Appendix J

NICEATM Analysis:
Reduced Eye Hazard Labeling Resulting from Using Globally Harmonized System (GHS) Instead of Current U.S. Regulatory Classification Criteria

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Summary

Recent analyses by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) reveal that up to 36% of substances currently classified and labeled as eye irritation hazards by U.S. hazard classification regulations would not be classified and labeled as eye hazards using United Nations (UN) Globally Harmonized System for the Classification and Labelling of Chemicals (GHS) eye irritation criteria (UN 2007). Current U.S. hazard classification regulations include the Federal Hazardous Substances Act (FHSA) regulations used by the U.S. Consumer Product Safety Commission (CPSC) and the Occupational Safety and Health Administration (OSHA), and U.S. Environmental Protection Agency (EPA) hazard regulations. U.S. agencies are currently considering implementation of GHS criteria, and OSHA has recently proposed to adopt the GHS criteria to replace the current OSHA Hazard Communication Standard (HCS).[1]

ICCVAM discovered the substantial differences in eye hazard labeling between the GHS and current U.S. classification systems while evaluating the validity of several *in vitro* methods proposed for regulatory ocular safety testing. NICEATM subsequently reviewed and analyzed two separate databases of *in vivo* eye irritation studies to assess the extent that using the GHS criteria would result in no hazard labeling for substances currently labeled as eye hazards in the United States.

The first ocular database evaluated for this analysis was constructed for chemicals used to prepare a 1999 OECD *Detailed Review Document on Classification Systems for Eye Irritation/Corrosion in OECD Member Countries* (DRD; **Annex I**[2]). This document proposed a potential harmonized classification scheme for eye hazards and compared the impact on eye hazard labeling for existing Canadian, EPA, EU, and FHSA classification systems. Careful review of the DRD reveals that using the GHS criteria resulted in no hazard labeling for up to 27% and 33% of substances labeled as eye hazards by current FHSA and EPA classification systems, respectively. This includes 76% of currently labeled EPA Category III irritants (those causing eye injuries persisting for 24 hours to 7 days) that would not require hazard labeling using the GHS criteria. Nonetheless, the scheme was subsequently adopted by GHS.

The second database consisted of a public database of eye irritation studies for 149 chemicals, which revealed similar classification disparities. Using the GHS criteria resulted in no hazard labeling for up to 31% and 36% of substances currently labeled as eye hazards by FHSA and EPA classification systems, respectively.

NICEATM further characterized the nature, duration, and severity of eye injuries produced in these studies for the substances that will no longer be labeled as eye hazards using GHS criteria. Over 50% of these chemicals produced visible eye injuries expected to interfere with normal vision, including corneal opacity, corneal ulceration, and/or iritis (visible damage inside of the eye). Of these substances, 10% produced corneal opacity of a severity grade described as *easily defined translucent areas of the cornea that obscured the details of the iris* (i.e., corneal opacity score of 2/4). While all of the lesions were reversible, they persisted from 24 hours to 7 days.

The high rate of reduced eye hazard labeling resulting from using the GHS criteria compared to U.S. criteria is attributable to two important differences. First, the minimum number/proportion of animals with positive eye injury responses required for classifying a substance as an eye irritation

[1] September 30, 2009, *Federal Register* notice (74 FR 50280): OSHA 29 CFR Parts 1910, 1915, and 1926 Hazard Communication: Proposed Rule.

[2] Available at http://www.olis.oecd.org/olis/1999doc.nsf/LinkTo/env-jm-mono%2899%294

hazard differs significantly. FHSA regulations classify substances as eye irritation hazards when as few as 22% (4/18) of animals produce positive eye injury responses. EPA regulations classify substances as eye irritants when *any* single test animal exhibits a positive response, regardless of the number of animals tested. In contrast, GHS criteria require *at least* 67% (2/3) of animals tested to produce a positive response for classification as an eye irritant hazard.

Secondly, there is a significant difference in the criteria that must be met for eye injuries to be considered positive responses. U.S. regulations (FHSA) consider it a positive response whenever the minimum severity is reached for any of the four types of ocular injuries at *any* of the three observation time points (24, 48, and 72 hours following test substance administration). In contrast, classification according to the GHS requires calculating the *average* severity across all three time points. This average score must meet or exceed the minimum severity level in order to be considered positive. Taken together, these two major differences account for the significant reduction in eye hazard labeling by GHS compared to current U.S. regulations.

The GHS incorporates the principle that the level of protection offered to workers, consumers, the general public, and the environment should not be reduced as a result of harmonizing the classification and labeling systems (UN 2007). In order to adhere to the GHS principle of not reducing protection that could result from the significant reduction in labeling of eye hazards, GHS classification criteria are needed that can provide hazard labeling at least equivalent to that currently provided by current U.S. hazard regulations. This paper summarizes the eye irritation hazard classification analyses and provides proposals for updating the GHS hazard criteria with an optional hazard category that could continue to provide the same level of hazard labeling and protection as current U.S. hazard regulations.

1.0 Background

Physical trauma or chemical burns due to contact with workplace or household products or chemicals result in about 125,000 household eye injuries each year and approximately 2,000 job-related eye injuries per day that require medical treatment.[3,4] In order to provide warnings to consumers and workers of the potential for chemicals and products to cause eye injuries, regulatory authorities require ocular safety testing to determine if substances may cause eye damage. Such testing characterizes the nature, duration, and severity of eye injuries in an animal model, and whether the injuries are reversible or permanent. Testing results are then used for hazard classification and labeling of eye injury potential according to relevant national and/or international classification systems. These classification systems are intended to warn users of the potential for substances to cause eye injuries, the precautions necessary to avoid injuries, and the immediate first-aid procedures that should be followed in the case of an accidental exposure.

Currently, U.S. Occupational Safety and Health Administration's Hazard Communication Standard (HCS) uses the FHSA classification scheme (16 CFR 1500.42) to classify the ocular irritation hazard potential of regulated substances. The FHSA classification system is based on the proportion of animals that exhibit a minimum severity score for each of three areas of the eye (i.e., corneal ulceration and opacity, conjunctival redness and swelling, iritis) that occur during the first 72 hours after test substance administration, with observations recorded at 24, 48, and 72 hours (**Table 1-1**). **Annex II** provides the grading criteria for each of the types of ocular lesions. By comparison, classification according to the EPA scheme uses the same threshold for positive results in each tissue type but has three severity categories, which are determined based on the maximum score for any of the three tissues in any one animal (**Table 1-2**).

Table 1-1 FHSA Classification System (16 CFR 1500.42)

Positive Response for a Single Rabbit[1] (≥1 of the following at 24, 48, or 72 hours)	***In Vivo* Effect**[2]
Corneal ulceration (other than a fine stippling) Corneal opacity ≥ 1 Iritis ≥ 1 Conjunctival swelling and/or redness ≥ 2	First Test - If ≥4/6 animals are positive, the test is positive. If ≤1 animal is positive, the test is negative.[1] If 2/6 or 3/6 animals are positive, the test is repeated using a different group of six animals. Second Test - If ≥3/6 animals are positive, the test is positive. If 0/6 are positive, the test is negative. If 1/6 or 2/6 animals are positive, the test is repeated using a different group of six animals. Third Test - Should a third test be needed, the test is positive if ≥1/6 animals are positive. If 0/6 are positive, the test is negative. **Note: Classification as an eye irritant hazard can result from as few as 22% of animals showing a positive response (e.g., 2/6 + 1/6 + 1/6 = 4/18).**

Abbreviations: CFR = U.S. Code of Federal Regulations; FHSA = U.S. Federal Hazardous Substances Act.
The following scores are considered positive: CO or IR ≥ 1 or CC or CR ≥ 2. Therefore, CO or IR scores of 0 and CC or CR scores of ≤1 are considered cleared.

[1] In this evaluation, a test was also considered negative for 0/3, 0/4, or 0/5 positive animals in 3-, 4-, or 5-animal tests.

[2] In this evaluation, a test was also considered negative for 0/3, 0/4, or 0/5 positive animals in 3, 4, or 5-animal tests.

[3] Available at: http://www.geteyesmart.org/eyesmart/injuries/home.cfm

[4] Available at: http://www.cdc.gov/niosh/topics/eye/

Table 1-2 EPA Classification System

EPA Category	*In Vivo* Effect
I	Corrosive (irreversible) or corneal involvement or other eye irritation persisting for more than 21 days
II[1]	Corneal involvement or other eye irritation clearing[2] in 8 to 21 days
III[1]	Corneal involvement or other eye irritation clearing[2] in 7 days or less
IV	Minimal effects clearing[3] in less than 24 hours

Abbreviations: CC = conjunctival chemosis; CO = corneal opacity; CR = conjunctival redness; EPA = U.S. Environmental Protection Agency; IR = iritis.

At least 3 animals per test (1-animal screen for corrosive/severe irritants permitted).

Maximum score in any animal used for classification.

[1] The EPA currently bases classification decisions on the criteria presented in the EPA Label Review Manual (2003). However, these requirements differ from 40 CFR 156.62 (e.g., EPA Category III is based on no corneal involvement [EPA 2006]).

[2] The following scores are considered positive: CO or IR ≥ 1 or CC or CR ≥ 2. Therefore CO or IR scores of 0 and CC or CR scores of ≤1 are considered cleared.

[3] The following scores are considered positive: CO or IR ≥ 1 or CC ≥ 2. Therefore CO or IR scores of 0 and CC or CR scores of ≤1 are considered cleared.
Most severe response used for classification of substance.

In September 2009, OSHA proposed to modify the HCS to conform to the GHS system.[5] The GHS classification system is based primarily on the severity and timing of reversibility of effects using *mean* values for each endpoint (i.e., corneal opacity, conjunctival redness and swelling, iritis) based on observations assessed at 24, 48, and 72 hours following test substance administration (**Table 1-3**).

Table 1-3 GHS Classification System (UN 2009)

GHS Category	*In Vivo* Effect
I	≥ 1 animal with CO ≥ 4 at any time or ≥ 2 animals with mean[1] CO ≥ 3 or IR ≥ 1.5 or ≥1 animal with CO or IR ≥ 1 or CC or CR ≥ 2 which is not expected to reverse or does not fully reverse[2] within 21 days
2A	≥ 2 animals with mean[1] CO or IR ≥ 1 or CC or CR ≥ 2 which fully reverses[2] within 21 days
2B	≥ 2 animals with mean[1] CO or IR ≥ 1 or CC or CR ≥ 2 which fully reverses[2] within 7 days

Abbreviations: CC = conjunctival chemosis; CO = corneal opacity; CR = conjunctival redness; GHS = UN Globally Harmonized System; IR = iritis; UN = United Nations.

[1] Mean value is calculated from grading at 24, 48, and 72 hours after instillation of the test material.

[2] Fully reversed requires a score of 0.

To understand the potential impact of this change, NICEATM and ICCVAM evaluated 149 Draize rabbit eye tests in the database of the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC; 1998). NICEATM searched for differences in classification

[5] September 30, 2009, *Federal Register* notice (74 FR 50280): OSHA 29 CFR Parts 1910, 1915, and 1926 Hazard Communication: Proposed Rule

of the test substances when comparing the GHS classification system to either the EPA classification system or the FHSA classification system.

NICEATM and ICCVAM also reviewed a 1999 OECD analysis of possible harmonized criteria for eye irritation and corrosion (which were ultimately adopted as the GHS criteria) that assessed the impact of the proposed criteria compared to current Canadian, EPA, EU, and FHSA labeling requirements based on 140 substances and 144 studies (4 repeat tests).

2.0 Overview of NICEATM and ICCVAM Analyses

To evaluate if and to what extent using the proposed HCS/GHS classification system might not identify substances as eye irritation hazards that would be classified as eye irritation hazards by FHSA and EPA criteria, NICEATM evaluated results from Draize rabbit eye test studies from two independent databases:[6] (1) 149 studies obtained from a publicly available database (ECETOC 1998) and (2) 144 studies included in the *Detailed Review Document on Classification Systems for Eye Irritation/Corrosion in OECD Member Countries* (DRD; **Annex I**[7]).

