**	**Total**	**Strong**	**Mod.**	**Weak**
Number of Studies	52	18	16	18	7	4	3	0	6	4	1	1	72	42	21	9
Total Number of Rabbits	234	72	84	78	34	21	13	0	27	15	6	6	327	173	112	42
Cat 1A	148	72	51	25	12	8	4	0	17	11	4	2	258	170	75	13
Cat 1B	4	0	3	1	19	13	6	0	4	4	0	0	9	3	5	1
Cat 2A	37	0	17	20	2	0	2	0	2	0	2	0	28	0	20	8
Cat 2B	41	0	11	30	1	0	1	0	3	0	0	3	21	0	10	11
NI	4	0	2	2	0	0	0	0	1	0	0	1	11	0	2	9

Abbreviation: Cat = Category; Mod. = Moderate

Criterion 1: Positive response based not on severity but on persistent lesion involving cornea, iris, and/or conjunctiva through to day 21 in at least one of three rabbits; Criterion 2: Positive response based on mean for first three days (corneal opacity ≥3 and < 4 or iritis ≥1.5) in at least two of three rabbits but lesions do not persist through day 21; Criterion 3: Positive response based on mean for first three days (corneal opacity ≥3 and < 4 or iritis ≥1.5) in at least two of three rabbits and lesions in at least one of three rabbits that persist through day 21; Criterion 4: Corneal opacity equal to 4 at any time in at least one of three rabbits.

Strong responders are GHS Category 1 substances that virtually always produce either a Cat 1A or 1B response in all tested rabbits; Moderate responders are GHS Category 1 substances that produced a Cat 1 response in at least 50% but not 100% of the rabbits tested; Weak responders are GHS Category 1 substances that resulted in more than half of the rabbits tested responding with a Cat 2A, 2B, or nonirritant response.

Table 13. Distribution of Rabbit Response Patterns in the Total Database for GHS Category 1 Substances Distinguished by the GHS Criterion used to Classify the Test Substance as a Corrosive or Severe Irritant and the Corresponding Likelihood of Classification

Distribution of Rabbit Outcomes					Number of Studies				Likelihood of GHS Classification				
Cat 1A	*Cat 1B*	*Cat 2A*	*Cat 2B*	*NI*	*Crit. 1*	*Crit. 2*	*Crit. 3*	*Crit. 4*	*1*	*2A*	*2B*	*NI*	*VR*
4	0	0	0	0	0	0	0	2	1.0000	0	0	0	0
0	6	0	0	0	0	1	0	0	1.0000	0	0	0	0
6	0	0	0	0	6	0	0	18	1.0000	0	0	0	0
5	0	0	0	0	1	0	0	0	1.0000	0	0	0	0
1	4	0	0	0	0	1	0	0	1.0000	0	0	0	0
3	0	0	0	0	10	0	2	13	1.0000	0	0	0	0
0	3	0	0	0	0	0	1	0	1.0000	0	0	0	0
2	0	0	0	0	0	0	0	2	1.0000	0	0	0	0
5	1	0	0	0	0	1	1	0	1.0000	0	0	0	0
2	2	0	0	0	0	1	0	0	1.0000	0	0	0	0
2	1	0	0	0	0	0	0	1	1.0000	0	0	0	0
1	0	0	0	0	1	0	0	5	1.0000	0	0	0	0
4	2	0	0	0	0	0	0	1	1.0000	0	0	0	0
4	0	0	2	0	0	0	0	2	0.8889	0	0.1111	0	0
5	0	1	0	0	1	0	0	6	0.9723	0.0278	0	0	0
4	1	1	0	0	0	1	0	0	0.9630	0.0370	0	0	0
3	0	0	3	0	1	0	0	1	0.7500	0	0.2500	0	0
5	0	0	1	0	1	0	0	1	0.9723	0	0.0278	0	0
4	0	2	0	0	1	0	1	3	0.8889	0.1111	0	0	0
2	2	2	0	0	1	0	0	0	0.8148	0.1852	0	0	0
3	0	3	0	0	1	0	0	0	0.7500	0.2500	0	0	0
2	1	3	0	0	1	0	0	1	0.6667	0.3333	0	0	0
2	0	1	0	0	1	0	0	1	0.8889	0.1111	0	0	0
1	1	1	0	0	0	0	0	1	0.8148	0.1852	0	0	0
0	3	1	0	0	0	1	0	1	0.8437	0.1563	0	0	0
3	0	1	2	0	1	0	0	0	0.8056	0.0463	0.1481	0	0
4	0	1	1	0	2	0	0	1	0.9259	0.0370	0.0370	0	0
4	0	1	0	1	2	0	0	1	0.9259	0.0370	0	0.0370	0
2	0	0	1	0	0	0	0	1	0.8889	0	0.1111	0	0
0	2	0	1	0	0	1	0	0	0.7407	0	0.2593	0	0
2	0	0	4	0	1	0	0	1	0.5556	0	0.4444	0	0
2	0	0	0	4	0	0	0	1	0.5556	0	0	0.4444	0
2	0	3	1	0	0	0	0	1	0.6111	0.3333	0.0556	0	0
1	0	0	2	0	4	0	0	0	0.5556	0	0.4444	0	0
1	1	3	1	0	0	0	0	1	0.4352	0.5000	0.0648	0	0
1	0	1	1	0	2	0	0	1	0.6296	0.1852	0.1852	0	0
1	0	2	0	0	2	0	0	0	0.5556	0.4444	0	0	0
1	0	0	1	1	2	0	0	1	0.6296	0	0.1852	0.1852	0

Distribution of Rabbit Outcomes					Number of Studies				Likelihood of GHS Classification				
Cat 1A	***Cat 1B***	***Cat 2A***	***Cat 2B***	***NI***	***Crit. 1***	***Crit. 2***	***Crit. 3***	***Crit. 4***	***1***	***2A***	***2B***	***NI***	***VR***
1	0	0	0	2	0	0	0	1	0.5556	0	0	0.4444	0
1	0	1	0	1	0	0	0	1	0.5556	0	0	0.4444	0
2	0	2	2	0	6	0	0	0	0.6296	0.1852	0.1852	0	0
2	0	0	3	1	0	0	1	1	0.6111	0	0.3333	0.0556	0
1	1	2	2	0	1	0	0	0	0.444	0.3333	0.2222	0	0

Abbreviations: Cat = Category; Crit. = criterion; NI = Nonirritant; VR = variable responder.
Criterion 1: Positive response based not on severity but on persistent lesion involving cornea, iris, and/or conjunctiva through to day 21 in at least one of three rabbits; Criterion 2: Positive response based on mean for first three days (corneal opacity ≥3 and < 4 or iritis ≥1.5) in at least two of three rabbits but lesions do not persist through day 21; Criterion 3: Positive response based on mean for first three days (corneal opacity ≥3 and < 4 or iritis ≥1.5) in at least two of three rabbits and lesions in at least one of three rabbits that persist through day 21; Criterion 4: Corneal opacity equal to 4 at any time in at least one of three rabbits.

in at least two of three rabbits but lesions do not persist through day 21). In contrast, the GHS Category 1 criterion with the highest estimated underclassification rate was for substances that were classified as corrosives or severe irritants based on criterion 1 (positive response based not on severity but on persistent lesion involving cornea, iris, and/or conjunctiva through to day 21 in at least one of three rabbits). The highest estimated underclassification rate varied with the calculation method used from between 2.8- to 6.4-fold higher than the lowest estimated underclassification rate.

3.4.2 Liquids/Gels versus Solids

Another subset of GHS Category 1 substances evaluated was its physical form (i.e., solids versus liquids/gels). The distributions of data in the total database, by physical property, are provided in **Table 15** and **16**.

