December 22, 2004

William Stokes, DVM
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NTP
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Dear Dr. Stokes

We are providing public comment in response to the Background Review Document (BRD) "Current Status of In Vitro Test Methods for Identifying Ocular Corrosives and Severe Irritants: The Bovine Opacity and Permeability (BCOP) Test Method", published in the Federal Register, Vol. 69, No. 212, pp 64081-64082, November 1, 2004.

As toxicologists for a consumer products company that manufactures a diverse array of product ranging from shave gels and air fresheners to household cleaners and pesticides, we find the BCOP assay to be a valuable tool for assessing the potential irritancy of products. For over 10 years, our toxicology staff has spearheaded efforts to reduce the use of animals in the hazard assessment process and has frequently used alternative irritancy assays for product development and labeling decisions in our weight-of-evidence assessment. We strongly support the efforts to gain regulatory acceptance of this assay that has become such a valuable part of our product development process.

We anticipated and welcomed a rigorous scientific review of the merits of the BCOP assay. Now that the BRD has been issued we appreciate the enormous effort that has gone into its production of the BRD, but are concerned by a number of clear inaccuracies and by the general tone of the review. In our comments, we hope to shed light on some of the misunderstandings with additional information and persuade the authors to reconsider their rejection of this valuable toxicologist's tool.

The most alarming aspect of the BRD is its conclusion that the BCOP assay is not only unacceptable for regulatory acceptance but is unsuitable even for a screening tool in a tiered testing strategy. The BRD seems to be saying that the Draize rabbit test is the only valid method for ocular irritancy because no other test method can satisfactorily replicate the Draize results. While the Draize eye irritation test has been used for over 60 years, the assumption that a given Draize test result performed at a single laboratory on one occasion is the standard by which a new test is to be judged flies in the face of historical experience. The Draize test has never gone through a rigorous validation process itself (except of the work of Drs. Weil and Scala published in 1971) and thus, the intra- and inter-laboratory reproducibility (precision) of the test is not documented.

To require that a new test reproduce any single result from a reference test seems contrary to our basic understanding of predictive capacity. A new test can do no better at predicting the result of a reference test than the reference test does at predicting itself over time and across laboratories. To note that the Draize test results, or any other test results, vary somewhat within each study, within laboratories and/or across laboratories does not condemn the test. Rather, to study the reproducibility of a given test is to seek a better understanding of what the test can offer. A test need not be perfect to be useful.

Our comment section will address in more detail the following points:

- S.C. Johnson, for one, does not follow the tiered testing strategy described in the Executive Summary, lines 58-60 and p. 1-9, lines 175-177. You may wish to solicit feedback from other companies on this point.
- S.C. Johnson does not follow the classification scheme for pharmaceutical intermediates described by Sina et al. (1995), relying instead on a comparative approach to assessing toxicity. For a discussion of this point, see our comments on the Executive Summary, p. xxxiii, lines 121-139.
- For our rationale for modifying the standard protocol to handle oxidizing/reactive test materials, see our comments to p. 1-15, lines 346-365.

We respectfully request that the comments that follow will be carefully considered as the BCOP Assay is an important part in our product evaluation process. While we realize that alternative assays including the BCOP are incomplete models compared to living animal models, we feel strongly that we have enough knowledge and experience with our formulations and this assay to make judicious, scientifically credible decisions. If ICCVAM ultimately choose to publicly discredit the BCOP assay, it will inflict grievous harm to our company and to the industry as a whole.

Sincerely yours,

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COMMENTS:

Acknowledgments: Correction:
p xxii – S.C. Johnson and Son, Inc.- Nicole Cuellar, M.S./Judith Swanson, B.S./B.A. – Remove Usha Vedula. Add JohnsonDiversey, Inc. - John D. Hamilton, Ph.D./Sarah S. Willems, B.S. as a separate entity.