All of the Draize eye test data used in these analyses are from studies that used no more than six animals. If the current FHSA criteria were applied to these studies, many substances could not be definitively classified for ocular hazard potential based on the results of the initial 6-animal test. To assign a definitive FHSA classification, these substances would require further testing in a second and, in some cases, a third 6-animal test. In order to establish a definitive FHSA classification for all substances, an analysis was first undertaken to determine the most appropriate minimum number of positive animals that could be used to assign an FHSA eye hazard label in such circumstances and that would provide the same level of hazard labeling as current FHSA hazard classification regulations. This analysis (see **Annex III**) indicates that a minimum of one positive response out of three test animals would provide nearly equivalent labeling as current FHSA requirements. Based on this analysis, a threshold of ≥33% positive animals was used to assign a definitive classification for all substances included in the two databases.

3.0 Analysis of the ECETOC Eye Irritation Database

The ECETOC database was assessed to identify examples of substances classified based on Draize rabbit eye test results as GHS Not Classified, but as FHSA Irritants or EPA Category I, II, or III irritants. Conversely, examples were also sought for substances classified as EPA Category IV or FHSA Not Labeled, but as GHS Category 1, 2A, or 2B.

3.1 Comparison of the FHSA and GHS Classification Systems

Where possible, NICEATM assigned FHSA and GHS hazard classifications for each substance in the ECETOC database.[8] Only substances that could be assigned a definitive FHSA and GHS classification were included, which yielded a total of 122 or 134 substances included in the analysis, depending on whether the current FHSA criteria or a threshold of 33% positive animals, respectively, was used. Among these substances, 69/122 (57%) and 81/134 (60%) were identified

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[6] As noted in **Section 4.0**, the OECD database includes 24 substances that are also in the ECETOC database.

[7] Available at http://www.olis.oecd.org/olis/1999doc.nsf/LinkTo/env-jm-mono%2899%294

[8] The ECETOC database is composed of 149 studies representing 145 substances. Three substances with duplicate studies, resulting in discordant hazard classifications among one or more of the hazard classification systems, were excluded from these analyses (i.e., 1% benzalkonium chloride is GHS Category 1 or 2A; 5% triton X-100 is GHS Category 2A or 2B; xylene is EPA Category II or IV).

as ocular irritants by the FHSA using the current FHSA criteria and 33% threshold, respectively. NICEATM compared the FHSA ocular hazard classification of these substances with the classification that would be assigned by the GHS system. As indicated in **Table 3-1**, using the GHS criteria would result in no hazard labeling for up to 31% (25/81) of the ECETOC substances that are identified as ocular hazards by FHSA (see also **Annex IV**). Conversely, no substances labeled as ocular hazards by the GHS were not also labeled as hazards by the FHSA (**Table 3-1**).

Table 3-1 ECETOC Database: Substances Classified as Ocular Irritants Using FHSA Compared to Each GHS Ocular Hazard Category

FHSA Classification	No. of ECETOC Substances Classified as FHSA Irritants	GHS Classification			
		1	2A	2B	NC
Irritant (33% threshold)	81	31/81 (38%)	18/81 (22%)	7/81 (9%)	25/81 (31%)
Irritant (16 CFR 1500.42)	69	31/69 (45%)	18/69 (26%)	7/69 (10%)	13/69 (19%)
Not Labeled (either criterion)	53	0/53 (0%)	0/53 (0%)	0/53 (0%)	53/53 (100%)

Abbreviations: CFR = U.S. Code of Federal Regulations; FHSA = U.S. Federal Hazardous Substances Act; GHS = UN Globally Harmonized System; NC = Not Classified.

A closer look at the individual rabbit eye test data for the 25 FHSA eye irritants based on the 33% threshold that would not be labeled using GHS criteria reveals that 48% (12/25) of these substances produced corneal opacity and/or corneal ulceration, including seven that also produced iritis (visible evidence of tissue damage inside the eye; **Table 3-2**). Many of these substances (28% [7/25]) produced corneal opacity that extended beyond 48 hours after test substance administration (**Table 3-2**). **Table 3-2** also provides these data for the subset of 13 substances classified using the current FHSA criteria.

Table 3-2 ECETOC Database: Frequency, Type, and Severity of Ocular Lesions Among Substances Classified as FHSA Irritants, but Not Classified as Ocular Hazards by the Proposed HCS and Current GHS Classification Criteria

In Vivo Finding	No. of Substances	No. of Substances Where More than One Animal Exhibited the *In Vivo* Finding[1]
FHSA Classification Based on ≥33% Positive Animals		
Any CO score ≥ 1	12/25 (48%)	10/12 (83%)
CO Score ≥ 1: duration of 48 hours or more	7/25 (28%)	2/7 (29%)
CR or CC score ≥ 2	22/25 (88%)	17/22 (68%)
CR or CC score ≥ 2: duration of 72 hours or more	5/25 (20%)	2/5 (40%)
Iritis: visible inflammation inside the eye	7/25 (28%)	5/7 (71%)
Iritis: duration of 48 hours or more	3/25 (12%)	-

continued

Table 3-2 ECETOC Database: Frequency, Type, and Severity of Ocular Lesions Among Substances Classified as FHSA Irritants, but Not Classified as Ocular Hazards by the Proposed HCS and Current GHS Classification Criteria (*continued*)

In Vivo Finding	No. of Substances	No. of Substances Where More than One Animal Exhibited the *In Vivo* Finding[1]
FHSA Classification Based on 16 CFR 1500.42		
Any CO score ≥ 1	10/13 (77%)	8/10 (80%)
CO Score ≥ 1: duration of 48 hours or more	7/13 (54%)	2/7 (29%)
CR or CC score ≥ 2	12/13 (92%)	12/12 (100%)
CR or CC score ≥ 2: duration of 72 hours or more	5/13 (38%)	2/5 (40%)
Iritis: visible inflammation inside the eye	6/13 (46%)	5/6 (83%)
Iritis: duration of 48 hours or more	3/13 (23%)	-

Abbreviations: CC = conjunctival chemosis; CFR = U.S. Code of Federal Regulations; CO = corneal opacity; CR = conjunctival redness; ECETOC = European Centre for Ecotoxicology and Toxicology of Chemicals; FHSA = U.S. Federal Hazardous Substances Act; HCS = OSHA Hazard Communication Standard; No. = number; OSHA = U.S. Occupational Safety and Health Administration.

[1] The total number of animals in each test ranged from 3 to 6.

3.2 Comparison of the EPA and GHS Classification Systems

NICEATM also compared the ocular hazard classifications for the ECETOC substances based on EPA and GHS classification systems. Again, NICEATM attempted to assign EPA and GHS hazard classifications for each substance. Only substances that could be assigned definitive EPA and GHS classifications were included in the analysis, a total of 134 substances. Among these substances, 87/134 (65%) are identified as ocular irritants (i.e., EPA Category I, II, or III) by the EPA system. NICEATM compared the EPA ocular hazard classification of these substances with the classification that would be assigned by the GHS system. As indicated in **Table 3-3**, using the GHS criteria would result in no hazard labeling for 36% (31/87) of the ECETOC substances that are identified as ocular hazards by EPA (see also **Annex IV**). This includes 78% of currently labeled EPA Category III irritants (those causing eye injuries persisting for 24 hours to 7 days) that would not require hazard labeling using the GHS (see **Table 3-4**). No substances were labeled as ocular hazards by the GHS that were not also labeled as hazards by the EPA (**Table 3-4**).

Table 3-3 ECETOC Database: Substances Classified in the U.S. as Ocular Hazards Using the EPA Hazard Category Criteria, but Not Classified as Ocular Hazards by GHS Classification Criteria

EPA Category I, II, or III	GHS Hazard Classification	No. of Substances
87	1	31/87 (36%)
	2A	18/87 (21%)
	2B	7/87 (8%)
	NC	31/87 (36%)

Abbreviations: ECETOC = European Centre for Ecotoxicology and Toxicology of Chemicals; EPA = U.S. Environmental Protection Agency; GHS = UN Globally Harmonized System; NC = Not Classified; No. = number.

Table 3-4 ECETOC Database: Comparison of Substances Classified Using Each EPA and GHS Eye Hazard Category

EPA Classification	No. of Substances	GHS Classification			
		1	2A	2B	NC
EPA I	28	27/27 (100%)	0/27 (0%)	0/27 (0%)	0/27 (0%)
EPA II	21	4/20 (20%)	14/20 (70%)	2/20 (10%)	0/20 (0%)
EPA III	42	0/40 (0%)	4/40 (10%)	5/40 (12%)	31/40 (78%)
EPA IV	47	0/47 (0%)	0/47 (0%)	0/47 (0%)	47/47 (100%)

Abbreviations: ECETOC = European Centre for Ecotoxicology and Toxicology of Chemicals; EPA = U.S. Environmental Protection Agency; GHS = UN Globally Harmonized System; NC = Not Classified; No. = number.

A closer look at the individual rabbit eye test data for the 31 EPA eye irritants that would not be labeled using GHS criteria reveals that 52% (16/31) of these substances produced corneal opacity and/or corneal ulceration, including eight (26% [8/31]) that extended beyond 48 hours after test substance administration (**Table 3-5**). A total of eight substances produced iritis (visible evidence of tissue damage inside the eye). Seven of the eight also produced corneal opacity.

Table 3-5 ECETOC Database: Responses, Frequency, and Severity of Ocular Lesions Among 31 Substances Classified in the U.S. as Ocular Hazards Using the EPA Hazard Category Criteria, but Not Classified as Ocular Hazards by the Proposed HCS and Current GHS Classification Criteria

In Vivo Finding	No. of Substances	No. of Substances Where More than One Animal Exhibited the *In Vivo* Finding[1]
Any CO Score ≥ 1	16/31 (52%)	10/16 (63%)
CO Score ≥ 1: duration of 48 hours or more	8/31 (26%)	2/8 (25%)
CR or CC score ≥ 2	25/31 (81%)	17/25 (68%)
CR or CC Score ≥ 2: duration of 72 hours or more	5/31 (16%)	2/5 (40%)
Iritis: visible inflammation inside the eye	8/31 (26%)	5/8 (63%)
Iritis: visible inflammation inside the eye; duration of 48 hours or more	3/31 (10%)	1/3 (33%)

Abbreviations: CC = conjunctival chemosis; CO = corneal opacity; CR = conjunctival redness; ECETOC = European Centre for Ecotoxicology and Toxicology of Chemicals; EPA = U.S. Environmental Protection Agency; GHS = UN Globally Harmonized System; HCS = OSHA Hazard Communication Standard; OSHA = U.S. Occupational Safety and Health Administration; No. = number.

[1] The total number of animals in each test ranged from 3 to 6.

4.0 Analysis of the 1999 OECD Detailed Review Document on Classification Systems for Eye Irritation/Corrosion in OECD Member Countries

During the development of possible harmonized criteria for eye irritation and corrosion hazard categories, the OECD coordinated preparation of a *Detailed Review Document on Classification Systems for Eye Irritation/Corrosion in OECD Member Countries* (DRD; **Annex I**). This document provides a potential harmonized classification scheme along with a comparison to the impact on eye hazard labeling for several existing national classification systems (i.e., Canada, EPA, EU, and FHSA). The DRD provides clear and concise documentation of the extent that the potential harmonization scheme would significantly reduce the number of chemicals identified as eye irritation hazards compared to current U.S. (EPA and FHSA) requirements. The scheme proposed in the DRD was subsequently incorporated into the GHS (UN 2009). However, it should be noted that the DRD does not provide any conclusions or recommendations, but instead details comparisons of sensitivity offered by the existing classification systems and the proposed scheme. There is no discussion in the document as to why *not* labeling substances currently labeled as eye hazards by EPA and FHSA criteria could be construed as providing the same level of protection. Efforts to locate documentation of further consideration of the severe underlabeling of eye hazards and reduced protection that would result from using the GHS scheme compared to current U.S. requirements were unsuccessful.

The OECD DRD (hereafter, OECD database) includes Draize rabbit eye test data for 140 substances (144 studies – 4 repeat tests) that were obtained from five different sources: (1) ECETOC industrial chemicals (n = 24), (2) EPA pesticide active ingredients (n = 60), (3) EPA pesticide products (n = 18), (4) EPA new industrial chemicals (n = 27), and (5) German

new industrial chemicals (n = 11). NICEATM obtained the individual animal data from all 144 studies and assigned EPA, FHSA, and GHS ocular hazard classifications where possible. However, using the classification rules described in **Tables 1-1** to **1-3**, NICEATM was unable to assign a definitive classification (i.e., either irritant or not classified) for some of the substances (EPA: n = 13; FHSA: n = 14; GHS: n = 19). Accordingly, there are some differences in the numbers of substances classified by NICEATM and those reported in the DRD (**see Annex V**). However, these differences did not result in substantive differences between NICEATM and the DRD database in the proportion of substances classified as irritants.