Using the three calculation methods described in **Section 2.0**, a range of estimated underclassification rates were calculated for each liquids/gels and solids (**Table 17**). Although the estimated underclassification rates for liquids/gels were a few percentage points higher than those calculated for solids, these differences are not significant, as determined by the Mann-Whitney U test.

Table 14. Estimated Underclassification Rates for GHS Category 1 Substances in the Total Database Distinguished by the GHS Criterion used to Classify the Test Substance as a Corrosive or Severe Irritant

Category	Calculation 1				Calculation 2				Calculation 3			
	Crit. 1	**Crit. 2**	**Crit. 3**	**Crit. 4**	**Crit. 1**	**Crit. 2**	**Crit. 3**	**Crit. 4**	**Crit. 1**	**Crit. 2**	**Crit. 3**	**Crit. 4**
GHS Category 2A	0.0412	0.0113	0.0179	0.0111	0.0753	0.0276	0.0185	0.0356	0.0702	0.0351	0.0185	0.0319
GHS Category 2B	0.0425	0.0020	0.0196	0.0053	0.0986	0.0370	0.0556	0.0266	0.0894	0.0053	0.0556	0.0194
GHS NI	0.0005	0.0000	0.0023	0.0015	0.0085	0.0000	0.0093	0.0203	0.0009	0.0000	0.0093	0.0113
VR	0.0006	0.0000	0.0061	0.0009	0.0000	0.0000	0.0000	0.0000	0.0010	0.000	0.0000	0.0021
Total	**0.0848 (8.48%)**	**0.0133 (1.33%)**	**0.0459 (4.59%)**	**0.0188 (18.8%)**	**0.1824 (18.24%)**	**0.0646 (6.46%)**	**0.0834 (8.34%)**	**0.0825 (8.25%)**	**0.1615 (16.15%)**	**0.0404 (4.04%)**	**0.0834 (8.34%)**	**0.0647 (6.47%)**

Abbreviations: Crit. = criterion; NI = Nonirritant; VR = variable responder
Criterion 1: Positive response based not on severity but on persistent lesion involving cornea, iris, and/or conjunctiva through to day 21 in at least one of three rabbits; Criterion 2: Positive response based on mean for first three days (corneal opacity ≥3 and < 4 or iritis ≥1.5) in at least two of three rabbits but lesions do not persist through day 21; Criterion 3: Positive response based on mean for first three days (corneal opacity ≥3 and < 4 or iritis ≥1.5) in at least two of three rabbits and lesions in at least one of three rabbits that persist through day 21; Criterion 4: Corneal opacity equal to 4 at any time in at least one of three rabbits.
Calculation 1 = homogeneity of response for GHS Category 1 irritants; Calculation 2 = heterogeneity of response for GHS Category 1 irritants; Calculation 3 = homogeneity of response for three subgroups of GHS Category 1 irritants.

Table 15. Distribution of GHS Category 1 Substances and Rabbits (Total and Total and by Responder Classification) for GHS Category 1 Substances Tested as Liquids/Gels or as Solids)

	Liquids/Gels				Solids			
	Total	**Strong**	**Moderate**	**Weak**	**Total**	**Strong**	**Moderate**	**Weak**
Number of Studies	92	43	27	22	22	11	7	4
Total Number of Rabbits	394	165	134	95	104	47	39	18
Cat 1A	263	156	82	25	73	41	27	5
Cat 1B	19	9	8	2	10	6	3	1
Cat 2A	40	0	20	20	13	0	8	5
Cat 2B	61	0	21	40	7	0	1	6
NI	11	0	3	8	1	0	0	1

Abbreviations: Cat = Category; NI = Nonirritant
Strong responders are GHS Category 1 substances that virtually always produce either a Cat 1A or 1B response in all tested rabbits; Moderate responders are GHS Category 1 substances that produced a Cat 1 response in at least 50% but not 100% of the rabbits tested; Weak responders are GHS Category 1 substances that resulted in more than half of the rabbits tested responding with a Cat 2A, 2B, or nonirritant response.

Table 16. Distribution of Rabbit Response Patterns for GHS Category 1 Substances in the Total Database for Liquids/Gels and Solids, and the Likelihood of GHS Classification

Distribution of Rabbit Outcomes					Number of Studies		Likelihood of GHS Classification				
Cat 1A	***Cat 1B***	***Cat 2A***	***Cat 2B***	***NI***	***Liquids/ Gels***	***Solids***	***1***	***2A***	***2B***	***NI***	***VR***
4	0	0	0	0	1	1	1.0000	0	0	0	0
0	6	0	0	0	1	0	1.0000	0	0	0	0
2	2	0	0	0	1	0	1.0000	0	0	0	0
5	0	0	0	0	1	0	1.0000	0	0	0	0
1	4	0	0	0	0	0	1.0000	0	0	0	0
2	0	0	0	0	2	0	1.0000	0	0	0	0
3	0	0	0	0	20	2	1.0000	0	0	0	0
0	3	0	0	0	0	1	1.0000	0	0	0	0
2	1	0	0	0	0	1	1.0000	0	0	0	0
1	0	0	0	0	4	1	1.0000	0	0	0	0
6	0	0	0	0	12	4	1.0000	0	0	0	0
5	1	0	0	0	1	0	1.0000	0	0	0	0
4	2	0	0	0	0	1	1.0000	0	0	0	0

Distribution of Rabbit Outcomes					Number of Studies		Likelihood of GHS Classification				
Cat 1A	***Cat 1B***	***Cat 2A***	***Cat 2B***	***NI***	***Liquids/ Gels***	***Solids***	***1***	***2A***	***2B***	***NI***	***VR***
5	0	1	0	0	3	3	0.9723	0.0278	0	0	0
4	0	0	2	0	2	0	0.8889	0	0.1111	0	0
4	1	1	0	0	0	1	0.9630	0.0370	0	0	0
3	0	0	3	0	2	0	0.7500	0	0.2500	0	0
5	0	0	1	0	2	0	0.9723	0	0.0278	0	0
4	0	2	0	0	0	2	0.8889	0.1111	0	0	0
2	2	2	0	0	0	0	0.8148	0.1852	0	0	0
3	0	3	0	0	1	0	0.7500	0.2500	0	0	0
2	1	3	0	0	1	0	0.6667	0.3333	0	0	0
3	0	1	2	0	1	0	0.8056	0.0463	0.1481	0	0
2	0	0	0	1	1	0	0.8889	0	0	0.1111	0
4	0	1	1	0	3	0	0.9259	0.0370	0.0370	0	0
4	0	1	0	1	2	0	0.9259	0.0370	0	0.0370	0
2	0	0	1	0	4	0	0.8889	0	0.1111	0	0
0	2	0	1	0	0	1	0.7407	0	0.2593	0	0
2	0	1	0	0	2	0	0.8889	0.1111	0	0	0
1	1	1	0	0	1	0	0.8148	0.1852	0	0	0
0	3	1	0	0	2	0	0.8437	0.1563	0	0	0
1	0	2	0	0	1	1	0.5556	0.4444	0	0	0
2	0	0	3	1	0	1	0.6111	0	0.3333	0.0556	0
1	0	0	1	1	2	0	0.6296	0	0.1852	0.1852	0
2	0	3	1	0	0	0	0.6111	0.3333	0.0556	0	0
2	0	0	4	0	2	0	0.5556	0	0.4444	0	0
2	0	0	0	4	0	0	0.5556	0	0	0.4444	0
1	0	0	2	0	2	1	0.5556	0	0.4444	0	0
1	1	3	1	0	0	1	0.4352	0.5000	0.0648	0	0
1	0	0	0	2	1	0	0.5556	0	0	0.4444	0
1	0	1	0	1	1	0	0.6296	0.1852	0	0.1852	0
2	0	2	2	0	5	0	0.6296	0.1852	0.1852	0	0
1	0	1	1	0	2	0	0.6296	0.1852	0.1852	0	0
1	1	2	2	0	1	0	0.4444	0.3333	0.2222	0	0
0	0	1	1	1	1	0	0	0.4815	0.2593	0.2593	0
0	1	0	5	0	1	0	0.0741	0	0.9259	0	0
0	0	0	2	1	1	0	0	0	0.7407	0.2593	0
0	0	2	2	0	1	0	0	0.5000	0.5000	0	0
1	0	0	2	1	1	0	0.5000	0	0.375	0.1250	0

Abbreviations: Cat = Category, NI = Nonirritant, VR = variable responder.