Executive Summary:
p xxx, line 32-35 and 37-40. S.C. Johnson data sets (Appendix H (H2-H3) were submitted including the required in vivo data with the expectation that the data sets would be included in the analysis of the BCOP.

p xxx, line 48-51. Histology is used for additional reasons beyond the two reasons listed here: discrimination of borderline cases and identification of ocular damage not identified in opacity or permeability in isolated corneas. Histology is typically used for new chemistries or formulas that aren't well characterized in the BCOP. It is used for known chemistries with delayed effects as demonstrated in reactive raw materials/formulas or in chemicals where the mode of action cannot be easily predicted. Histology can be used with known chemistries when a complete picture is needed. Histology would be conducted on the test sample as well as the benchmark for definitive assessment of degree and depth of injury.

p xxxi, line 53-54. **Correction:** Industry has submitted BCOP data for specific formulas to EPA and FDA. Registrations have been granted on these data submitted to EPA.

p. xx1, line 55-56. Mention is made of "validated *in vitro* test methods that are capable of detecting false negative corrosives and severe irritants." We are curious to know what these methods might be.

p xxxi, line 55-60. S.C. Johnson's strategy differs from approach listed here for both non-registered and registered products. The strategy described below is very important and has been consistently used for many years to evaluate our products.

> **Non-registered household products**
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> Over the years, we have approached new product chemistries carefully, attempting to match each test material/formulation with a relevant benchmark material/formulation for which the irritancy potential is already well established. With a combination of in-house historical data, information available in scientific literature, and in-house consumer experience from post-market surveillance, we have become comfortable using the BCOP assay alone, without in vivo confirmatory testing.
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> **Registered household disinfectants, pesticides and repellents**
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> In the area of registered products, our use of the BCOP has been limited to product development (e.g. initial screening of formulas) issues and worker safety.

p. xxxi, lines 58-60 & p. 1-9, lines 175-177:

> S.C. Johnson does not normally proceed to in vivo testing even if materials tested in the BCOP are predicted to be nonirritating or reversibly irritating. Historical consumer usage data, toxicology information on raw materials and/or similar products and use of histology, in conjunction with BCOP results are usually sufficient for hazard evaluation without resorting to whole animal testing.
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> In the household product industry, we are not usually dealing with new, novel molecules. From a risk assessment standpoint, the raw materials have been in use for some time and any systemic toxicity associated with them is generally known and available in the public realm. Hence, our

main concerns as an industry are the irritancy potential of mixtures (formulations) and occasionally, raw materials.

p. xxxii, line 86-90. For many years, it has been an established practice at S.C. Johnson to use 3 and 10 minute exposure times. We have evaluated 1, 3, and 10 minute exposure times and found that 3 and 10 minute are the most appropriate for many of our product types. We have found that the 3 minute is more appropriate than the 10 minute for volatile organic solvents (Cuellar et al. (2004).

p. xxxii, line 90-93. For the testing of our solid formulas, we use the standard BCOP protocol for solids. We have had only one formula over the past 10 years that was less dense than water and thus, floated causing an issue with corneal coverage. Thus, floating test articles have had little impact on our studies.

p. xxxii, line 93-96. Gettings et al. (1996) has shown that anionic and non-ionic surfactants or formulations containing these will not be underpredicted by the BCOP assay when assessed using the permeability score in a classification scheme rather than the individual score. Since cationic surfactants cause tissue coagulation, the opacity and permeability scores are required for assessment.

p. xxxiii, line 121-139. We take issue with the method of accuracy evaluation for the BCOP Assay. The accuracy evaluation was based on a comparison of ocular corrosives and severe irritants, as defined by the Sina et al. (1995) criteria for classification of pharmaceutical intermediates, to in vivo classifications as defined by 3 different regulatory guidelines, EPA (1996), EU (2001) and GHS (2003).

S.C. Johnson does not utilize the classification system as described in the original by Sina et al. (1995) paper to classify severe irritants, i.e., an In Vitro Score of $\geq$55.1. Rather than relying on an absolute cut-off system for the wide variety of products that we evaluate on a daily basis, we believe that comparative toxicity is more reliable basis for classification. This is the reason why S.C. Johnson always utilizes appropriate concurrent benchmark materials, i.e., similar chemistries with previously well-defined toxicity, to evaluate new formulations. Histology is an increasingly important endpoint for us because we believe that depth of injury as seen in histological evaluation is a good predictor of degree and duration of injury as described by Maurer et al. (2002).