The OECD database was assessed to identify examples of substances classified based on Draize rabbit eye test results as GHS Not Classified, but as FHSA Irritants or EPA Category I, II, or III irritants. Conversely, examples were also sought for substances classified as EPA Category IV or FHSA Not Labeled, but as GHS Category 1, 2A, or 2B.

4.1 Comparison of the FHSA and GHS Classification Systems

Where possible, NICEATM assigned FHSA and GHS hazard classifications for each substance in the OECD database. Only substances that could be assigned a definitive FHSA and GHS classification were included, which yielded a total of 114 or 125 substances included in the analysis, depending on whether the current FHSA criteria or a threshold of 33% positive animals, respectively, was used. Among these substances, 85/114 (76%) and 95/125 (76%) were identified as ocular irritants by the FHSA using the current FHSA and 33% threshold criteria, respectively. NICEATM compared the FHSA ocular hazard classification of these substances with the classification that would be assigned by the GHS system. As indicated in **Table 4-1**, using the GHS criteria would result in no hazard labeling for up to 27% (26/95) of the OECD substances that are identified as ocular hazards by FHSA (see also **Annex VI**). Conversely, there were no substances labeled as ocular hazards by the GHS that were not also labeled as hazards by the FHSA (**Table 4-1**).

Table 4-1 OECD Database: Substances Classified as Ocular Irritants Using FHSA Compared to Each GHS Ocular Hazard Category

FHSA Classification	No. of OECD Substances Classified as FHSA Irritants	GHS Classification			
		1	2A	2B	NC
FHSA Classification Based on ≥33% Positive Animals					
Irritant	95	38/95 (40%)	22/95 (23%)	9/95 (9%)	26/95 (27%)
Not Labeled	30	0/30 (0%)	0/30 (0%)	0/30 (0%)	30/30 (100%)
FHSA Classification Based on 16 CFR 1500.42					
Irritant	85	38/85 (45%)	22/85 (26%)	9/85 (10%)	16/85 (19%)
Not Labeled	29	0/29 (0%)	0/29 (0%)	0/29 (0%)	29/29 (100%)

Abbreviations: CFR = U.S. Code of Federal Regulations; FHSA = U.S. Federal Hazardous Substances Act; GHS = UN Globally Harmonized System; OECD = Organisation for Economic Co-operation and Development; NC = Not Classified; No. = number.

A closer look at the individual rabbit eye test data for the 26 FHSA eye irritants based on the 33% threshold that would not be labeled using GHS criteria reveals that 46% (12/26) of these

substances produced corneal opacity and/or corneal ulceration, including twelve that also produced iritis (visible evidence of tissue damage inside the eye; **Table 4-2**). Many of these substances (27% [7/26]) produced corneal opacity that extended beyond 48 hours after test substance administration (**Table 4-2**). **Table 4-2** also provides these data for the subset of 16 substances classified using the current FHSA criteria.

Table 4-2 OECD Database: Frequency, Type, and Severity of Ocular Lesions Among Substances Classified as FHSA Irritants, but Not Classified as Ocular Hazards by the Proposed HCS and Current GHS Classification Criteria

***In Vivo* Finding**	**No. of Substances**	**No. of Substances Where More than One Animal Exhibited the *In Vivo* Finding[1]**
FHSA Classification Based on ≥33% Positive Animals		
Any CO score ≥ 1	12/26 (46%)	8/12 (67%)
CO score ≥ 1: duration of 48 hours or more	7/26 (27%)	6/7 (86%)
CR or CC score ≥ 2	22/26 (85%)	20/22 (91%)
CR or CC score ≥ 2: duration of 72 hours or more	4/26 (15%)	4/4 (100%)
Iritis: visible inflammation inside the eye	12/26 (46%)	6/12 (50%)
Iritis: duration of 48 hours or more	2/26 (8%)	1/2 (50%)
FHSA Classification Based on 16 CFR 1500.42		
Any CO score ≥ 1	8/16 (50%)	5/8 (62%)
CO score ≥ 1: duration of 48 hours or more	5/16 (31%)	4/5 (80%)
CR or CC score ≥ 2	16/16 (100%)	15/16 (94%)
CR or CC score ≥ 2: duration of 72 hours or more	3/16 (19%)	2/3 (67%)
Iritis: visible inflammation inside the eye	8/16 (50%)	5/8 (62%)
Iritis: duration of 48 hours or more	2/16 (12%)	2/2 (100%)

Abbreviations; CC = conjunctival chemosis; CO = corneal opacity; CR = conjunctival redness; FHSA = U.S. Federal Hazardous Substances Act; GHS = UN Globally Harmonized System; HCS = OSHA Hazard Communication Standard; No. = number; OECD = Organisation for Economic Co-operation and Development; OSHA = U.S. Occupational Safety and Health Administration; UN = United Nations.

[1] The total number of animals in each test ranged from 3 to 6.

4.2 Comparison of the EPA and GHS Classification Systems

NICEATM also compared the ocular hazard classifications for the ECETOC substances based on EPA and GHS classification systems. Again, NICEATM attempted to assign EPA and GHS hazard classifications for each substance, and only substances that could be assigned a definitive EPA and GHS classification were included. A total of 122 substances were included in the analysis. Among these substances, 99/122 (81%) are identified as ocular irritants (i.e., EPA Category I, II, or III) by the EPA system. NICEATM compared the EPA ocular hazard classification of these substances with the classification that would be assigned by the GHS

system. As indicated in **Table 4-3**, using the GHS criteria would result in no hazard labeling for 33% (33/99) of the ECETOC substances that are identified as ocular hazards by EPA. This includes 76% (31/41) of currently labeled EPA Category III irritants (those causing eye injuries persisting for 24 hours to 7 days) that would not require hazard labeling using the GHS (see **Table 4-4** and **Annex VI**). There were no substances labeled as ocular hazards by the GHS that were not also labeled as hazards by the EPA (**Table 4-4**).

Table 4-3 OECD Database: Substances Classified in the U.S. as Ocular Hazards Using the EPA Hazard Category Criteria, but Not Classified as Ocular Hazards by GHS Classification Criteria

EPA Category I, II, or III	GHS Hazard Classification	No. of Substances
99	1	36/99 (36%)
	2A	22/99 (22%)
	2B	8/99 (8%)
	NC	33/99 (33%)

Abbreviations: EPA = U.S. Environmental Protection Agency; GHS = UN Globally Harmonized System; NC = Not Classified; No. = number; OECD = Organisation for Economic Co-operation and Development; UN = United Nations.

Table 4-4 OECD Database: Comparison of Substances Classified Using Each EPA and GHS Eye Hazard Category

EPA Classification	No. of Substances	GHS Classification			
		1	2A	2B	NC
EPA I	36	35/36 (97%)	1/36 (3%)	0/36 (0%)	0/36 (0%)
EPA II	22	1/22 (4%)	18/22 (82%)	1/22 (4%)	2/22 (9%)
EPA III	41	0/41 (0%)	3/41 (7%)	7/41 (17%)	31/41 (76%)
EPA IV	23	0/23 (0%)	0/23 (0%)	0/23 (0%)	23/23 (100%)

Abbreviations: EPA = U.S. Environmental Protection Agency; GHS = UN Globally Harmonized System; NC = Not Classified; No. = number; OECD = Organisation for Economic Co-operation and Development; UN = United Nations.

A closer look at the individual rabbit eye test data for the 33 EPA eye irritants that would not be labeled using GHS criteria reveals that 39% (13/33) of these substances produced corneal opacity and/or corneal ulceration, including seven (21% [7/33]) that extended beyond 48 hours after test substance administration (**Table 4-5**). A total of twelve substances produced iritis (visible evidence of tissue damage inside the eye), six of which also produced corneal opacity.

Table 4-5 ECETOC Database: Responses, Frequency, and Severity of Ocular Lesions Among 33 Substances Classified in the U.S. as Ocular Hazards Using the EPA Hazard Category Criteria, but Not Classified as Ocular Hazards by the Proposed HCS and Current GHS Classification Criteria

In Vivo Finding	No. of Substances	No. of Substances Where More than One Animal Exhibited the *In Vivo* Finding[1]
Corneal opacity/ulceration score ≥ 1	13/33 (39%)	8/13 (62%)
CO score ≥ 1: duration of 48 hours or more	7/33 (21%)	6/7 (86%)
CR or CC score ≥ 2	28/33 (85%)	20/28 (71%)
CR or CC score ≥ 2: duration of 72 hours or more	6/33 (18%)	2/6 (33%)
Iritis: visible inflammation inside the eye	12/33 (36%)	6/12 (50%)
Iritis: visible inflammation inside the eye; duration of 48 hours or more	2/33 (6%)	1/2 (50%)

Abbreviations: CC = conjunctival chemosis; CO = corneal opacity; CR = conjunctival redness; ECETOC = European Centre for Ecotoxicology and Toxicology of Chemicals; EPA = U.S. Environmental Protection Agency; GHS = UN Globally Harmonized System; HCS = OSHA Hazard Communication Standard; OSHA = U.S. Occupational Safety and Health Administration; No. = number; UN = United Nations.

[1] The total number of animals in each test ranged from 3 to 6.

5.0 Summary of Analyses

These results from two independent databases of Draize rabbit eye test results are consistent and indicate that a significantly greater proportion of substances causing eye irritation, including some substances producing eye injuries lasting more than seven days (EPA Category II), will not be labeled using the GHS criteria. Taken together, these data indicate that the GHS hazard classification criteria will significantly reduce eye hazard labeling compared to that provided by current HCS/FHSA regulations. *Of greatest concern is that the proposed HCS and current GHS classification criteria will not identify many substances as eye irritants that produce significant ocular damage, including extended corneal opacity, which can result in visual impairment and internal ocular inflammation.*

6.0 Possible Options for GHS Hazard Categories for Classification and Labeling of Reversible Eye Irritation

Paragraph 1.1.1.6 of the GHS states that during the development of the GHS, "the requirements of [the U.S., Canada, EU, and] other countries were also examined as the work developed, but the primary task was to find ways to adopt the best aspects of these existing systems and develop a harmonized approach. This work was done based on agreed principles of harmonization that were adopted early in the process: (a) the level of protection offered to workers, consumers, the general public and the environment should not be reduced as a result of harmonizing the classification and labeling systems..." (UN 2007).

The current GHS criteria for classification of reversible ocular irritants (Category 2) involve scoring 3-animal tests for eye lesions (corneal opacity, iritis, conjunctival redness and chemosis)

on days 1, 2, and 3 (see also **Table 6-1**). A mean score is calculated for each animal using the three daily observation scores. Category 2 is assigned to those substances that induce any of the following *mean* animal scores in at least *two* animals: corneal opacity or iritis ≥1 or conjunctival redness or chemosis ≥ 2 that persists beyond 7 days but reverses within 21 days. Any substances not meeting this requirement would not be labeled as ocular hazards. An optional category (2B) is also provided for regulatory authorities to subcategorize Category 2 eye irritants as mild irritants if positive responses reverse by day 7.

Given the large number of substances that are labeled as eye hazards by current U.S. regulatory classification systems (EPA and FHSA) but that are not labeled as eye hazards by the current GHS classification system, NICEATM and ICCVAM performed technical analyses to support three optional GHS hazard categories that would achieve the GHS principle stated above. Countries and regulatory authorities could then choose to adopt the optional categories as necessary in order to not reduce the protection compared to the current level of protection afforded by the respective national or agency classification regulations. Each of the three proposals below provide classification criteria for a 3-animal test that will provide the same level of hazard labeling as current EPA, FHSA, and HCS hazard classification regulations. The proposals are as follows:

- **Proposal #1** (**Table 6-1**):
  Current GHS Category 2 is unchanged. An optional Category 3 is included for those countries that need such a category to maintain the current level of hazard labeling.
  - Assign Category 3 based on positive ocular lesions obtained in any animal at any time point.
    Category 3A: Any lesions that reverse within 21 days.
    Category 3B: Any lesions that reverse within 7 days.
- **Proposal #2 (Table 6-2):**
  Current GHS Category 2A is unchanged. Current GHS Category 2B criteria are changed based on ocular lesions that appear in at least one animal at any time point and that reverse within 21 days.
  - Use an optional Category 2C when ocular lesions in Category 2B reverse within 7 days.
- **Proposal #3 (see Table 6-3):**
  Current GHS Category 2A and 2B are modified.
  - Assign category based on ocular lesions obtained in at least one animal at any of the three time points.