Table 17. Estimated Underclassification Rates for GHS Category 1 Substances in the Total Database Tested as Liquids/Gels or Solids

Category	Calculation 1		Calculation 2		Calculation 3	
	Liquid/Gel	Solids	Liquid/Gel	Solids	Liquid/Gel	Solid
GHS Category 2A	0.0222	0.0264	0.0528	0.0585	0.0482	0.0546
GHS Category 2B	0.0325	0.0066	0.0864	0.0501	0.0797	0.0363
GHS Nonirritant	0.0013	0.0002	0.0199	0.0250	0.0042	0.0013
Variable Responder	0.0021	0.0011	0.0	0.0000	0.0023	0.0021
Total	**0.0608 (6.08%)**	**0.0343 (3.43%)**	**0.1591 (15.91%)**	**0.1111 (11.11%)**	**0.1344 (13.44%)**	**0.0943 (9.43%)**

Calculation 1 = homogeneity of response for GHS Category 1 irritants; Calculation 2 = heterogeneity of response for GHS Category 1 irritants; Calculation 3 = homogeneity of response for three subgroups of GHS Category 1 irritants.

3.4.3 Subsets of GHS Category I Substances, based on Chemical Class

Another set of analyses compared the estimated underclassification rates for GHS Category I substances based on chemical class. For the total database, the number of studies in each chemical class and the number of rabbits in each GHS Category are provided in **Table 18**. Because the small numbers of studies per chemical class make it difficult to assess whether or not heterogeneity is present within a given chemical class, a single homogeneous calculation (Calculation 1) was conducted for the chemical classes judged to have sufficient data (a minimum of 20 animals) for a meaningful calculation. The homogeneity approach was considered reasonable because the data suggest that one important factor contributing to the heterogeneity in the overall database is that some chemical classes are associated with lower variability in responses among tested rabbits. Thus, while there still could be some heterogeneity within the chemical subclasses, it should be relatively minor compared to the heterogeneity for the database as a whole. The results of the estimated underclassification rate calculations for the 13 chemical classes with 20 or more rabbits (formulations, organic salts, amines, aromatics, quaternary ammonium compounds, alcohols, esters, phenols, carboxylic acids, heterocyclics, alkanolamines, ethanolamines, acyl halides) are provided in **Table 19**. The estimated

Table 18. Number of GHS Category 1 Substances in Each Chemical Class and the Irritant Category Distribution for Treated Rabbits, by Chemical Class*

Chemical Class	Studies	Distribution of Rabbits among GHS Classifications					Total Animals
		1A	1B	2A	2B	NI	
Formulations	**32**	**109**	**1**	**25**	**31**	**1**	**167**
Organic salt	**21**	**35**	**5**	**13**	**16**	**7**	**76**
Amine	**9**	**37**	**3**	**3**	**0**	**1**	**44**
Aromatic	**11**	**18**	**12**	**7**	**2**	**0**	**39**
Quaternary ammonium compound	**10**	**23**	**7**	**6**	**2**	**1**	**39**
Alcohol	**8**	**23**	**3**	**5**	**5**	**2**	**38**
Ester	**6**	**26**	**0**	**1**	**3**	**0**	**30**
Phenol	**5**	**22**	**8**	**0**	**0**	**0**	**30**
Carboxylic acid	**7**	**17**	**3**	**6**	**2**	**0**	**28**
Acyl halide	**5**	**25**	**2**	**0**	**1**	**0**	**28**
Heterocycle	**8**	**16**	**5**	**1**	**4**	**0**	**26**
Alkanolamine	**4**	**21**	**0**	**2**	**0**	**1**	**24**
Ethanolamine	**4**	**21**	**0**	**2**	**0**	**1**	**24**
Sulfur Containing Compound	6	9	0	1	6	1	17
Ether	3	8	0	0	7	0	15
Sulfonate	3	6	0	1	4	1	12
Chlorophosphate	2	12	0	0	0	0	12
Inorganic salt	2	5	0	2	0	0	7
Acetophenone	1	4	2	0	0	0	6
Acid	1	6	0	0	0	0	6
Alkyl acid phosphate	1	6	0	0	0	0	6
Aromatic amine	1	2	0	0	3	1	6
Aromatic sulfonate	1	2	0	0	3	1	6
Ketone	1	4	2	0	0	0	6
Metal oxide	1	6	0	0	0	0	6
Organometallic compound	1	4	0	0	2	0	6
Organotin	1	4	0	0	2	0	6
Poly(oxyethylene)	1	4	0	0	2	0	6
Polyether	1	4	0	0	2	0	6
Silane	1	6	0	0	0	0	6
Isocyanate	2	5	0	0	0	0	5
Soap	2	2	0	2	0	0	4
Polycyclic aromatic	1	4	0	0	0	0	4
Aldehyde	1	2	0	0	1	0	3
Alkylpolyglycoside	1	3	0	0	0	0	3
Amide	1	3	0	0	0	0	3
Fatty acid	1	3	0	0	0	0	3
Fluorinated compound	1	1	0	1	1	0	3
Nitrile	1	3	0	0	0	0	3

Chemical Class	Studies	Distribution of Rabbits among GHS Classifications					Total Animals
		1A	1B	2A	2B	NI	
Phenothiazine	1	0	3	0	0	0	3
Polycyclic aromatic nitrogen compound	1	3	0	0	0	0	3
Siloxane	1	2	0	0	0	0	2
Alkali	1	1	0	0	0	0	1

* Chemical class assignments are based on chemical structures; formulations are mixtures of chemicals, therefore individual chemical class assignments could not be made. Not all substances could be classified by chemical class and some substances were classified into more than one chemical class.
Chemical class arranged in descending order by number of rabbits; bolded chemical classes are those analyzed using the Calculation 1 method.

underclassification rates for six (formulations, aromatics, quaternary ammonium compounds, alcohols, carboxylic acids, heterocyclics) of the 13 chemical classes analyzed were similar to each other and within the range of underclassification rates estimated for the total database; these rates ranged from 4.39% for heterocyclics to 8.05% for carboxylic acids. Among the remaining seven chemical classes analyzed, the estimated underclassification rates for six classes were relatively low (0.00% for phenols, 0.13% for acyl halides, 0.66% for amines, 0.95% for alkanolamines, 0.95% for ethanolamines, 1.20% for esters) and the estimated underclassification rate for organic salts (18.85%) was relatively high. The low estimated underclassification rates suggests that the rabbit ocular response to GHS Category 1 substances in these chemical classes are relatively consistent, while the high estimated underclassification rate for organic salts suggests that the rabbit ocular responses to GHS Category 1 substances in this chemical class are more likely to be variable.