p.xxxv, line 184-187. Based on our experience for the past decade, S.C. Johnson believes that the BCOP is a viable alternative to the Draize test to identify ocular corrosives and severe irritants for regulatory hazard classification and labeling purposes. The conclusion stated in the BRD is unsubstantiated until the variability and reliability (p 4-20, lines 469-479) in the animal model is addressed. We have routinely used the BCOP with concurrent benchmarks and histology, if needed, to assess numerous formulations (insecticides, repellents, air fresheners, cleaning products, etc.). Using the BCOP in combination with our weight-of-evidence approach (See xxxi, line 56-60), we feel confident in our use of the BCOP assay to assess ocular irritation in our consumer products.

p.xxxv, llne 187-192. The current in vitro categorization scheme used in the BRD evaluation is not used by all companies to classify raw materials/formulas. The categorization scheme was designed specifically for pharmaceutical intermediates and not all other chemical classes. Because we use benchmarks in all of our BCOP studies, we look at relative toxicity rather than an absolute score.

Chapter 1:
p. 1-2, l. 42: Correction. It should be stated that the rabbit eye test provides “qualitative” rather than “quantitative” scoring.

p. 1-4, lines 83-85. Scientific interest and need for consistency have been the primary drivers that have led to the development of alternative in vitro test methods. Cost and time are not contributing factors to the development of alternative assays. The price to conduct a full, two time course GLP BCOP study with benchmarks, controls and histology is similar in comparison to a GLP Draize study. Timing is similar from study initiation to receipt of final report between the GLP BCOP and Draize studies. Animal welfare is a

contributor to the continued commitment to pursue alternatives to animal testing, but not the primary driver.

p. 1-8, lines 169-171. One use of the BCOP by S.C. Johnson is as a screening tool, however more importantly as mentioned above, we use it routinely as a part of weight-of-evidence approach to assess irritation of our nonregistered products and label accordingly.

p. 1-9, lines 175-177. See p. xxxi, lines 58-60.

p. 1-9, lines 177-181. See p xxxi, line 55-60. Strength of BCOP justifies SCJ's internal approach to the routine use of BCOP for non-registered products.

p. 1-13, lines 297-300. It is generally accepted that the rabbit eye test overpredicts human experience (see Buehler (1974), Marzulli and Simon (1971) and Freeberg et al. (1986) among others). Depending on the degree of overprediction, the result could be excessive overlabeling which is not very helpful to the consumer. It is rather like "crying wolf" so that the consumer will grow to ignore appropriate hazard warnings.

p. 1-13, Section 1.2.2.3: There is no discussion of reproducibility or variability for the in vivo rabbit eye test.

p. 1-14, line 333: Depending on the physical properties of the test material, post-exposure measurement may be from 2 to up to 24 hours, due to delayed responses of some chemicals (see Conclusions in Gran et al. (2003)).

p. 1-15, lines 346-365. Advantages of the BCOP in comparison to the Draize Eye test for evaluation of irritation potential of substances in human eye.

- Although, the BCOP assay addresses only corneal injury, it accounts for the most significant parameter in the Draize test. Corneal injury comprises a possible 80 out of the maximum possible score of 110 in the Draize test.
- We agree that the BCOP assay affords more control over coverage of the cornea with the test material. There also should be less variability in concentration of the test material since the test material cannot be expelled or diluted during the assay.
- While reversibility of corneal effects cannot be directly measured in the BCOP assay, the assay affords the opportunity to explore the extent and depth of injury through post-assay histology. Maurer et al. (2002) have shown the type and depth of injury are good predictors of the degree and duration of injury.
- While the BCOP assay lacks the ability to account for systemic effects following ocular instillation as may be seen in the rabbit in vivo test, in the consumer products industry, products are usually formulated with well-characterized raw materials with known systemic toxicity.

p. 1-18, line 431-435. We believe the BCOP is a suitable alternative to Draize test for addressing potential eye irritation using a standard BCOP protocol including benchmarks, controls, and histology, which is tailored to exposure and post-exposure times appropriate for the formula and/or chemistry. Other criteria (mentioned above) is used in combination with the BCOP results to allow an integrated approach to evaluation of a formula for appropriate product labeling.

p-1-8, Criteria 5. For S.C. Johnson, typical GLP studies conducted at IIVS with benchmarks and histology cost ~ $4,500 (2-time course for 1 sample + 1 benchmark = ~$2,200 plus storage and histology at $850/sample). Typically, our in vitro studies are more expensive than our in vivo studies. Timing for final reports for both is ~ 3 months.