Table 6-4 compares these three proposals to the current GHS hazard categories. In conclusion, each of these three proposals will provide GHS classification criteria that can be used to maintain the same level of labeling and protection afforded by current EPA and FHSA hazard criteria regulations.

Table 6-1 Proposal #1 – Add an Optional Category 3

Category	Current GHS Criteria	Proposal #1
2A	≥ 2 animals with mean[1] CO or IR ≥ 1 or CC or CR ≥ 2 that reverses within 21 days	Same as current GHS
2B (optional)	≥ 2 animals with mean[1] CO or IR ≥ 1 or CC or CR ≥ 2 that reverses within 7 days	Same as current GHS
3A (optional)	—	≥ 1 animal with CO or IR ≥ 1 or CC or CR ≥ 2 which fully reverses within 21 days
3B (optional)	—	≥ 1 animal with CO or IR ≥ 1 or CC or CR ≥ 2 which reverses within 7 days

Abbreviations: CC = conjunctival chemosis; CO = corneal opacity; CR = conjunctival redness; GHS = UN Globally Harmonized System; IR = iritis.

[1] Mean values are calculated over 24 to 72 hours.

Table 6-2 Proposal #2 – Modify the Optional Category 2B and Add Another Optional Category

Category	Current GHS Criteria	Proposal #2
2A	≥ 2 animals with mean[1] CO or IR ≥ 1 or CC or CR ≥ 2 which reverses within 21 days	Same as current GHS
2B (optional)	≥ 2 animals with mean[1] CO or IR ≥ 1 or CC or CR ≥ 2 which reverses within 7 days	≥ 1 animal with CO or IR ≥ 1 or CC or CR ≥ 2 at any time which reverses within 21 days
2C (optional)	—	>1 animal with CO or IR ≥ 1 or CC or CR ≥ 2 which reverses within 7 days

Abbreviations: CC = conjunctival chemosis; CO = corneal opacity; CR = conjunctival redness; GHS = UN Globally Harmonized System; IR = iritis.

[1] Mean values are calculated over 24 to 72 hours.

Table 6-3 Proposal #3 – Categorize Based on Individual Animal Scores Instead of Mean Animal Scores

Category	Current GHS Criteria	Proposal #3
2A	≥ 2 animals with mean[1] CO or IR ≥ 1 or CC or CR ≥ 2 that reverses within 21 days	≥ 1 animal with CO or IR ≥ 1 or CC or CR ≥ 2 at any time which reverses within 21 days
2B (optional)	≥ 2 animals with mean[1] CO or IR ≥ 1 or CC or CR ≥ 2 that reverses within 7 days	≥ 1 animal with CO or IR ≥ 1 or CC or CR ≥ 2 at any time which reverses within 7 days

Abbreviations: CC = conjunctival chemosis; CO = corneal opacity; CR = conjunctival redness; GHS = UN Globally Harmonized System; IR = iritis.

[1] Mean values are calculated over 24 to 72 hours.

Table 6-4 Comparison of Current GHS Categories to Possible Optional Categories

Category	Current GHS	Proposal #1	Proposal #2	Proposal #3
2A	≥ 2 animals with mean[1] CO or IR ≥ 1 or CC or CR ≥ 2 that reverses within 21 days	Same as current GHS	Same as current GHS	≥ 1 animal with CO or IR ≥ 1 or CC or CR ≥ 2 at any time which reverses within 21 days
2B (optional)	≥ 2 animals with mean[1] CO or IR ≥ 1 or CC or CR ≥ 2 that reverses within 7 days	Same as current GHS	≥ 1 animals with CO or IR ≥ 1 or CC or CR ≥ 2 at any time which reverses within 21 days	≥ 1 animal with CO or IR ≥ 1 or CC or CR ≥ 2 at any time which reverses within 7 days
2C (optional)	—	—	>1 animal with CO or IR ≥ 1 or CC or CR ≥ 2 which reverses within 7 days	—
3A (optional)	—	≥ 1 animal with CO or IR ≥ 1 or CC or CR ≥ 2 that fully reverses within 21 days	—	—
3B (optional)	—	≥ 1 animal with CO or IR ≥ 1 or CC or CR ≥ 2 that reverses within 7 days	—	—

Abbreviations: CC = conjunctival chemosis; CO = corneal opacity; CR = conjunctival redness; GHS = UN Globally Harmonized System; IR = iritis.

[1] Mean values are calculated over 24 to 72 hours.

7.0 References

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Annex I

OECD Series on Testing and Assessment – Number 14:
Detailed Review Document on Classification Systems for Eye Irritation/Corrosion in OECD Member Countries (**ENV/JM/MONO(99)4)**

An electronic version of this document can be obtained at
http://www.olis.oecd.org/olis/1999doc.nsf/LinkTo/env-jm-mono%2899%294

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Annex II

Grades for Ocular Lesions

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Grades for Ocular Lesions[9]

Cornea	**Score**
Opacity: Degree of density (area most dense taken for reading). No ulceration or opacity	0
Scattered or diffuse areas of opacity (other than slight dulling of normal luster), details of iris clearly visible	*1
Easily discernible translucent area, details of iris slightly obscured	*2
Nacrous area, no details or iris visible, size of pupil barely discernible	*3
Opaque cornea, iris not discernible through the opacity	*4

Iris	
Normal	0
Markedly deepened rugae, congestion, swelling moderate circumcorneal hyperemia, or injection, any of these or combination of any thereof, iris still reacting to light (sluggish reaction is positive)	*1
No reaction to light, hemorrhage, gross destruction (any or all of these)	*2

Conjunctivae	
Redness (refers to palpebral and bulbar conjunctivae, excluding cornea and iris).	
Blood vessels normal	0
Some blood vessels definitely hyperemic (injected)	1
Diffuse, crimson color, individual vessels not easily discernible	*2
Diffuse beefy red	*3

Chemosis (refers to lids and/or nictitating membranes)	
No swelling	0
Any swelling above normal (includes nictitating membranes)	1
Obvious swelling with partial eversion of lids	*2
Swelling with lids about half closed	*3
Swelling with lids more than half-closed	*4

*Starred figures indicate positive grades.

[9] Reproduced from EPA (1998).

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Annex III

Consideration of the Minimum Number of Animals with Positive Eye Injury Responses Required for Classification of a Chemical as an Eye Irritation Hazard

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1.0 Summary

Current regulations under the U.S. Federal Hazardous Substances Act (FHSA) specify a classification system based on using up to three sequential tests for each substance, with six animals used per test. Decisions on further sequential testing are based on the number of positive responses observed in each test. However, current best practices for eye irritation/corrosion testing involve sequential testing of up to three animals. Therefore, an analysis was undertaken to determine the most appropriate minimum number of positive animals that should be required for FHSA eye hazard labeling based on results from a 3-animal test. The analysis compared three different classification strategies and the frequency at which each would identify substances as ocular irritants. The different response rates and the resulting classifications that would be assigned by each strategy were also compared. These analyses indicate that using a criterion of at least one positive animal in a 3-animal test as the basis for classifying an eye irritation hazard would be considered at least as protective as the current FHSA testing requirements and criteria that use 6 to 18 animals. Accordingly, a proposal is presented that includes classification criteria for a 3-animal test that will provide the same or a more protective level of hazard labeling as current FHSA requirements, while using up to 83% fewer animals.

2.0 Introduction

Physical trauma or chemical burns due to contact with workplace or household products or chemicals result in about 125,000 household eye injuries each year and approximately 2,000 job-related eye injuries per day that require medical treatment.[10,11] In order to provide warnings to consumers and workers of the potential for chemicals and products to cause eye injuries, regulatory authorities require ocular safety testing to determine if substances may cause eye damage. Testing results are then used for hazard classification and labeling of eye injury potential according to relevant national and/or international classification systems. These classification systems are intended to warn users of the potential for substances to cause eye injuries, the precautions necessary to avoid injuries, and the immediate first-aid procedures that should be followed in the case of an accidental exposure.

The guidelines for classification of ocular irritation hazard potential for substances regulated under the Federal Hazardous Substances Act (FHSA 2005) are described in 16 CFR 1500.42 (CPSC 2003). The FHSA system is based on the severity of effects for each endpoint (i.e., corneal ulceration and opacity, conjunctival redness and swelling, iritis) that occur during the first 72 hours following test substance administration with observations recorded at 24, 48, and 72 hours (**Table J-III-1**).

[10] Available at: http://www.geteyesmart.org/eyesmart/injuries/home.cfm
[11] Available at: http://www.cdc.gov/niosh/topics/eye/

Table J-III-1 FHSA Classification System (16 CFR 1500.42)

Positive Response for a Single Rabbit[1] (≥1 of the following at 24, 48, and/or 72 hours)	***In Vivo* Effect**
Corneal ulceration (other than a fine stippling) Corneal opacity ≥1 Iritis ≥1 Conjunctival swelling and/or redness ≥2	First Test - If ≥4/6 animals are positive, the test is positive. If ≤1 animal is positive, the test is negative. If 2/6 or 3/6 animals are positive, the test is repeated using a different group of six animals. Second Test - If ≥3/6 animals are positive, the test is positive. If 0/6 are positive, the test is negative. If 1/6 or 2/6 are positive, the test is repeated using a different group of six animals. Third Test - Should a third test be needed, the test is positive if ≥1/6 animals are positive. If 0/6 are positive, the test is negative.

Abbreviations: CC = conjunctival chemosis; CFR = U.S. Code of Federal Regulations; CO = corneal opacity; CR = conjunctival redness; FHSA = U.S. Federal Hazardous Substances Act; IR = iritis.

For the FHSA Classification System (2005), the testing guidelines and associated regulations are included in 16 CFR 1500.42 (CPSC 2003).

At least three animals per test (1-animal screen for corrosive/severe irritants permitted). Maximum score in any animal used for classification.

[1] The following scores are considered positive: CO or IR ≥1 or CR or CC ≥2. Therefore, CO and IR scores of 0 or CR and CC scores ≤1 are considered negative.

Current best practices for eye irritation/corrosion testing involve sequential testing of up to three animals (e.g., OECD Test Guideline 405 [OECD 2002]), given that statistical analyses demonstrated that results from rabbit eye tests using only three animals consistently agreed with the outcome of a 6-animal test (DeSousa et al. 1984; Springer et al. 1993; Talsma et al. 1988). However, as indicated in **Table J-III-1**, the current FHSA regulations for ocular hazard classification and labeling are based on using up to three sequential tests for each substance, with six animals used per test. Decisions on further sequential testing are based on the number of positive responses in each test. Therefore, there is a need to develop criteria for hazard classification and labeling under the FHSA that could be applied to results from a 3-animal test, while providing the same level of protection achieved by the more extensive testing strategy. Accordingly, an analysis was undertaken to determine the most appropriate minimum number of positive animals that should be required for FHSA eye hazard labeling if only a 3-animal test is used.

3.0 Methods

In order to determine the optimal number of positive animals that would require FHSA hazard classification and labeling, the current FHSA requirements were evaluated to determine the minimum number of animals that would be required under the sequential testing strategy to assign a definitive classification (**Table J-III-2**). The weakest possible response that is considered positive by the FHSA classification system is 22% (2/6+1/6+1/6 or 4/18). However, it is possible for an even higher positive response rate, 28% (3/6+2/6+0/6 or 5/18), to be considered negative according to the FHSA system (see **Table J-III-2**). Ideally, a classification system should not produce such internal inconsistencies. For this evaluation, the current sequential testing strategy used to assign an FHSA classification, which could use up to 18 animals, is designated as Strategy 1.

Because all of the Draize eye test data used in the NICEATM analyses are from studies that used no more than six animals, NICEATM also evaluated a potential criterion where a minimum of one positive out of three animals (i.e., ≥33% positive animals) would be required to assign an irritant classification. For this evaluation, the ≥1/3 threshold is designated as Strategy 2.