Table 19. Estimated Underclassification Rates for GHS Category 1 Substances in the Total Database, Based on Chemical Class*

	Formulations	Organic Salts	Amines	Aromatics	Quaternary Ammonium Compounds	Alcohols
Number of Studies	32	21	9	11	10	8
Number of Rabbits	167	76	44	39	39	38
GHS Category 2A	0.0333	0.0850	0.0054	0.0723	0.0455	0.0401
GHS Category 2B	0.0456	0.0735	0.0000	0.0052	0.0045	0.0264
GHS Nonirritant	0.0001	0.0161	0.0006	0.0000	0.0012	0.0047
Variable Responder	0.0001	0.0139	0.0006	0.0000	0.0056	0.0066
Total	**0.0791 (7.91%)**	**0.1885 (18.85%)**	**0.0066 (0.66%)**	**0.0775 (7.75%)**	**0.0568 (5.68%)**	**0.0778 (7.78%)**

	Esters	Phenols	Carboxylic Acids	Acyl Halides	Heterocyclics	Alkanolamines	Ethanolamines
Number of Studies	6	5	7	5	8	4	4
Number of Rabbits	30	30	28	28	26	24	24
GHS Category 2A	0.0013	0.0000	0.0721	0.0000	0.0093	0.0075	0.0075
GHS Category 2B	0.0107	0.0000	0.0084	0.0013	0.0346	0.0000	0.0000
GHS Nonirritant	0.0000	0.0000	0.0000	0.0000	0.0000	0.0020	0.0020
Variable Responder	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Total	**0.0120 (1.20%)**	**0.0000 (0.00%)**	**0.0805 (8.05%)**	**0.0013 (0.13%)**	**0.0439 (4.39%)**	**0.0095 (0.95%)**	**0.0095 (0.95%)**

Chemical class assignments are based on chemical structures; formulations are mixtures of chemicals, therefore individual chemical class assignments could not be made. Not all substances could be classified by chemical class and some substances were classified into more than one chemical class.

Estimated underclassification rates based on Calculation 1, which assumes homogeneity of response among rabbits for GHS Category 1 irritants within a chemical class.

4.0 SUMMARY

This report estimates the potential for substances classified as ocular corrosives/severe irritants in the current rabbit test to be underclassified as nonsevere irritants/nonirritants based on the variation in individual rabbit responses for 142 studies on 128 substances. The focus of the evaluation is on the underclassification rate for GHS Category 1 substances. This classification system was used because it has been internationally harmonized through the UN and will be implemented globally in the near future. Among the 142 GHS Category 1 studies in the NICEATM database, only nine studies on four substances represent repeat test data (i.e., the same substance tested multiple times at the same concentration, other substances were tested at different concentrations). Three substances (100% 2-benzyl-4-chlorophenol, 100% phosphorodichloridic acid, ethyl ester, 1% benzalkonium chloride) were tested two times, and one substance (10% sodium lauryl sulfate) was tested three times. These data are inadequate for assessing test method intra- and inter-laboratory reproducibility.

It is fully appreciated that using data for substances already classified as corrosive or severely irritating based on a single study only might introduce a bias in the analysis (i.e., result in an underestimate of the underclassification rate). However, considering the relatively large numbers of studies involved, the fact that they originate from multiple laboratories across several decades of testing, and that there is a reasonable expectation that some of the substances included in this database represent those that might have been classified as non-severe irritants in a different study, we consider these estimates a reasonable reflection of the true underclassification potential using the current three animal sequential testing procedure for identifying ocular corrosives and severe irritants, as defined by the GHS hazard classification system (UN 2003).

The estimated underclassification rates obtained using the three different calculation methods are summarized for the ECETOC database and the total database in **Table 20**. Calculation 1 assumes homogeneity of response for GHS Category 1 irritants (i.e., treated rabbits for GHS Category 1 substances responded relatively the same). While this makes the computation relatively simple, it ignores the potentially significant contribution of animal variability in response to the underclassification rate. In contrast, Calculation 2 assumes heterogeneity of

Table 20. Overall Estimated Underclassification Rates for GHS Category 1 Substances in the Total and ECETOC Databases

Category	Calculation 1		Calculation 2		Calculation 3	
	Total	**ECETOC**	**Total**	**ECETOC**	**Total**	**ECETOC**
Category 2A	0.0250	0.0795	0.0547	0.0913	0.0523	0.1001
Category 2B	0.0207	0.0442	0.0720	0.1080	0.0618	0.0958
Nonirritants	0.0014	0.0002	0.0184	0.0040	0.0056	0.0005
Variable Reponders	0.0024	0.0031	0.0000	0.0000	0.0024	0.0027
Total	**0.0495 (4.95%)**	**0.1270 (12.70%)**	**0.1451 (14.51%)**	**0.2033 (20.33%)**	**0.1221 (12.21%)**	**0.1991 (19.91%)**

ECETOC = European Centre for Ecotoxicology and Toxicology of Chemicals.
Calculation 1 = homogeneity of response for GHS Category 1 irritants; Calculation 2 = heterogeneity of response for GHS Category 1 irritants; Calculation 3 = homogeneity of response for three subgroups of GHS Category 1 irritants.

response for GHS Category 1 irritants (i.e., that rabbits have a different [heterogeneous] pattern of response for each GHS Category 1 irritant in the database) and then pools the results across all substances. One significant limitation of this approach is that the distribution of observed rabbit responses for each substance is based on a small number of rabbits. As a result, this method leads to a higher estimated underclassification rate than Calculation 1. Calculation 3 attempts to incorporate aspects of both the homogeneity and heterogeneity approaches used for Calculation 1 and 2, respectively, by dividing the GHS Category 1 substances into subgroups based on the proportion of affected rabbits. In the analysis conducted here, the GHS Category 1 substances were divided into three groups: (1) strong responders, where all treated rabbits expressed a severe response; (2) moderate responders, where the majority but not all treated rabbits expressed a severe response; and (3) weak responders, where the majority of treated rabbits expressed a nonsevere irritant or nonirritant response. This last approach probably provides the most reasonable estimate of the underclassification rate for GHS Category 1 substances. Using the three calculation methods, the estimated underclassification rates for the total database ranged from 4.95% for Calculation 1 to 12.21% for Calculation 3 to 14.51% for Calculation 2. When the analysis was restricted to the ECETOC database, the corresponding values were 12.70%, 19.91%, and 20.33%, respectively.

For the three calculation methods used, the difference between the estimated underclassification rates for the ECETOC database and the total database ranged between 5.82% to 7.75%, with lower rates estimated in each case for the total database. All three calculation methods depend on the distribution of responses among rabbits exposed to ocular corrosives and severe irritants, and a greater proportion of GHS Category 1 substances in the ECETOC database were associated with increased rabbit-to-rabbit heterogeneity compared to those in the total database. This is demonstrated by the fact that among the animals in each database, the percentage of rabbits classified as Cat 1A was 68% (436 of 642 rabbits) in the total base and 48% (54 of 112 rabbits) in the ECETOC database (see **Table 3**). This greater propensity for strong responses among treated rabbits in the total database resulted in the lower estimated underclassification rates. The reason for this difference is not obvious. However, the selection criteria for the substances included in the ECETOC database were that:

- they were single chemical entities at known and consistent high purity or commercial chemicals that were manufactured and distributed to a specification that ensures a consistent composition,
- they were stable in storage,
- the *in vivo* rabbit eye studies had been conducted since 1981 according to OECD TG 405 following GLP principles, and
- the chemicals had been tested undiluted (except that data from studies using dilutions were acceptable when higher concentrations could be expected to cause severe effects).