Chapter 2:

p. 2-2, line 47-48. As stated previously, S.C. Johnson does not use the classification system developed for pharmaceutical intermediates. We rely on comparison to well-defined benchmarks.

p. 2-19, line 578. See additional situations where histology may be used in the BCOP under p xxx, line 48-51.

p. 2-26, line 790-791. Is this really an issue anymore with increased awareness and testing advancements of BSE?

p. 2-37, line 1084-1089. As stated previously, S.C. Johnson does not use the classification system developed for pharmaceutical intermediates to identify severe irritants/corrosives (55.1 and above). We rely on comparison to well-defined benchmarks in combination with histological evaluation, if needed.

Chapter 3:

p. 3-1, section 3.1: S.C. Johnson data sets (Appendix H (H2-H3) were submitted including the required in vivo data with the expectation that the data sets would be included in the analysis of the BCOP.

> H2 (Cuellar et al. (2002) poster) included 4 benchmark formulas with full in-vivo data. In-vivo data on test material #1, fragrance benchmark, test material #2, ethanol/fragrance benchmark, and test material #5, ethanol, were included with the submission package. In-vivo data for test material #3 & #4, alcohol-based benchmark, is included as test substance #12 & #13, benchmark, in Swanson and Harbell (2000).
>
> H3 (Gran et al. (2003) poster) included full in-vivo data on sodium percarbonate. Due to severe irritation, animals were only carried out to 96 hours resulting in a Category 1 classification.

p. 3-8, line 187-188. Correction. Sentence should be corrected to say, “The formulas are from S.C. Johnson & Son, Inc and JohnsonDiversy, Inc.”

p. 3-9, line 215. Correction. Sentence should be corrected to say, “The test substances were obtained from S.C. Johnson & Son, Inc”. JohnsonDiversy, Inc. did not supply these materials.

p. 3-10, lines 268-269: Correction. The testing for this assay was performed by laboratory personnel with knowledge that the formulations were solvent-based (primarily ethanol) insect repellents.

Chapter 4:

p. 4-20, lines 469-479. It is imperative that this document is published and shared publicly in order for us to review the reliability of the in vivo rabbit test. This in vivo evaluation should be included in the BRD for the analysis of the BCOP. When will it be available for review? When will it be completed? An analysis of the variation on the in vivo test method with regard to severe irritation and corrosives was presented at the ICCVAM SAP in October 2004. Will this analysis be presented at the Peer Review Panel meeting in January 2005?

Chapter 5:

p. 5-3, line 65-79. We don’t agree with the use of the 55.1 and greater for classifying severe irritants in this analysis since the classification scheme was developed for pharmaceutical intermediates. We rely on comparison to well-defined benchmarks.

p. 5-5, lines 129-143: As stated above, S.C. Johnson does not use the classification system developed for pharmaceutical intermediates to identify severe irritants/corrosives. We rely on comparison to well-defined benchmarks.

Chapter 6

p. 6-5, Table 6-1. Corrections: Under the accuracy column for Gettings et al. (1996), the percentage should be corrected from 80% to 88%. Under positive predictivity for Southee (1998), the percentage should be corrected from 60% to 40%.

p. 6-5, 6-8, and 6-11. Tables. What are the test material numbers for the 9 samples used out of 13 for Swanson and Harbell (2000)? There are a total of 16 test samples evaluated in Swanson and Harbell (2000) and we don't understand which ones were used for the analysis listed in Chapter 6. Of the 16 samples, 11 include in vivo data. Clarification is needed in order to correctly evaluate the analysis performed on our data set in this section. Correction: Test material #13, ethanol, in which 3 rabbits were tested, involved a 60 second rinse and not a 30 minute rinse.

p. 6-8, Table 6-2, Footnote d: Correction. We need clarification on the test material that was evaluated in this table. If the test substance is ethanol (#14 or #15) or the ethanol-based repellent formulation entitled, benchmark #12 &#13, there is no discordance between the two studies done with the same test material. For both test substances, there were two in vivo tests conducted, for a total of 4 in-vivo tests. All in vivo studies conducted resulted in EPA Category 1 classification. There was not a study that resulted in an EPA Category III.