Table J-III-2 Number of Animals Required to Assign an Irritant Classification According to the Current FHSA Requirements[1]

Positive Test Criteria for "Irritant" Classification	Positive Animals	Positive Animals	Positive Animals	Positive Animals	Positive Animals	Positive Animals
First Test	≥4/6	2/6 or 3/6	3/6	3/6	2/6	2/6
Second Test	-	≥3/6	2/6	1/6	2/6	1/6
Third Test	-	-	≥1/6	≥1/6	≥1/6	≥1/6
Minimum Number of Positive Animals for Irritant Classification	**4/6 (67%)**	**5/12 (42%)**	**6/18 (33%)**	**5/18 (28%)**	**5/18 (28%)**	**4/18 (22%)**
Maximum Number of Positive Animals for Not Labeled Classification	**1/6 (17%)**	**2/12 (17%)**	**5/18 (28%)**	**4/18 (22%)**	**4/18 (22%)**	**3/18 (17%)**

Abbreviation: FHSA = U.S. Federal Hazardous Substances Act.

[1] For the FHSA Classification System (2005), the testing guidelines and associated regulations are included in 16 CFR 1500.42 (CPSC 2003).

By comparison, the United Nations Globally Harmonized System of Classification and Labelling of Chemicals (GHS; UN 2007) is based on a 3-animal test in which at least 67% (2/3) of animals tested must produce a positive response[12] in order to assign an irritant classification (i.e., GHS Category 2). Therefore, a threshold of 2/3 (67%) is designated as Strategy 3 but is based on the same criterion as Strategies 1 and 2, that a positive is based on a positive response at any of the three observation points, rather than the mean of the response over all three time points as currently required by the GHS classification system.

4.0 Results

In order to compare the three strategies with regard to the frequency at which each strategy would identify substances as ocular irritants, NICEATM compared a number of different response rates and the resulting classification that would be assigned by each strategy. As indicated in **Table J-III-3**, Strategy 3 will identify far fewer irritants than either Strategy 1 (current FHSA requirements) or Strategy 2. For example, if half of all animals tested with a given substance produce a positive response, on average, then Strategy 3 has only a 50% chance of classifying that substance an eye irritant, compared with 88% for Strategy 1 or Strategy 2.

[12] Based on mean values for each test animal calculated from grading at 24, 48, and 72 hours following test substance administration.

Table J-III-3 Percentage of Substances That Would Be Labeled as Ocular Irritants Based on Three Different Evaluation Strategies

Underlying Response Rate	Percentage of Substances That Would Be Labeled as Ocular Irritants		
	Strategy 1 Current FHSA[1]	Strategy 2 ≥1/3 positive animals	Strategy 3 ≥2/3 positive animals
20%	20.4%	48.8%	10.4%
40%	72.6%	78.4%	35.2%
50%	87.9%	87.5%	50.0%
75%	>99%	98.4%	84.3%

[1] For the U.S. Federal Hazardous Substances Act Classification System (2005), the testing guidelines and associated regulations are included in 16 CFR 1500.42 (CPSC 2003).

To illustrate the calculations summarized in **Table J-III-3**, suppose that, on average, 20% of all animals tested will produce a positive response. Using the current FHSA requirements, a negative classification could require either the first, second, or third tests. Based on the binomial distribution, the likelihood of observing 0/6, 1/6, 2/6, 3/6, or >3/6 positives is 0.262, 0.393, 0.246, 0.082, and 0.017, respectively. The probability that the first test will produce a negative classification is simply the sum of the likelihood of observing 0/6 and 1/6 positive responses or 0.655. Thus, 65.5% of the time, no further testing would be necessary, and the substance would not be labeled.

A second test would be needed if the first test positive outcome rate was either 2/6 or 3/6 (likelihood = 0.328). The second test would result in a negative classification if 0/6 positive responses were observed, making the likelihood of a negative classification by the second test (0.328)(0.262) or 0.086 (8.6%).

The third test would be needed if the second test showed 1/6 or 2/6 positives responses, which would occur with a likelihood of 0.639. Then the third test would produce a negative classification if 0/6 positive responses were observed. Thus, the likelihood that a negative classification will result from the third test is simply (0.328)(0.639)(0.262) or 0.055 (5.5%). Adding these three probabilities results in the overall likelihood of a negative classification of 0.655+0.086+0.055 or 0.796 (79.6%), and thus the likelihood of a positive classification by subtraction is 1-0.796 or 0.204 (20.4%; see **Table J-III-3**).

These calculations are much simpler for Strategies 2 and 3. The likelihood of a positive classification using Strategy 2 is just 1 minus the likelihood of observing 0/3 positives or 1-(0.8)(0.8)(0.8) or 0.488 (48.8%). For Strategy 3, a positive response rate of 1/3 (likelihood = 0.384) would also lead to a negative classification, making the overall likelihood of a positive classification for Strategy 3: 0.488-0.384 or 0.104 (10.4%).

Three important results are evident from **Table J-III-3**:

- Even though it uses fewer animals, Strategy 2 is more powerful than the current FHSA requirements for detecting positive response rates of 20% to 40%.
- Strategy 3 has low power in all cases considered.
- Strategy 2 is the only strategy that always regards a single positive outcome as indicating an irritant response.

For example, the current FHSA requirements may have as many as five animals showing a positive response, yet the substance is still not considered an irritant (**Table J-III-2**), whereas

Strategy 3 considers a positive response rate of 33% (1/3) to not be indicative of an irritant response.

5.0 Discussion

Given that many national and international ocular safety testing guidelines now require only three animals, it is unlikely that users are conducting ocular safety tests as described in the current FHSA requirements. Thus, an update to these hazard classification guidelines appears in order. These analyses can be used to establish criteria that are needed to maintain the same level of eye hazard classification and labeling as the current FHSA criteria using a 3-animal test. The results detailed here indicate that the minimum number of animals with a positive response in a 3-animal test required for eye hazard classification and labeling that would be considered at least equivalent to the current FHSA requirements is one of three positives (Strategy 2), rather than two of three positives (Strategy 3).

It should also be emphasized that Strategy 3 approximates the GHS classification system with one important exception: it assumes that any positive response at any time point is used for a positive animal. In contrast, the GHS classification system uses mean values for each test animal calculated from grading at 24, 48, and 72 hours following test substance administration. Therefore, the criteria for a positive response under the proposed GHS system require an even higher threshold for identifying an irritant than does Strategy 3. One can assume that the actual differences between Strategy 1 or 2 and Strategy 3, developed based on mean calculations, are even greater than presented in **Table J-III-3**. For this reason, the criteria for a positive animal response provided in the current FHSA eye hazard regulations (i.e., a positive score at any time point during the observation period) are preferred for any revised classification system, rather than a mean value calculated from three time points (as in the GHS system).

Applying these rules to revised FHSA requirements will substantially reduce the number of animals required to assign a definitive classification for ocular hazard potential of substances and materials that are regulated under the FHSA classification system. Creating hazard classification criteria that are based on a 3-animal test, rather than the currently required sequential 6-animal test that could require up to 18 animals, would have an immediate impact on reducing the number of animals required for ocular safety testing by up to six-fold.

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Annex IV

Nature, Duration, and Severity of Ocular Lesions for 31 ECETOC Substances that are EPA Irritants (Category I, II, or III) or FHSA Irritants but Not Classified as Ocular Hazards by GHS Classification Criteria

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Test Substance	EPA Cat.[1]	FHSA-33%[2]	FHSA HCS[3]	Animal Number[4]	Maximum Observed Draize Lesion Score[5] and Duration[6] Last day positive score present (Last day any lower score present)							
					CO	Day	IR	Day	CR	Day	CC	Day
Ethyl thioglycolate	III	Irritant	Irritant	1	3	3 (5)	1	6	3	2 (6)	2	2 (3)
				2	1	1	1	1	2	1 (2)	2	1
				3	0	-	0	-	0	-	0	-
Sodium lauryl sulfate (3%)	III	Irritant	Irritant	1	2	2	0	-	2	2 (3)	2	2
				2	2	1	1	1	2	1 (2)	2	1
				3	2	1	0	-	2	1 (3)	2	1
				4	1	1	0	-	2	2 (3)	1	(1)
				5	0	-	0	-	2	1	1	(1)
				6	0	-	0	-	1	(1)	1	(1)
Glycidyl methacrylate	III	Irritant	Irritant	1	2	3	1	3	3	1 (3)	4	1 (3)
				2	1	1	1	1	2	1 (2)	1	1
				3	1	1	0	-	2	1 (2)	1	(2)
Ethyl acetate	III	Irritant	Irritant	1	2	1	0	-	2	1 (3)	1	(2)
				2	1	1	1	1	2	1 (3)	1	(2)
				3	1	1	0	-	2	1 (3)	1	(2)
				4	1	1	0	-	1	(3)	1	(1)
2,2-Dimethyl-3-pentanol	III	Irritant	Irritant	1	2	2 (3)	0	-	1	(4)	1	(2)
				2	1	2	0	-	1	(2)	1	(1)
				3	0	-	0	-	1	(2)	0	-
Tetraaminopyrimidine sulfate	III	Irritant	Irritant	1	2	1	0	-	2	1 (3)	1	(1)
				2	1	1	0	-	2	1 (3)	1	(1)
				3	0	-	0	-	1	(3)	1	(1)

Test Substance	EPA Cat.[1]	FHSA-33%[2]	FHSA HCS[3]	Animal Number[4]	Maximum Observed Draize Lesion Score[5] and Duration[6] Last day positive score present (Last day any lower score present)							
					CO	Day	IR	Day	CR	Day	CC	Day
Cellosolve acetate	III	Irritant	Irritant	1	2	2 (3)	0	-	2	2 (7)	2	2 (3)
				2	0	-	0	-	2	1 (3)	1	(2)
				3	0	-	0	-	2	1 (2)	1	(1)
				4	0	-	0	-	1	(3)	0	-
Methyl amyl ketone	III	Irritant	Irritant	1	1	1 (3)	1	1	2	2 (3)	2	1 (3)
				2	1	1	1	1	2	1 (7)	2	1 (3)
				3	1	1	0	-	2	1 (3)	2	1 (3)
				4	0	-	0	-	1	(1)	1	(3)
Fomesafen, acid form (solid)	III	Irritant	Irritant	1	1	3	0	-	2	2 (3)	1	(7)
				2	1	2	1	1	2	2 (3)	2	1 (3)
				3	0	-	1	1	1	(7)	1	(2)
				4	0	-	0	-	2	1 (3)	1	(1)
				5	0	-	0	-	2	2 (3)	2	1 (3)
				6	0	-	0	-	1	(1)	0	-
n-Butyl acetate	III	Irritant	Inconcl	1	1	1	0	-	1	(7)	1	(1)
				2	1	1	0	-	1	(3)	1	(1)
				3	0	-	0	-	1	(3)	1	(1)
				4	0	-	0	-	1	(3)	0	-

Test Substance	EPA Cat.[1]	FHSA-33%[2]	FHSA HCS[3]	Animal Number[4]	Maximum Observed Draize Lesion Score[5] and Duration[6] Last day positive score present (Last day any lower score present)							
					CO	Day	IR	Day	CR	Day	CC	Day
Cetylpyridinium bromide (0.1%)	III	Irritant	Need 2nd test	1	1	1	0	-	0	-	0	-
				2	1	1	0	-	0	-	0	-
				3	0	-	0	-	1	(1)	0	-
				4	0	-	0	-	1	(2)	0	-
				5	0	-	0	-	1	(2)	0	-
				6	0	-	0	-	0	-	0	-
Myristyl myristate	III	Irritant	Irritant	1	1	1	2	2	2	1	0	-
				2	0	-	1	2	1	(1)	0	-
				3	0	-	0	-	3	2	1	(2)
Allyl methacrylate	III	Irritant	Need 2nd test	1	0	-	1	1	1	(3)	1	(1)
				2	0	-	0	-	2	1 (3)	1	(1)
				3	0	-	0	-	1	(3)	1	(1)
				4	0	-	0	-	1	(2)	1	(1)
				5	0	-	0	-	1	(2)	1	(1)
				6	0	-	0	-	1	(1)	0	-
Trichloroacetic acid (3%)	III	Irritant	Need 2nd test	1	0	-	0	-	2	1 (7)	2	2 (7)
				2	0	-	0	-	2	1 (7)	1	(7)
				3	0	-	0	-	2	2 (3)	1	(2)
				4	0	-	0	-	1	(3)	0	-
				5	0	-	0	-	1	(1)	0	-
				6	0	-	0	-	1	(1)	0	-