The last criterion suggests that there may have been a bias in the ECETOC database away from substances that caused severe ocular effects in rabbits. In contrast, the 111 other studies in the total database include 61 (55%) studies submitted to the EPA and FDA for regulatory purposes, 20 (18%) studies used by NIHS to evaluate the validation status of *in vitro* ocular tests, and the 33 (30%) studies from various companies and trade organizations. With the exceptions noted in **Section 2.0**, the only requirements for inclusion in the NICEATM database was that the *in vivo* rabbit eye studies had been conducted according to OECD TG 405 (adopted in 1981 and first revised in 1987) and that sufficient individual animal and sample time data was available for classification of the test substance according to the GHS classification system (UN 2003).

Therefore, the potential bias in the ECETOC database is not present in the non-ECETOC studies included in the total database.

One of the factors that increased the estimated underclassification rate was the presence of studies for substances not originally classified as a GHS Category 1 irritant (five studies were present in the total database, three of which originated in the ECETOC database). These studies represented substances that resulted in a GHS Category 1 classification at one concentration but in a nonsevere classification when tested at a higher concentration. These studies were included in the database under the assumption that with increasing concentration, the same or a more severe response would be expected. However, these results may represent, at least for some substances, true outcomes due to diminished bioavailability at higher concentrations associated with, for example, polymerization.

Another factor that impacted on the estimated underclassification rate was the presence of substances that could not be classified according to the GHS classification system (i.e., the Variable Responder Category). In the testing strategy used to mimic a three-animal sequential test, two different outcomes could lead to the inability to assign an unequivocal GHS classification. In normal testing circumstances, it is likely that additional animals would be sequentially tested in order to arrive at a definitive classification. In the analysis conducted here, the contribution of this category of GHS Category 1 substances to the estimated underclassification rate is considered negligible.

In terms of the analysis of subsets of substances in the total database, an analysis was conduced to estimate the underclassification rates for:

- GHS Category 1 substances separated into four subcategories based on the GHS criterion used to classify them as ocular corrosives or severe irritants. These included:
  - Criterion 1: Positive response based not on severity but on persistent lesion involving cornea, iris, and/or conjunctiva through to day 21 in at least one of three rabbits

  - Criterion 2: Positive response based on mean for first three days (corneal opacity ≥3 and < 4 or iritis ≥1.5) in at least two of three rabbits but lesions do not persist through day 21
  - Criterion 3: Positive response based on mean for first three days (corneal opacity ≥3 and < 4 or iritis ≥1.5) in at least two of three rabbits and lesions in at least one of three rabbits that persist through day 21
  - Criterion 4: Corneal opacity equal to 4 at any time in at least one of three rabbits.
- solids versus liquids/gels, and
- chemical classes that contained sufficient data for an analysis (i.e., at least 20 rabbits per chemical class).

When an analysis was conducted, using the three calculation methods described in **Section 2.0**, of GHS Category 1 subcategories, the lowest estimated underclassification rate (1.33% to 6.46%, depending on the calculation method used) was for criterion 2 and the highest estimated underclassification rate (8.48% to 18.24%, depending on the calculation method used) was for GHS criterion 1. Although the numbers of substances in Criterion 2 is very small, which impacts on the validity of this analysis, the difference is not surprising considering that this criterion is based on a severe response averaged across three days in at least two of three rabbits while criterion 1 is based on a persistent lesion to 21 days in a single rabbit.

For solids versus liquids/gels, regardless of which of the three calculation methods was used, the estimated underclassification rate for liquids/gels was a few percentage points higher than that calculated for solids. However, these differences were not statistically significant.

Because the small numbers of studies per chemical class make it difficult to assess whether or not heterogeneity is present within a given chemical class, a single homogeneous calculation (Calculation 1) was conducted for the 13 chemical classes (formulations, organic salts, amines, aromatics, quaternary ammonium compounds, alcohols, esters, phenols, carboxylic acids, heterocyclics, alkanolamines, ethanolamines, acyl halides) judged to have sufficient data (**≥**20 rabbits) for a meaningful calculation. The estimated underclassification rates for six

(formulations, aromatics, quaternary ammonium compounds, alcohols, carboxylic acids, heterocyclics) of the 13 chemical classes analyzed were similar to each other and within the range of underclassification rates estimated for the total database; these rates ranged from 4.39% for heterocyclics to 8.05% for carboxylic acids. Among the remaining seven chemical classes analyzed, the estimated underclassification rates for six classes were relatively low (0.00% for phenols, 0.13% for acyl halides, 0.66% for amines, 0.95% for alkanolamines, 0.95% for ethanolamines, 1.20% for esters) and the estimated underclassification rate for organic salts (18.85%) was relatively high. The low estimated underclassification rates suggests that the rabbit ocular response to GHS Category 1 substances in these chemical classes are relatively consistent, while the high estimated underclassification rate for organic salts suggests that the rabbit ocular responses to GHS Category 1 substances in this chemical class are more likely to be variable.

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APPENDIX A

DATABASE OF SUBSTANCES CLASSIFIED AS GHS CATEGORY 1 SUBSTANCES (OCULAR CORROSIVES AND SEVERE IRRITANTS)

SUBSTANCE NAME	CASRN	DATA SOURCE	CHEMICAL CLASS	PHYSICAL FORM	PURITY	GHS Cat 1 Criterion	CONC.	RABBIT 1	RABBIT 2	RABBIT 3	RABBIT 4	RABBIT 5	RABBIT 6
Amway automatic dishwashing compound for soft water		Access Business Group	Formulation	Solid		4	100%	Cat 1A	Cat 1A	Cat 1A	Cat 2A	Cat 1A	Cat 1A
Amway automatic dishwashing compound, standard formula		Access Business Group	Formulation	Solid		4	100%	Cat 1A	Cat 2A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
Amway chlorine bleach		Access Business Group	Formulation	Solid		4	100%	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 2A	Cat 1A
Amway concrete floor cleaner		Access Business Group	Formulation	Solid		4	100%	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
Amway Pursue disinfectant cleaner		Access Business Group	Formulation	Liquid		1	100%	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
Amway SA8 laundry liquid		Access Business Group	Formulation	Liquid		1	100%	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	
Amway SA8 limited phos laundry powder		Access Business Group	Formulation	Solid		2	100%	Cat 1A	Cat 1A	Cat 1A	Cat 1B	Cat 1A	Cat 2A
HZA-1		CTFA	Formulation	Liquid		1	undiluted	Cat 2B	Cat 1A	Cat 2B	Cat 2A	Cat 1A	Cat 2A
HZB-1		CTFA	Formulation	Liquid		1	undiluted	Cat 1A	Cat 1A	Cat 1A			
HZC-1		CTFA	Formulation	Liquid		1	undiluted	Cat 1A	Cat 2A	Cat 1A			
HZF-1		CTFA	Formulation	Liquid		1	undiluted	Cat 2A	Cat 2B	Cat 1A	Cat 1A	Cat 2A	Cat 2B
HZG-1		CTFA	Formulation	Liquid		1	undiluted	Cat 1A	Cat 1A	Cat 1A			
HZI-1		CTFA	Formulation	Liquid		1	undiluted	Cat 2B	Cat 2A	Cat 1A	Cat 1A	Cat 2B	Cat 1A
HZK-1		CTFA	Formulation	Liquid		1	undiluted	Cat 2B	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
HZL-1		CTFA	Formulation	Liquid		1	undiluted	Cat 1A	Cat 2B	Cat 2B	Cat 2B	Cat 1A	Cat 1A
HZM-1		CTFA	Formulation	Liquid		1	undiluted	Cat 1A	Cat 1A	Cat 1A			
HZN-1		CTFA	Formulation	Liquid		1	undiluted	Cat 2B	Cat 2B	Cat 1A			
HZR		CTFA	Formulation	Liquid		1	Undiluted	Cat 1A	Cat 2B	Cat 1A	Cat 1A	Cat 1A	Cat 2A
HZR-1		CTFA	Formulation	Liquid		1	undiluted	Cat 1A	Cat 1A	Cat 2B			
HZS-1		CTFA	Formulation	Gel		1	undiluted	Cat 2A	Cat 2A	Cat 2B	Cat 1A	Cat 2B	Cat 1A
HZV-1		CTFA	Formulation	Liquid		1	undiluted	Cat 1A	Cat 1A	Cat 2B			
HZW-1		CTFA	Formulation	Liquid		1	undiluted	Cat 2A	Cat 1A	Cat 2B			
HZX-1		CTFA	Formulation	Liquid		1	undiluted	Cat 1A	Cat 2B	Cat 2B	Cat 2A	Cat 1A	Cat 2A
HZY-1		CTFA	Formulation	Liquid		1	undiluted	Cat 2B	Cat 2A	Cat 2B	Cat 2A	Cat 1A	Cat 1A
1,2,4-Triazole, Sodium Salt	41253-21-8	ECETOC	Organic Salt, Heterocycle, Aromatic	Solid	99.0%	4	100%	Cat 1A					
1-Naphthalene acetic acid (solid)	86-87-3	ECETOC	Aromatic, Carboxylic Acid	Solid	96 %	4	100%	Cat 2B	Cat 2A	Cat 2A	Cat 1B	Cat 2A	Cat 1A
1-Naphthalene acetic acid, sodium salt (solid)	61-31-4	ECETOC	Aromatic, Carboxylic Acid	Solid	95%	3	100%	Cat 1A	Cat 2A	Cat 1A	Cat 1A	Cat 1A	Cat 2A
2,2-Dimethyl butanoic acid	595-37-9	ECETOC	Carboxylic Acid	Liquid	96%	1	100%	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
2,5-Dimethylhexanediol	110-03-2	ECETOC	Alcohol	Solid	99.5%	1	100%	Cat 1A	Cat 2B	Cat 2B			