p. 6-13, Table 6-4, Bathroom Cleaner (#6): Correction. The chemical class should include 1-5% chelator (not 10-15%) and the formulation also contains <1% of a quaternary ammonium compound.

p. 6-17, lines 371-375. For benchmark-Group 1 (#12) in vivo study, the one animal that had a opacity score of 4 on day 14, 21, and beyond escalated from a 2 on day 1. All other animals decreased in the severity of their scores over time and cleared in 21 days.

p. 6-22, lines 388-393: We do not agree that the BCOP results are mostly predictive of the "early, acutely irritating effects noted in vivo…" and that reversibility cannot be addressed. With the use of histology, the degree and depth of injury can be assessed and correlated to long-term outcome as described by Maurer et al. (2002). In addition, the 24-hour post-incubation exposure time mentioned in lines 392-394 was not done to assess reversibility but to assess delayed effects caused by reactive chemistries such as oxidizers.

p. 6-22, lines 396-403 and lines 416-460. We disagree with the conclusions that Benchmark Group 1 (#12) and 1-1 (#1) are false positive substances. In a weight of evidence approach, using BCOP with histology and benchmarks, the analysis would easily classify these substances as severely irritating.

Chapter 7:

p. 7-14, 7-16, 7-18, Tables. Why were in vivo data with insufficient data, represented by "?" included in this analysis and if they were not included in the analysis in Chapter 3 and Chapter 6? For the BRD, in vivo criteria were stated to be full volume Draize testing of 3 or 6 animals through recovery period.

p. 7-19 – 7-23. How was median CV% calculated?

p. 7-19, line 344. The median CV% is miscalculated for the 17 substances.

p. 7-26, lines 385-386. As stated above, S.C. Johnson does not use the classification system developed for pharmaceutical intermediates to identify severe irritants/corrosives. We rely on comparison to well-defined benchmarks.

Chapter 9:

p. 9-5, lines 107-119. Why wasn't this study included? In the summary of each study listed in this section, there should be consistency including the rationale of why the study was not included in the analysis of the BCOP.

p.9-20, section 9.1.18. S.C. Johnson data sets (Appendix H (H2-H3) were submitted including the required in vivo data with the expectation that the data sets would be included in the analysis of the BCOP. H2-Refers to poster, Cuellar et al. (2002) and H-3 refers to poster, Gran et al. (2003).

9-24, line 655. Correction. Sentence should read, "An evaluation of the potential ocular irritancy of aerosol fragrance formulations with the BCOP assay." Or replaced by of.

p. 9-25, lines 693-706. Correction. Rationale for modifying standard protocol for solids was incorrect for this study. See below.

> The standard BCOP protocol for solids was not utilized in this investigation of sodium percarbonate. The standard protocol, developed for pharmaceutical intermediates that are relatively insoluble, calls for using a 20% suspension with a 4-hour exposure time. Based on past experience with the BCOP assay, the eye irritancy potential of more aqueous-soluble solids such as laundry powders using the standard solids protocol is vastly overpredictive of the outcome resulting from accidental human exposure. Furthermore, experience has shown that reactive/oxidizing chemistries (such as bleach, percarbonates and peroxides) have a delayed toxicity response in the assay necessitating increased post-exposure observation time.
>
> The question the investigators faced in this case study of sodium percarbonate was what protocol parameters were needed to model the bolus exposure for an extended period that occurs in the Draize eye irritation protocol as well as what might be expected to be a realistic maximum exposure for humans. The following parameters were chosen: A 50% suspension of the solid with a 30-minute exposure time to model the *in vivo* exposure and 10-minute exposure time to model maximum accidental human exposure. While post-exposure time in the BCOP is typically 2 hours, times of 4 and 20-24 hours were chosen.
>
> Utilizing the protocol considerations discussed above, the BCOP assay was able to adequately predict the irritancy potential of two different concentrations of sodium percarbonate for both a realistic human exposure scenario and an *in vivo* exposure scenario. Reduction of sodium percarbonate concentration predictably reduced the irritancy potential of the end-use formulation. Histology as a third endpoint in the BCOP assay was critical in evaluating the depth and degree of injury.

Chapter 11:

p. 11-4 and 11-5, lines 96-117. As previously stated, typical cost of a BCOP test with benchmark and histology is more expensive than an in vivo test. Per our experience, timing is similar for both studies from initiation to receipt of final report.