Test Substance	EPA Cat.[1]	FHSA-33%[2]	FHSA HCS[3]	Animal Number[4]	Maximum Observed Draize Lesion Score[5] and Duration[6] Last day positive score present (Last day any lower score present)							
					CO	Day	IR	Day	CR	Day	CC	Day
cis-Cyclo-octene	III	Irritant	Irritant	1	0	-	0	-	2	1 (3)	0	-
				2	0	-	0	-	2	1 (3)	0	-
				3	0	-	0	-	2	1 (3)	0	-
				4	0	-	0	-	2	1 (2)	0	-
				5	0	-	0	-	1	(2)	0	-
				6	0	-	0	-	2	1 (3)	0	-
N,N-Dimethylguanidine sulfate	III	Irritant	Irritant	1	0	-	0	-	2	2 (4)	0	-
				2	0	-	0	-	2	4	1	(2)
				3	0	-	0	-	2	3 (4)	1	(4)
Toluene	III	Irritant	Irritant	1	0	-	0	-	2	3	2	2 (3)
				2	0	-	0	-	1	(7)	1	(3)
				3	0	-	0	-	2	2 (7)	2	2 (3)
				4	0	-	0	-	2	1 (3)	2	1 (3)
2,4-Difluoronitrobenzene	III	Irritant	Need 2nd test	1	0	-	0	-	2	3 (7)	1	(3)
				2	0	-	0	-	2	3	2	3
				3	0	-	0	-	1	3	0	-
				4	0	-	0	-	1	(3)	0	-
				5	0	-	0	-	1	(3)	0	-
				6	0	-	0	-	1	(3)	0	-

Test Substance	EPA Cat.[1]	FHSA-33%[2]	FHSA HCS[3]	Animal Number[4]	Maximum Observed Draize Lesion Score[5] and Duration[6] Last day positive score present (Last day any lower score present)							
					CO	Day	IR	Day	CR	Day	CC	Day
Tween 20	III	Irritant	Inconcl	1	0	-	0	-	2	1(3)	1	(1)
				2	0	-	0	-	2	1 (3)	1	(1)
				3	0	-	0	-	1	(3)	0	-
				4	0	-	0	-	1	(1)	0	-
1,5-Hexadiene	III	Irritant	Need 2nd test	1	0	-	0	-	2	1 (3)	1	(1)
				2	0	-	0	-	1	(3)	1	(1)
				3	0	-	0	-	1	(3)	1	(1)
				4	0	-	0	-	2	1 (3)	1	(1)
				5	0	-	0	-	1	1	0	-
				6	0	-	0	-	1	(1)	0	-
Triton X-100 (1%)	III	Irritant	Need 2nd test	1	0	-	0	-	2	1 (2)	0	-
				2	0	-	0	-	2	1	0	-
				3	0	-	0	-	0	-	0	-
				4	0	-	0	-	0	-	0	-
				5	0	-	0	-	0	-	0	-
				6	0	-	0	-	0	-	0	-
1,5-Dibromopentane	III	Irritant	Inconcl	1	0	-	0	-	2	1 (2)	1	(1)
				2	0	-	0	-	1	(1)	1	(2)
				3	0	-	0	-	1	(1)	0	-
1,4-Dibromobutane	III	Irritant	Inconcl	1	0	-	0	-	2	1	2	1
				2	0	-	0	-	1	(1)	1	(1)
				3	0	-	0	-	0	-	0	-

Test Substance	EPA Cat.[1]	FHSA-33%[2]	FHSA HCS[3]	Animal Number[4]	Maximum Observed Draize Lesion Score[5] and Duration[6] Last day positive score present (Last day any lower score present)							
					CO	Day	IR	Day	CR	Day	CC	Day
Thiodiglycol	III	Irritant	Inconcl	1	0	-	0	-	2	1 (2)	1	(1)
				2	0	-	0	-	1	(2)	1	(2)
				3	0	-	0	-	0	-	0	-
iso-Myristyl alcohol	III	Irritant	Inconcl	1	0	-	0	-	1	(3)	2	1 (2)
				2	0	-	0	-	1	(1)	1	(1)
				3	0	-	0	-	0	-	0	-
Ethyl trimethyl acetate	III	NL	NL	1	1	3	0	-	1	(3)	1	(3)
				2	0	-	0	-	1	(2)	1	(2)
				3	0	-	0	-	1	(2)	1	(2)
				4	0	-	0	-	1	(2)	0	-
				5	0	-	0	-	1	(1)	0	-
				6	0	-	0	-	0	-	0	-
1,5-Dimethyl cyclo-octadiene	III	NL	NL	1	1	2	0	-	1	(3)	0	-
				2	0	-	0	-	1	(7)	0	-
				3	0	-	0	-	1	(1)	0	-
				4	0	-	0	-	1	(1)	0	-
				5	0	-	0	-	1	(1)	0	-
				6	0	-	0	-	1	(1)	0	-
Methyl isobutyl ketone	III	NL	Inconcl	1	1	1	0	-	2	1 (2)	0	-
				2	0	-	0	-	1	(3)	0	-
				3	0	-	0	-	1	(2)	1	(1)
				4	0	-	0	-	1	(2)	1	(1)

Test Substance	EPA Cat.[1]	FHSA-33%[2]	FHSA HCS[3]	Animal Number[4]	Maximum Observed Draize Lesion Score[5] and Duration[6] Last day positive score present (Last day any lower score present)							
					CO	Day	IR	Day	CR	Day	CC	Day
Styrene	III	NL	Inconcl	1	1	1	0	-	1	(7)	1	(3)
				2	0	-	0	-	1	(3)	1	(1)
				3	0	-	0	-	1	(2)	1	(1)
				4	0	-	0	-	1	(1)	1	(1)
Methyl cyclopentane	III	NL	NL	1	0	-	0	-	2	2 (3)	1	(2)
				2	0	-	0	-	1	(2)	0	-
				3	0	-	0	-	1	(2)	0	-
				4	0	-	0	-	1	(2)	0	-
				5	0	-	0	-	1	(2)	0	-
				6	0	-	0	-	1	(2)	0	-

Abbreviations: Cat. = category; CC = conjunctival chemosis; CO = corneal opacity; CR = conjunctival redness; EPA = U.S. Environmental Protection Agency; FHSA = Federal Hazardous Substances Act; HCS = FHSA Hazard Communication Standard; Inconcl = Inconclusive; IR = iritis; NL = Not Labeled (as irritant).

[1] Substances classified using the EPA hazard classification based on the EPA Label Review Manual (EPA 2003).

[2] Substances classified based on the FHSA HCS using a proportionality rule of 33% for studies with fewer than six animals.

[3] Current FHSA HCS classification (16 CFR 1500.42).

[4] The animal number represents the sequence of lesion severity in a study from most severe to least severe where CO>IR>CR>CC and does not correlate to the animal number used in the study report.

[5] Maximum score observed in the Draize rabbit eye test.

[6] Duration of lesions is expressed as the last day in which an FHSA positive score of CO or IR ≥1 or CR or CC ≥2 was present and the last day in which any lower lesion score was present and in parentheses the last day in which any lower lesion score was present.

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Annex V

OECD Database: Comparison of Percent Irritant Classification Using EPA, FHSA, and GHS Classification Systems

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Classification System/ Category	NICEATM DRD Analyses (2010) Number of Substances Classified (%)	Number of Substances Excluded from NICEATM Database	Rationale for Exclusion	OECD DRD Analyses (1999) Number of Substances Classified (%)	Number of Substances Excluded from OECD DRD Database	Rationale for Exclusion
EPA I	41/130 (32)	14	Reversibility of positive lesions not determined	34/139 (25)	5 *NOTE: All are EPA Category IV in NICEATM analyses (no positive animals any test)*	N = 4 3-animal tests N = 1 4-animal tests
EPA II	22/130 (17)			42/139 (30)		
EPA III	44/130 (34)			47/139 (34)		
EPA I, II, or III	107/130 (82)			123/139 (89)		
GHS 1	38/125 (30)	19	Reversibility of positive lesions not determined	39/143 (27)	1 *NOTE: GHS Not Classified in NICEATM analyses (no positive animals any test)*	N = 1 4-animal tests
GHS 2A	22/125 (18)			31/143 (22)		
GHS 2B	9/125 (7)			12/143 (8)		
GHS 1, 2A, or 2B	69/125 (55)			82/143 (57)		
FHSA Irritant (33% threshold)	112/142 (79)	2	N = 2 1-animal tests	-	-	-
FHSA Irritant (16 CFR 1500.42)	102/131 (78)	13	N = 2 1-animal tests N = 11 (inconclusive)	83/106 (78)	38	N = 2 1-animal tests N = 25 3-animal tests N = 4 4-animal tests N = 7 6-animal tests (inconclusive)

Abbreviations: DRD = Detailed Review Document; EPA = U.S. Environmental Protection Agency; FHSA = Federal Hazardous Substances Act; GHS = Globally Harmonized System; NICEATM = National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods; OECD = Organisation for Economic Co-operation and Development; N = number.

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Annex VI

Nature, Duration, and Severity of Ocular Lesions for 33 OECD DRD Substances that are EPA Irritants (Category I, II, or III) or FHSA Irritants but Not Classified as Ocular Hazards by GHS Classification Criteria

Test Substance	EPA Category[1]	FHSA-33%[2]	FHSA HCS[3]	Animal Number[4]	Maximum Observed Draize Lesion Score[5] and Duration[6] Last day positive score present (Last day any lower score present)							
					CO	Day	IR	Day	CR	Day	CC	Day
PROD-00125	III	Irritant	Irritant	1	2	2	1	1	2	1 (3)	2	1 (3)
				2	2	2	0	-	2	2 (3)	1	(1)
				3	0	0	1	1	2	1 (3)	1	(2)
				4	0	-	0	-	2	1 (3)	1	(2)
				5	0	-	0	-	2	1 (2)	1	(2)
				6	0	-	0	-	2	1 (2)	1	(1)
PROD-00215	III	Irritant	Irritant	1	2	2 (3)	0	-	2	2 (7)	2	2 (3)
				2	0	-	0	-	2	1 (3)	1	(2)
				3	0	-	0	-	2	1 (2)	1	(1)
				4	0	-	0	-	1	(3)	0	-
PROD-00214	III	Irritant	Irritant	1	2	1	0	-	2	1 (3)	1	(2)
				2	1	1	1	1	2	1 (3)	1	(2)
				3	1	1	0	-	2	1 (3)	1	(2)
				4	1	1	0	-	1	(3)	1	(1)
PROD-00094	II	Irritant	Needs 2nd test	1	2	1 (2)	0	-	1	(1)	0	-
				2	1	7	0	-	1	(2)	1	(1)
				3	1	4	0	-	0	-	0	-
				4	0	-	0	-	0	-	0	-
				5	0	-	0	-	0	-	1	(1)
				6	0	-	0	-	0	-	0	-
PROD-00143	III	Irritant	Irritant	1	1	3	1	3	1	(7)	2	2 (7)
				2	1	3	1	2	2	2 (7)	2	1 (3)
				3	1	3	1	3	1	(7)	2	2 (3)
				4	1	2	1	2	2	2 (7)	2	1 (7)
				5	0	-	1	2	1	(7)	1	(7)
				6	0	-	1	1	1	(3)	1	(2)