SUBSTANCE NAME	CASRN	DATA SOURCE	CHEMICAL CLASS	PHYSICAL FORM	PURITY	GHS Cat 1 Criterion	CONC.	RABBIT 1	RABBIT 2	RABBIT 3	RABBIT 4	RABBIT 5	RABBIT 6
Benzalkonium chloride	8001-54-5	ECETOC	Quaternary Ammonium Compound, Organic Salt	Liquid	98%	not classified	1%	Cat 2B	nonirritant	Cat 2B	Cat 1A		
Benzalkonium chloride	8001-54-5	ECETOC	Quaternary Ammonium Compound, Organic Salt	Liquid	98%	4	10%	Cat 1A	Cat 1A	Cat 1A			
Benzalkonium chloride	8001-54-5	ECETOC	Quaternary Ammonium Compound, Organic Salt	Liquid	98%	2	5%	Cat 1A	Cat 1B	Cat 1A	Cat 1B		
Benzalkonium chloride	8001-54-5	ECETOC	Quaternary Ammonium Compound, Organic Salt	Liquid	98%	1	1%	Cat 1A	Cat 2A	Cat 2A	Cat 2A	Cat 1A	Cat 1B
Calcium sulfhydrate solution	12133-28-7	ECETOC	Inorganic Salt, Sulfur Containing Compound	Liquid		1	20%	Cat 1A					
Captan 90-concentrate (solid)	133-06-2	ECETOC	Heterocycle	Solid	90 %	4	100%	Cat 1A	Cat 1A	Cat 1A			
Cetylpyridinium bromide	140-72-7	ECETOC	Aromatic, Quaternary Ammonium Compound	Liquid	99%	4	6%	Cat 1B	Cat 1B	Cat 2A	Cat 1B		
Cetylpyridinium bromide	140-72-7	ECETOC	Aromatic, Quaternary Ammonium Compound	Liquid	99%	2	10%	Cat 1A	Cat 1A	Cat 1B	Cat 1A	Cat 1A	Cat 1A
Cyclohexanol	108-93-0	ECETOC	Alcohol	Liquid	95%	2	100%	Cat 1B	Cat 2A	Cat 1B	Cat 1B		
Dibenzoyl-L-tartaric acid	2743-38-6	ECETOC	Aromatic, Carboxylic Acid	Solid	99%	2	100%	Cat 2B	Cat 1B	Cat 1B			
Diethylaminopropionitrile	5351-04-2	ECETOC	Nitrile	Liquid	99-99.8%	4	100%	Cat 1A	Cat 1A	Cat 1A			
Imidazole	288-32-4	ECETOC	Aromatic, Heterocycle	Solid	99%	4	100%	Cat 1A	Cat 1B	Cat 1A			
Lauric acid	143-07-7	ECETOC	Fatty Acid	Solid	>92%	1	100%	Cat 1A	Cat 1A	Cat 1A			
Methoxyethyl acrylate	3121-61-7	ECETOC	Ester, Ether	Liquid	99.6%	4	100%	Cat 1A	Cat 1A	Cat 2B			
Methylthioglycolate	2365-48-2	ECETOC	Ester, Sulfur Containing Compound	Liquid	99.7%	1	100%	Cat 2B	Cat 2B	Cat 1A			
n-Butanol	71-36-3	ECETOC	Alcohol	Liquid	99.8%		100%	Cat 2B	Cat 2B	Cat 2A	Cat 2A		
Promethazine hydrochloride	58-33-3	ECETOC	Aromatic, Heterocycle, (Tertiary) Amine, Phenothiazine	Solid	98%	3	100%	Cat 1B	Cat 1B	Cat 1B			
Pyridine	110-86-1	ECETOC	Aromatic, Heterocycle	Liquid	99.9+%	4	100%	Cat 2A	Cat 1A	Cat 1B			
Quinacrine	69-05-6	ECETOC	Aromatic, Heterocycle, Amine (Secondary And Tertiary), Polycyclic Aromatic Nitrogen Compound	Liquid		3	100%	Cat 1A	Cat 1A	Cat 1A			
Soap from 80/20-tallow/coconut oil (solid)	No single CAS No.	ECETOC	Organic Salt, Soap	Solid		1	100%	Cat 2A	Cat 2A	Cat 1A			
Sodium hydroxide	1310-73-2	ECETOC	Alkali	Liquid	Reagent Grade	4	10%	Cat 1A					