Chapter 12:

p. 12-1, line 6, footnote 2. We disagree with the regulatory tiered testing strategy as previously mentioned in the executive summary, p. xxxi, lines 58-60 & 1-9, lines 175-177.

p. 12-3, line 56-60. Based on our experience for the past decade, S.C. Johnson believes that the BCOP is a viable alternative to the Draize test to identify ocular corrosives and severe irritants for regulatory hazard classification and labeling purposes. The conclusion stated in the BRD is unsubstantiated until the variability and reliability (p 4-20, lines 469-479) in the animal model is addressed. We have routinely used the BCOP with concurrent benchmarks and histology, if needed, to assess numerous formulations (insecticides, repellents, air fresheners, cleaning products, etc.). Using the BCOP in combination with our

weight-evidence approach (See xxxi, line 56-60), we feel confident in our use of the BCOP assay to assess ocular irritation in our consumer products.

p. 12-10, line 217-247. How were median CV % percentages calculated?

p.12-13, line 328-332. Based on our experience for the past decade, S.C. Johnson believes that the BCOP is a viable alternative to the Draize test to identify ocular corrosives and severe irritants for regulatory hazard classification and labeling purposes. The conclusion stated in the BRD is unsubstantiated until the variability and reliability (p 4-20, lines 469-479) in the animal model is addressed. We have routinely used the BCOP with concurrent benchmarks and histology, if needed, to assess numerous formulations (insecticides, repellents, air fresheners, cleaning products, etc.). Using the BCOP in combination with our weight-evidence approach (See xxxi, line 56-60), we feel confident in our use of the BCOP assay to assess ocular irritation in our consumer products.

p. 12-14, line 362-365: The suggestion to consider different exposure times for substances with different physicochemical properties has been done throughout our work with the BCOP and is reflected in the numerous posters presented by S.C. Johnson in the last decade.

p. 12-15, Table 12-4: The BCOP is capable of assessing corneal swelling and epithelial integrity with histology. The fluorescein dye passage used in assessing the permeability endpoint also indicates whether the epithelial integrity has been preserved.

p. 12-23, 486-490. Based on our experience for the past decade, S.C. Johnson believes that the BCOP is a viable alternative to the Draize test to identify ocular corrosives and severe irritants for regulatory hazard classification and labeling purposes. The conclusion stated in the BRD is unsubstantiated until the variability and reliability (p 4-20, lines 469-479) in the animal model is addressed. We have routinely used the BCOP with concurrent benchmarks and histology, if needed, to assess numerous formulations (insecticides, repellents, air fresheners, cleaning products, etc.). Using the BCOP in combination with our weight-evidence approach (See xxxi, line 56-60), we feel confident in our use of the BCOP assay to assess ocular irritation in our consumer products.

Appendix C-3:

p. C-19, Bathroom Cleaner #6- Correction: Chelator should be listed at 1-5% and not 10-15%.

Appendix E-1:

p. E-31. Correction. Swanson and Harbell (2000) test material #2 and #3 should be classified by EPA as Category III irritants and not Category II due to all animals clearing within 7 days.

Appendix E-2:

p. E-35. Correction. Swanson and Harbell (2000) test material #2 and #3 should be classified by EPA as Category III irritants and not Category II due to all animals clearing within 7 days.

p. E-35. Correction. In vitro scores need to be added to Appendix E-2 for Swanson and Harbell (2000) test materials numbers #1-4 and #7-8. Correct in vitro scores are listed in Appendix E-1, p-31 for all substances listed here.

p. E-37. Correction. In vitro scores need to be added to Appendix E-2 for Swanson and Harbell (2000) test materials numbers #12 & #13. Correct in vitro score of 60.1 is listed in Appendix E-1, p-31 for both substances listed here.

p. E-44. Correction. In vitro score needs to be added to Appendix E-2 for Swanson and Harbell (2000) test material number #14. Correct in vitro score of 52.7 is listed in Appendix E-1, p-31 for this substance. listed here.

References:

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Swanson JE, Lake LK, Donnelly TA, Harbell JW, Huggins J (1995). Prediction of ocular irritancy of full-strength cleaners and strippers by tissue equivalent and bovine corneal assays. Journal of Toxicology - Cutaneous and Ocular Toxicology 14(3): 179-195.

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