Test Substance	EPA Category[1]	FHSA-33%[2]	FHSA HCS[3]	Animal Number[4]	Maximum Observed Draize Lesion Score[5] and Duration[6] Last day positive score present (Last day any lower score present)							
					CO	Day	IR	Day	CR	Day	CC	Day
PROD-00129	III	Irritant	Irritant	1	1	3	0	-	2	3	2	3
				2	1	2	0	-	2	2 (3)	2	2 (3)
				3	1	2	0	-	2	2 (3)	2	1 (3)
				4	1	1	0	-	2	2 (3)	2	1 (2)
				5	0	-	0	-	2	1 (3)	2	1 (3)
				6	0	-	0	-	2	1 (3)	1	(3)
PROD-00091	III	Irritant	Irritant	1	1	4	0	-	2	2 (3)	1	(4)
				2	1	2	1	1	2	2 (3)	2	1 (4)
				3	0	-	1	1	1	(7)	1	(2)
				4	0	-	0	-	2	2 (4)	2	1 (2)
				5	0	-	0	-	2	1 (3)	1	(1)
				6	0	-	0	-	1	(1)	0	-
PROD-00056	III	IrritantI	Inconcl	1	1	2	1	2	1	(1)	0	-
				2	1	2	0	-	0	-	0	-
				3	0	-	0	-	1	(2)	0	-
				4	0	-	0	-	0	-	0	-
PROD-00213	III	Irritant	Inconcl	1	1	1	0	-	1	(7)	1	(1)
				2	1	1	0	-	1	(3)	1	(1)
				3	0	-	0	-	1	(3)	0	-
				4	0	-	0	-	1	(3)	1	(1)
PROD-00134	II	Irritant	Irritant	1	1	1	0	-	2	7 (10)	2	1 (2)
				2	0	-	0	-	2	1 (7)	2	1 (3)
				3	0	-	0	-	2	1 (7)	2	1 (2)

Test Substance	EPA Category[1]	FHSA-33%[2]	FHSA HCS[3]	Animal Number[4]	Maximum Observed Draize Lesion Score[5] and Duration[6] Last day positive score present (Last day any lower score present)							
					CO	Day	IR	Day	CR	Day	CC	Day
PROD-00120	III	Irritant	Irritant	1	1	1	0	-	1	(2)	1	(2)
				2	0	-	0	-	2	1 (7)	1	(7)
				3	0	-	0	-	2	1 (7)	1	(2)
				4	0	-	0	-	2	1 (2)	1	(2)
				5	0	-	0	-	2	1 (7)	1	(2)
				6	0	-	0	-	1	(2)	1	(1)
PROD-00093	III	Irritant	Needs 2nd test	1	1	1	0	-	1	(2)	2	1 (2)
				2	0	-	1	1	2	1 (2)	3	1 (2)
				3	0	-	0	-	1	(2)	1	(1)
				4	0	-	0	-	1	(2)	1	(1)
				5	0	-	0	-	1	(2)	0	-
				6	0	-	0	-	1	(1)	1	(1)
PROD-00105	III	Irritant	Needs 2nd test	1	0	-	1	1	2	2 (3)	3	2 (3)
				2	0	-	1	1	2	1 (3)	1	(1)
				3	0	-	1	1	1	(2)	1	(1)
				4	0	-	0	-	1	(1)	1	(1)
				5	0	-	0	-	1	(1)	0	-
				6	0	-	0	-	1	(1)	0	-
PROD-00075	III	Irritant	Irritant	1	0	-	1	1	1	(1)	0	-
				2	0	-	1	1	1	(1)	0	-
				3	0	-	1	1	1	(1)	0	-
				4	0	-	0	-	2	1 (2)	0	-
				5	0	-	0	-	1	(1)	0	-
				6	0	-	0	-	1	(1)	0	-

Test Substance	EPA Category[1]	FHSA-33%[2]	FHSA HCS[3]	Animal Number[4]	Maximum Observed Draize Lesion Score[5] and Duration[6] Last day positive score present (Last day any lower score present)							
					CO	Day	IR	Day	CR	Day	CC	Day
PROD-00103	III	Irritant	Irritant	1	0	-	1	1	3	1 (3)	2	1 (2)
				2	0	-	1	1	2	2 (3)	2	1 (3)
				3	0	-	0	-	3	1 (3)	1	(2)
				4	0	-	0	-	2	1 (2)	1	(1)
				5	0	-	0	-	1	(3)	2	1 (2)
				6	0	-	0	-	1	(3)	2	1 (2)
PROD-00064	III	Irritant	Irritant	1	0	-	1	1	1	(3)	4	1 (7)
				2	0	-	0	-	1	(3)	2	4
				3	0	-	0	-	1	(3)	2	2 (3)
				4	0	-	0	-	1	(2)	2	3
				5	0	-	0	-	1	(2)	2	2
				6	0	-	0	-	1	(1)	2	1
PROD-00118	III	Irritant	Irritant	1	0	-	1	1	3	1 (4)	3	1 (4)
				2	0	-	0	-	2	2 (4)	3	2 (4)
				3	0	-	0	-	2	1 (2)	2	1 (2)
				4	0	-	0	-	1	(2)	2	2 (4)
				5	0	-	0	-	1	(1)	1	(4)
				6	0	-	0	-	1	(1)	1	(2)
PROD-00119	III	Irritant	Inconcl	1	0	-	1	1	1	(1)	0	-
				2	0	-	0	-	1	(1)	0	-
				3	0	-	0	-	1	(1)	0	-
PROD-00124	III	Irritant	Irritant	1	0	-	0	-	2	2 (7)	2	2 (7)
				2	0	-	0	-	2	2 (4)	3	1 (4)
				3	0	-	0	-	2	2 (3)	1	(2)
				4	0	-	0	-	2	1 (2)	2	1 (2)
				5	0	-	0	-	1	(3)	1	(2)
				6	0	-	0	-	1	(2)	1	(2)

Test Substance	EPA Category[1]	FHSA-33%[2]	FHSA HCS[3]	Animal Number[4]	Maximum Observed Draize Lesion Score[5] and Duration[6] Last day positive score present (Last day any lower score present)							
					CO	Day	IR	Day	CR	Day	CC	Day
PROD-00132	III	Irritant	Irritant	1	0	-	0	-	2	2 (3)	0	-
				2	0	-	0	-	2	1 (7)	1	(1)
				3	0	-	0	-	2	1 (7)	1	(1)
				4	0	-	0	-	2	1 (3)	1	(1)
				5	0	-	0	-	1	(2)	1	(2)
				6	0	-	0	-	1	(1)	1	(1)
PROD-00109	III	Irritant	Needs 2nd test	1	0	-	0	-	2	2 (3)	2	2 (3)
				2	0	-	0	-	2	1 (3)	3	1 (2)
				3	0	-	0	-	2	1(3)	2	1 (3)
				4	0	-	0	-	1	(2)	1	(2)
				5	0	-	0	-	1	(1)	1	(1)
				6	0	-	0	-	1	(1)	1	(1)
PROD-00218	III	Irritant	Needs 2nd test	1	0	-	0	-	2	2 (3)	1	(2)
				2	0	-	0	-	2	1 (7)	2	2 (7)
				3	0	-	0	-	2	1 (7)	1	(7)
				4	0	-	0	-	1	(3)	0	-
				5	0	-	0	-	1	(1)	0	-
				6	0	-	0	-	1	(1)	0	-
PROD-00131	III	Irritant	Irritant	1	0	-	0	-	2	2 (4)	2	1 (2)
				2	0	-	0	-	2	1 (4)	1	(1)
				3	0	-	0	-	2	1 (3)	2	1 (2)
PROD-00082	III	Irritant	Needs 2nd test	1	0	-	0	-	2	1 (2)	1	(1)
				2	0	-	0	-	2	1 (2)	1	(2)
				3	0	-	0	-	1	(2)	1	(1)
				4	0	-	0	-	1	(1)	0	-
				5	0	-	0	-	0	-	0	-
				6	0	-	0	-	0	-	0	-

Test Substance	EPA Category[1]	FHSA-33%[2]	FHSA HCS[3]	Animal Number[4]	Maximum Observed Draize Lesion Score[5] and Duration[6] Last day positive score present (Last day any lower score present)							
					CO	Day	IR	Day	CR	Day	CC	Day
PROD-00108	III	Irritant	Irritant	1	0	-	0	-	2	1	2	1 (3)
				2	0	-	0	-	2	1	2	1
				3	0	-	0	-	1	(1)	2	1
				4	0	-	0	-	1	(1)	2	1
				5	0	-	0	-	1	(2)	1	(7)
				6	0	-	0	-	1	(3)	2	2 (3)
PROD-00150	III	Irritant	Inconcl	1	0	-	0	-	2	2 (3)	1	(1)
				2	0	-	0	-	1	(2)	0	-
				3	0	-	0	-	1	(2)	0	-
PROD-00212	III	NL	NL	1	1	3	0	-	1	(3)	1	(3)
				2	0	-	0	-	1	(2)	1	(2)
				3	0	-	0	-	1	(2)	1	(2)
				4	0	-	0	-	1	(2)	0	-
				5	0	-	0	-	1	(1)	0	-
				6	0	-	0	-	0	-	0	-
PROD-00133	III	NL	Needs 2nd test	1	0	-	0	-	2	1 (3)	1	(1)
				2	0	-	0	-	1	(4)	1	(1)
				3	0	-	0	-	1	(2)	2	1 (2)
				4	0	-	0	-	1	(2)	1	(1)
				5	0	-	0	-	1	(1)	1	(1)
				6	0	-	0	-	1	(1)	1	(1)
PROD-00084	III	NL	NL	1	0	-	0	-	2	1	0	-
				2	0	-	0	-	1	(2)	0	-
				3	0	-	0	-	0	-	0	-
				4	0	-	0	-	0	-	0	-
				5	0	-	0	-	0	-	0	-
				6	0	-	0	-	0	-	0	-

Test Substance	EPA Category[1]	FHSA-33%[2]	FHSA HCS[3]	Animal Number[4]	Maximum Observed Draize Lesion Score[5] and Duration[6] Last day positive score present (Last day any lower score present)							
					CO	Day	IR	Day	CR	Day	CC	Day
PROD-00107	III	NL	NL	1	0	-	0	-	2	1 (7)	2	1 (2)
				2	0	-	0	-	1	(7)	0	-
				3	0	-	0	-	1	(3)	0	-
				4	0	-	0	-	1	(3)	0	-
				5	0	-	0	-	1	(1)	1	(1)
				6	0	-	0	-	1	(1)	0	-
PROD-00117	III	NL	NL	1	0	-	0	-	0	-	0	-
				2	0	-	0	-	2	1	0	-
				3	0	-	0	-	1	(2)	0	-
				4	0	-	0	-	1	(1)	0	-
				5	0	-	0	-	1	(1)	0	-
				6	0	-	0	-	1	(1)	0	-
PROD-00121	III	NL	NL	1	0	-	0	-	1	(7)	0	-
				2	0	-	0	-	1	(3)	2	1 (2)
				3	0	-	0	-	1	(1)	0	-
				4	0	-	0	-	0	-	0	-
				5	0	-	0	-	0	-	0	-
				6	0	-	0	-	0	-	0	-
PROD-00128	III	NL	NL	1	0	-	0	-	0	-	1	(1)
				2	0	-	0	-	0	-	2	1 (2)
				3	0	-	0	-	0	-	1	(2)
				4	0	-	0	-	0	-	1	(1)
				5	0	-	0	-	0	-	1	(1)
				6	0	-	0	-	0	-	1	(1)

Abbreviations: CC = conjunctival chemosis; CO = corneal opacity; CR = conjunctival redness; DRD = Detailed Review Document; EPA = U.S. Environmental Protection Agency; FHSA = Federal Hazardous Substances Act; HCS = FHSA Hazard Communication Standard; Inconcl = Inconclusive; IR = iritis; OECD = Organisation for Economic Co-operation and Development; NL = NL (as irritant).

[1] Substances classified using the EPA hazard classification based on the EPA Label Review Manual (EPA 2003).

[2] Substances classified based on the FHSA HCS using a proportionality rule of 33% for studies with fewer than six animals.

[3] Current FHSA HCS classification (16 CFR 1500.42).

[4] The animal number represents the sequence of lesion severity in a study from most severe to least severe where CO>IR>CR>CC and does not correlate to the animal number used in the study report.

[5] Maximum score observed in the Draize rabbit eye test.

[6] Duration of lesions is expressed as the last day in which an FHSA positive score of CO or IR ≥1 or CR or CC ≥2 was present and the last day in which any lower lesion score was present.

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Annex VII

Representative Rabbit Eye Test Data Used in the NICEATM Evaluation of the GHS Classification System

Recent analyses reveal that a significant percentage of substances classified and labeled as eye irritation hazards by current U.S. hazard classification regulations[13] will not be classified and labeled as eye hazards using the United Nations Globally Harmonized System for the Classification and Labelling of Chemicals (GHS) eye irritation criteria (UN 2007). To evaluate if and to what extent using the GHS classification criteria might not identify substances as eye irritation hazards that are currently classified as eye irritation hazards by the GHS and EPA criteria, NICEATM evaluated 149 rabbit eye irritation test studies obtained from a publicly available database (ECETOC 1998). Within this database, a total of 31 substances that would require hazard labeling as eye irritants using the EPA classification criteria were "Not Classified" for eye irritation using the GHS classification criteria. Of these 31 substances, 17 produced corneal opacity and/or corneal ulceration, including seven that also produced iritis. Eight of these substances produced corneal opacity that extended beyond 48 hours after test substance administration. A representative set of data from seven Draize rabbit eye tests are provided on the pages that follow.