SUBSTANCE NAME	CASRN	DATA SOURCE	CHEMICAL CLASS	PHYSICAL FORM	PURITY	GHS Cat 1 Criterion	CONC.	RABBIT 1	RABBIT 2	RABBIT 3	RABBIT 4	RABBIT 5	RABBIT 6
Sodium lauryl sulfate	151-21-3	ECETOC	Organic Salt	Liquid	98%	not classified	30%	Cat 2B	Cat 2B	Cat 2B	Cat 2B	Cat 1B	Cat 2B
Sodium lauryl sulfate	151-21-3	ECETOC	Organic Salt	Liquid	98%	1	15%	Cat 2A	Cat 2B	Cat 1B	Cat 2B	Cat 1A	Cat 2A
Sodium perborate tetrahydrate	10486-00-7	ECETOC	Inorganic Salt	Solid	98.6%	1	100%	Cat 1A	Cat 2A	Cat 1A	Cat 1A	Cat 1A	Cat 2A
Sodium undecylenate solution	3398-33-2	ECETOC	Organic Salt, Soap	Liquid		4	33.2%	Cat 1A					
Trichloroacetic acid	76-03-9	ECETOC	Carboxylic Acid	Liquid	Reagent Grade	4	30%	Cat 1A					
2-Ethylhexyl acid phosphate	1070-03-7	ExxonMobil Biomedical Sciences	Ester, Acid, Alkyl Acid Phosphate	Liquid		4	100%	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
Alkyl phosphoric acid ester amine salt (Class)		ExxonMobil Biomedical Sciences	Organic Salt, Ester, Amine	Liquid		4	100%	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 2A
Carboxylic acid amides (Class)		ExxonMobil Biomedical Sciences	Amide	Liquid		3	100%	Cat 1A	Cat 1A	Cat 1A			
PROD-00044		FDA/CPSC		*		1	100%	Cat 2B	Cat 2A	Cat 1A			
PROD-00045		FDA/CPSC		*		1	100%	Cat 1A	nonirritant	Cat 2B			
PROD-00046		FDA/CPSC		*		1	100%	Cat 1A	Cat 1A	Cat 1A			
PROD-00047		FDA/CPSC		*		1	100%	Cat 2B	Cat 1A	Cat 2B			
PROD-00048		FDA/CPSC		*		1	100%	Cat 1A	Cat 1A	Cat 1A			
PROD-00141		FDA/CPSC		*		1	100%	Cat 2A	Cat 1A	Cat 2A	Cat 1A	Cat 2B	Cat 2B
PROD-00146		FDA/CPSC		*		4	100%	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 2A	Cat 2A
PROD-00147		FDA/CPSC		*		3	100%	Cat 1A	Cat 1A	Cat 1A	Cat 1B	Cat 1A	Cat 1A
PROD-00149		FDA/CPSC		*		1	100%	Cat 2A	Cat 1B	Cat 1B	Cat 2A	Cat 1A	Cat 1A
PROD-00153		FDA/CPSC		*		4	100%	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
PROD-00157		FDA/CPSC		*		4	100%	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
PROD-00159		FDA/CPSC		*		3	100%	Cat 2B	Cat 1A	Cat 1A	Cat 2B	Cat 2B	nonirritant
PROD-00182		FDA/CTFA	Formulation	Liquid		1		Cat 1A	Cat 1A	Cat 2B	Cat 1A	Cat 1A	Cat 2A
PROD-00188		FDA/CTFA	Formulation	Liquid		1		Cat 2B	Cat 2B	Cat 1A	Cat 1A	Cat 2B	Cat 2B
PROD-00189		FDA/CTFA	Formulation	Liquid		1		Cat 1A	Cat 2A	Cat 1A	Cat 2A	Cat 2A	Cat 1A
PROD-00057		FDA/EPA Technicals		*		2		Cat 1A	Cat 1B	Cat 1B	Cat 1B	Cat 1B	
PROD-00058		FDA/EPA Technicals		*		4		nonirritant	Cat 1A	nonirritant	Cat 1A	nonirritant	nonirritant
PROD-00062		FDA/EPA Technicals		*		1		Cat 1A	Cat 1A	Cat 1A	Cat 2A	Cat 1A	nonirritant
PROD-00063		FDA/EPA Technicals		*		4		Cat 2A	Cat 2A	Cat 2B	Cat 2A	Cat 1A	Cat 1A
PROD-00068		FDA/EPA Technicals		*		4		Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
PROD-00070		FDA/EPA Technicals		*		4		Cat 2A	Cat 2A	Cat 2A	Cat 1A	Cat 1B	Cat 1A
PROD-00072		FDA/EPA Technicals		*		4		Cat 1A	Cat 2A	Cat 1A	Cat 1A	Cat 1A	Cat 2A
PROD-00074		FDA/EPA Technicals		*		4		Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A

SUBSTANCE NAME	CASRN	DATA SOURCE	CHEMICAL CLASS	PHYSICAL FORM	PURITY	GHS Cat 1 Criterion	CONC.	RABBIT 1	RABBIT 2	RABBIT 3	RABBIT 4	RABBIT 5	RABBIT 6
PROD-00078		FDA/EPA Technicals		*		4		Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
PROD-00081		FDA/EPA Technicals		*		1		Cat 1A	Cat 1A	Cat 2A	Cat 1A	Cat 1A	Cat 1A
PROD-00098		FDA/EPA Technicals		*		4		Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
PROD-00102		FDA/EPA Technicals		*		4		Cat 1A	Cat 2A	Cat 1A	Cat 1A	Cat 1A	Cat 2A
PROD-00110		FDA/EPA Technicals		*		1		Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
PROD-00114		FDA/EPA Technicals		*		1		Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
PROD-00138		FDA/EPA TSCA		*		1		Cat 1A	Cat 1A	Cat 1A			
aromatic Sulfonate (Class)		GlaxoSmithKline	Aromatic, Sulfur Containing Compound	*		4	100%	Cat 1A					
22-C		NIHS		Liquid		4	100%	Cat 1A	Cat 1A	Cat 1A			
22-D		NIHS		Liquid		4	100%	Cat 1A	Cat 1A	Cat 1A			
22-D		NIHS		Liquid		4	10%	Cat 1A	nonirritant	Cat 2B			
22-G		NIHS		Liquid		4	100%	Cat 1A	Cat 1A	Cat 1A			
22-I		NIHS		Liquid		4	100%	Cat 1A	Cat 1A	Cat 1A			
22-L		NIHS		Liquid		4	10%	Cat 1A	Cat 1A	Cat 1A			
22-N		NIHS		Liquid		4	100%	Cat 1A	Cat 1A	Cat 1A			
22-O		NIHS		Liquid		4	100%	Cat 1A	Cat 1A	nonirritant			
Acetic acid	64-19-7	NIHS	Carboxylic Acid	Liquid		4	10%	Cat 1A	Cat 1A	Cat 2A			
Benzalkonium chloride	8001-54-5	NIHS	Quaternary Ammonium Compound, Organic Salt	Liquid		1	100%	Cat 1A	Cat 2A	Cat 2A			
Butanol	71-36-3	NIHS	Alcohol	Liquid		1	10%	nonirritant	Cat 2B	Cat 1A			
Cetyltrimethylammonium bromide	57-09-0	NIHS	Organic Salt, Quaternary Ammonium Compound	Liquid		1	10%	Cat 1A	Cat 1A	Cat 1A			
Domiphen bromide	538-71-6	NIHS	Organic Salt, Quaternary Ammonium Compound	Liquid		4	10%	Cat 1A	Cat 1A	Cat 1A			
Lactic acid	50-21-5	NIHS	Carboxylic Acid	Liquid		4	100%	Cat 1A	Cat 1A	Cat 1A			
Potassium laurate	10124-65-9	NIHS	Organic Salt	Liquid		4	10%	Cat 1A	nonirritant	nonirritant			
Sodium lauryl sulfate	151-21-3	NIHS	Organic Salt	Liquid		4	10%	Cat 1A	Cat 1A	Cat 1A			
Sodium lauryl sulfate	151-21-3	NIHS	Organic Salt	Liquid		4	10%	Cat 1A	Cat 2A	nonirritant			
Sodium lauryl sulfate	151-21-3	NIHS	Organic Salt	Liquid			100%	nonirritant	Cat 2B	Cat 2B			
Sodium lauryl sulfate	151-21-3	NIHS	Organic Salt	Liquid			10%	Cat 2B	Cat 2A	nonirritant			
Stearyltrimethylammonium chloride	15461-40-2	NIHS	Organic Salt, Quaternary Ammonium Compound	Liquid		4	10%	Cat 1A	Cat 1A	Cat 1A			

SUBSTANCE NAME	CASRN	DATA SOURCE	CHEMICAL CLASS	PHYSICAL FORM	PURITY	GHS Cat 1 Criterion	CONC.	RABBIT 1	RABBIT 2	RABBIT 3	RABBIT 4	RABBIT 5	RABBIT 6
Degreaser (sample 16)		S.C. Johnson & Son, Inc.	Formulation	Liquid		4	100%	Cat 1A	Cat 1A	Cat 2B	Cat 1A	Cat 2B	Cat 2B
Floor stripper (sample 18)		S.C. Johnson & Son, Inc.	Formulation	Liquid		4	100%	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 2A
Glass cleaner (sample 19)		S.C. Johnson & Son, Inc.	Formulation	Liquid		4	100%	Cat 2B	Cat 1A	Cat 2A	Cat 1A	Cat 1A	Cat 1A
Insect repellent benchmark (Group 2)		S.C. Johnson & Son, Inc.	Formulation	Liquid		1	100%	Cat 1A	Cat 1A	Cat 1A	nonirritant	Cat 2A	Cat 1A
Metal cleaner (sample 20)		S.C. Johnson & Son, Inc.	Formulation	Liquid		4	100%	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
1,3-Diiminobenz (*f*)-isoindoline	65558-69-2	TSCA	Heterocycle, Polycyclic Aromatic	Solid		4	100%	Cat 1A	Cat 1A	Cat 1A	Cat 1A		
2-Benzyl-4-chlorophenol	120-32-1	TSCA	Phenol	Solid		4	100%	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
2-Benzyl-4-chlorophenol	120-32-1	TSCA	Phenol	Liquid		1	100%	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
3,4-Dichlorophenyl isocyanate	102-36-3	TSCA	Isocyanate	Liquid		1	100%	Cat 1A	Cat 1A	Cat 1A			
4-tert-Butylcatechol	98-29-3	TSCA	Phenol	Liquid		4	85%	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
Acid blue 40	6424-85-7	TSCA	Aromatic Amine, Organic Salt, Aromatic Sulfonate (Salt), Sulfur Containing Compound	Solid		4	n.a.	Cat 1A	nonirritant	Cat 2B	Cat 2B	Cat 1A	Cat 2B
Antimony oxide	1309-64-4	TSCA	Metal Oxide	Solid	83.45%	4	100%	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
Benzenesulfonyl chloride	98-0909	TSCA	Acyl Halide	Liquid	99.6%	4		Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 2B	Cat 1A
Bis(3-aminopropyl) tetramethyl disiloxane	2469-55-8	TSCA	Amine, Siloxane	Liquid		4	100%	Cat 1A	Cat 1A				
Chlorophenacyle	6305-04-0	TSCA	Acyl Halide, Phenol, Acetophenone, Ketone	Solid		4	100%	Cat 1A	Cat 1B	Cat 1A	Cat 1A	Cat 1A	Cat 1B
Cyclohexyl isocyanate	3173-53-3	TSCA	Isocyanate	Liquid		4	100%	Cat 1A	Cat 1A				
Diethylethanolamine	100-37-8	TSCA	Amine, Alcohol, Ethanolamine, Alkanolamine	Liquid		4	50%	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
Diethylethanolamine	100-37-8	TSCA	Amine, Alcohol, Ethanolamine, Alkanolamine	Liquid		4	25%	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
Diethylethanolamine	100-37-8	TSCA	Amine, Alcohol, Ethanolamine, Alkanolamine	Liquid		4	100%	Cat 1A	Cat 1A	Cat 2A	Cat 1A	Cat 1A	Cat 1A
gamma-Aminopropyltriethoxy silane	919-30-2	TSCA	Silane	Liquid	99%	1	100%	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
N,N,N',N'-Tetramethylhexanediamine	111-18-2	TSCA	Amine	Liquid		4	100%	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
N,N-Dimethylethanolamine	108-01-0	TSCA	Alcohol, Amine, Ethanolamine, Alkanolamine	Liquid		4	undiluted	nonirritant	Cat 1A	Cat 1A	Cat 2A	Cat 1A	Cat 1A
Phosphorodichloridic acid, ethyl ester	1498-51-7	TSCA	Acyl Halide, Ester, Chlorophosphate	Liquid	96%	4	100%	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
Phosphorodicloridic acid, ethyl ester	1498-51-7	TSCA	Acyl Halide, Ester, Chlorophosphate	Liquid	>90%	4	100%	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
p-Octylphenol	140-66-9	TSCA	Phenol	Liquid	85%	2	100%	Cat 1B	Cat 1B	Cat 1B	Cat 1B	Cat 1B	Cat 1B

SUBSTANCE NAME	CASRN	DATA SOURCE	CHEMICAL CLASS	PHYSICAL FORM	PURITY	GHS Cat 1 Criterion	CONC.	RABBIT 1	RABBIT 2	RABBIT 3	RABBIT 4	RABBIT 5	RABBIT 6
Polyethylene Glycol 400, dichloride	27252-69-3	TSCA	Ether, Polyether, Poly(Oxyethylene)	Liquid		4	100%	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 2B	Cat 2B
Protectol PP	80-54-6	TSCA	Aldehyde	Liquid	84.80%	1	100%	Cat 2B	Cat 1A	Cat 1A			
T-1585		TSCA		Solid		4	undiluted	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 1A
Tetrahydrofuran	109-99-9	TSCA	Heterocycle, Ether	Liquid		4	100%	Cat 2B	Cat 2B	Cat 2B	Cat 1A	Cat 2B	Cat 1A
Tributyltin oxide	56-35-9	TSCA	Organotin, Organometallic Compound	Liquid		4		Cat 1A	Cat 1A	Cat 1A	Cat 1A	Cat 2B	Cat 2B
Trichloroacetyl chloride	76-02-8	TSCA	Acyl Halide	Liquid		4		Cat 1A	Cat 1A	Cat 1A	Cat 1A		
AU-358 LTV (CBI Mixture)	n.a.	TSCA 8(e) Website	Alkylpolyglycoside, Sulfonate, Sulfur Containing Compound	Liquid		1	100%	Cat 1A	Cat 1A	Cat 1A			
Diphenyliodonium trifluoromethanesulfonate	66003-76-7	TSCA 8(e) Website	Organic Salt, Fluorinated Compound, Sulfonate, Sulfur Containing Compound	Liquid		4	100%	Cat 1A	Cat 2A	Cat 2B			

Abbreviations: CASRN = Chemical Abstracts Services Registry Number; CPSC = U.S. Consumer Product Safety Commission; CTFA = Cosmetics, Toiletry, and Fragrance Association; ECETOC = European Centre for Ecotoxicology and Toxicology of Chemicals; EPA = U.S. Environmental Protection Agency; FDA = U.S. Food and Drug Administration; n.a. = not available; NIHS = Japanese National Institute of Health Sciences; TSCA = Toxic Substances Control Act.

* = Physical form tested unclear from data.

GHS Category 1 criterion: Criterion 1: Positive response based not on severity but on persistent lesion involving cornea, iris, and/or conjunctiva through to day 21 in at least one of three rabbits; Criterion 2: Positive response based on mean for first three days (corneal opacity >3 and < 4 or iritis >1.5) in at least two of three rabbits but lesions do not persist through day 21; Criterion 3: Positive response based on mean for first three days (corneal opacity >3 and < 4 or iritis >1.5) in at least two of three rabbits and lesions in at least one of three rabbits that persist through day 21; Criterion 4: Corneal opacity equal to 4 at any time in at least one of three rabbits.