[13] The following lesions/scores are considered positive and therefore used to assign an EPA or FHSA irritant category: corneal opacity or iritis score ≥ 1 or conjunctival swelling or redness score ≥ 2.

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NICEATM–ICCVAM
In Vivo
2,2-Dimethyl-3-pentanol

[Chemical intermediate used in the manufacture of flame retardants and lubricants. 2,2-Dimethyl-3-pentanol is not on the OECD or the EPA HPV chemical list.]

CASRN:	3970-62-5	**Number of Animals:**	3
Data Source:	ECETOC	**Data ID:**	Technical Report No. 48 (2); June 1998
Data Page:	59	**Study ID:**	32
Testing Lab:		**Study Date:**	
Species/Strain:	RABBIT	**Study Class:**	IN VIVO
Concentration:	100%	**Amount:**	0.1 ml
pH:		**Purity:**	97%
Substance Source:	Aldrich	**MMAS:**	8.3
Product Class:		**Chemical Class:**	ALCOHOL
EPA:	Category III	**EU:**	Not labeled
GHS:	Not labeled	**FHSA:**	Irritant (2/3 pos animals)
Physical Form:			

Animal Number 1

			HR 1	Day 1	Day 2	Day 3	Day 4	Day 7
Cornea	Opacity	**A**	2	2	2	1	0	0
	Area Involved	**B**	1	1	1	1	0	0
Iris		**C**	0	0	0	0	0	0
Conjunctiva	Redness	**D**	1	1	1	1	1	0
	Chemosis	**E**	2	1	1	0	0	0
	Discharge	**F**	2	0	0	0	0	0
EPA: Category III	**EU:** Not labeled		**GHS:** Cat2B		**FHSA:** Irritant			
Notes:								

Animal Number 2

			HR 1	Day 1	Day 2	Day 3	Day 4	Day 7
Cornea	Opacity	**A**		1	1	0	0	0
	Area Involved	**B**	1	1	1	0	0	0
Iris		**C**	0	0	0	0	0	0
Conjunctiva	Redness	**D**	1	1	1	0	0	0
	Chemosis	**E**	2	1	0	0	0	0
	Discharge	**F**	3	0	0	0	0	0
EPA: Category III	**EU:** Not labeled		**GHS:** Not labeled		**FHSA:** Irritant			
Notes: Corneal Opacity - 1 Hour - Dulling of cornea								

Animal Number 3

			HR 1	Day 1	Day 2	Day 3	Day 4	Day 7
Cornea	Opacity	**A**		0	0	0	0	0
	Area Involved	**B**	2	0	0	0	0	0
Iris		**C**	0	0	0	0	0	0
Conjunctiva	Redness	**D**	1	1	1	0	0	0
	Chemosis	**E**	2	0	0	0	0	0
	Discharge	**F**	2	0	0	0	0	0
EPA: Category IV **EU:** Not labeled **GHS:** Not labeled **FHSA:** Not labeled								
Notes: Corneal Opacity - 1 Hour - Dulling of cornea								

NICEATM–ICCVAM
In Vivo
Ethyl acetate

[Chemical used in automobile and household paints and surface coatings, paint thinners and glazes, pharmaceutical preparations, flavors and perfume essences, flexible packaging (e.g. aluminum foil and plastic films), contact cement, manufacturing of adhesives, cleaning fluids, inks, nail polish and removers, coated papers, liquid bandages, explosives, artificial leather, and photographic film. Ethyl acetate is an OECD HPV chemical with greater than 1,011 kilotons produced worldwide in 1998 and 118 kilotons produced in the U.S. in 1997.]

CASRN:	141-78-6	**Number of Animals:**	4
Data Source:	ECETOC	**Data ID:**	Technical Report No 48(2); June 1998
Data Page:	24	**Study ID:**	5
Testing Lab:		**Study Date:**	
Species/Strain:	RABBIT	**Study Class:**	IN VIVO
Concentration:	100%	**Amount:**	0.1 ml
pH:		**Purity:**	99%
Substance Source:	Fisher	**MMAS:**	15
Product Class:		**Chemical Class:**	ESTER
EPA:	Category III	**EU:**	Not labeled
GHS:	Not labeled	**FHSA:**	Irritant (4/4 pos animals)
Physical Form:			

Animal Number 1

			Day 1	Day 2	Day 3	Day 7
Cornea	Opacity	**A**	2	0	0	0
	Area Involved	**B**	1	0	0	0
Iris		**C**	0	0	0	0
Conjunctiva	Redness	**D**	2	1	1	0
	Chemosis	**E**	1	1	0	0
	Discharge	**F**	1	0	0	0
EPA: Category III **EU:** Not labeled **GHS:** Not labeled **FHSA:** Irritant						
Notes:						

Animal Number 2

			Day 1	Day 2	Day 3	Day 7
Cornea	Opacity	**A**	1	0	0	0
	Area Involved	**B**	1	0	0	0
Iris		**C**	1	0	0	0
Conjunctiva	Redness	**D**	2	1	1	0
	Chemosis	**E**	1	1	0	0
	Discharge	**F**	1	0	0	0
EPA: Category III **EU:** Not labeled **GHS:** Not labeled **FHSA:** Irritant						
Notes:						

Animal Number 3

			Day 1	Day 2	Day 3	Day 7
Cornea	Opacity	**A**	1	0	0	0
	Area Involved	**B**	1	0	0	0
Iris		**C**	0	0	0	0
Conjunctiva	Redness	**D**	2	1	1	0
	Chemosis	**E**	1	1	0	0
	Discharge	**F**	1	0	0	0
EPA: Category III **EU:** Not labeled **GHS:** Not labeled **FHSA:** Irritant						
Notes:						

Animal Number 4

			Day 1	Day 2	Day 3	Day 7
Cornea	Opacity	**A**	1	0	0	0
	Area Involved	**B**	1	0	0	0
Iris		**C**	0	0	0	0
Conjunctiva	Redness	**D**	1	1	1	0
	Chemosis	**E**	1	0	0	0
	Discharge	**F**	1	0	0	0
EPA: Category III **EU:** Not labeled **GHS:** Not labeled **FHSA:** Irritant						
Notes:						

NICEATM–ICCVAM
In Vivo
Ethyl thioglycolate

[Thioglycolic salts and esters are widely used as hair straighteners, in hair dyes and colorings, and in the manufacture of food flavoring concentrates. Thioglycolic acid and its derivatives are widely used in the fields of PVC stabilizers, down-hole acidizing, corrosion inhibition in the oil field industry, manufacturing of pharmaceuticals, agrochemicals and dyes, shrink-resistant treatment of wool, fabric dying, and leather processing. Ethyl thioglycolate is also used as a depilitory agent. Ethyl thioglycolate is not on the OECD HPV chemical list.]

CASRN:	623-51-8	**Number of Animals:**	3
Data Source:	ECETOC	**Data ID:**	Technical Report No. 48 (2); June 1998
Data Page:	222	**Study ID:**	229
Testing Lab:		**Study Date:**	
Species/Strain:	RABBIT	**Study Class:**	IN VIVO
Concentration:	100%	**Amount:**	0.1 ml
pH:		**Purity:**	99.1%
Substance Source:	Sigma	**MMAS:**	24.67
Product Class:		**Chemical Class:**	ESTER, SULFUR COMPOUND, ORGANIC, ALCOHOL
EPA:	Category III	**EU:**	Not labeled
GHS:	Not labeled	**FHSA:**	Irritant (2/3 pos animals)
Physical Form:			

Animal Number 1

			HR 1	Day 1	Day 2	Day 3	Day 5	Day 6	Day 7
Cornea	Opacity	**A**	0	1	0	0			
	Area Involved	**B**	0	2	0	0			
Iris		**C**	0	1	0	0			
Conjunctiva	Redness	**D**	1	2	1	0			
	Chemosis	**E**	2	2	0	0			
	Discharge	**F**		1	0	0			

EPA: Category III **EU:** Not labeled **GHS:** Not labeled **FHSA:** Irritant

Notes: Discharge - 1 Hr - Evaluation obscured by residual test substance

Animal Number 2

			HR 1	Day 1	Day 2	Day 3	Day 5	Day 6	Day 7
Cornea	Opacity	**A**	2	2	3	3	2	0	0
	Area Involved	**B**	4	3	1	1	1	0	0
Iris		**C**	1	1	1	1	1	1	0
Conjunctiva	Redness	**D**	1	3	3	2	1	1	0
	Chemosis	**E**	3	2	2	1	0	0	0
	Discharge	**F**		2	1	0	0	0	0

EPA: Category III **EU:** R36(posCO),R36(posI),R36(posCR) **GHS:** Cat2B **FHSA:** Irritant

Notes: Discharge - 1 Hr - Evaluation obscured by residual test substance; Day 1 - White purulent discharge; score of 2 assigned

Animal Number 3

			HR 1	Day 1	Day 2	Day 3	Day 5	Day 6	Day 7
Cornea	Opacity	**A**	0	0	0	0			
	Area Involved	**B**	0	0	0	0			
Iris		**C**	0	0	0	0			
Conjunctiva	Redness	**D**	0	0	0	0			
	Chemosis	**E**	0	0	0	0			
	Discharge	**F**	0	0	0	0			

EPA: Category IV **EU:** Not labeled **GHS:** Not labeled **FHSA:** Not labeled

Notes:

NICEATM–ICCVAM
In Vivo
Glycidyl methacrylate

[Chemical used in the production of polymer coatings and finishes, adhesives, plastics, and elastomers. Consumer exposure is unlikely (Dow Chemical Co.), but workers potentially might be exposed during manufacturing operations. Glycidyl methacrylate is an OECD HPV chemical with 3,000 tons/year produced in Japan.]

CASRN:	106-91-2	**Number of Animals:**	3
Data Source:	ECETOC	**Data ID:**	Technical Report No 48(2); June 1998
Data Page:	47	**Study ID:**	23
Testing Lab:		**Study Date:**	
Species/Strain:	RABBIT	**Study Class:**	IN VIVO
Concentration:	100%	**Amount:**	0.1 ml
pH:		**Purity:**	>99%
Substance Source:	Elf Atochem	**MMAS:**	28
Product Class:		**Chemical Class:**	ETHER
EPA:	Category III	**EU:**	Not labeled
GHS:	Not labeled	**FHSA:**	Irritant (3/3 pos animals)
Physical Form:			

Animal Number: 1

			HR 1	Day 1	Day 2	Day 3	Day 7
Cornea	Opacity	**A**		1	2	2	0
	Area Involved	**B**	4	4	2	2	0
Iris		**C**	1	1	1	1	0
Conjunctiva	Redness	**D**	2	3	2	2	0
	Chemosis	**E**	3	4	2	2	0
	Discharge	**F**	3	3	1	0	0

EPA: Category III **EU:** R36(posI),R36(posCC) **GHS:** Cat2B **FHSA:** Irritant

Notes: Corneal Opacity - 1 Hr - Dulling of the cornea

Animal Number 2

			HR 1	Day 1	Day 2	Day 3	Day 7
Cornea	Opacity	**A**		1	0	0	
	Area Involved	**B**	4	2	0	0	
Iris		**C**	1	0	0	0	
Conjunctiva	Redness	**D**	2	2	1	0	
	Chemosis	**E**	2	1	1	0	
	Discharge	**F**	3	0	0	0	
EPA: Category III **EU:** Not labeled **GHS:** Not labeled **FHSA:** Irritant							
Notes: Corneal Opacity - 1 Hr - Dulling of the cornea							

Animal Number 3

			HR 1	Day 1	Day 2	Day 3	Day 7
Cornea	Opacity	**A**		1	0	0	
	Area Involved	**B**	4	2	0	0	
Iris		**C**	1	1	0	0	
Conjunctiva	Redness	**D**	2	2	1	0	
	Chemosis	**E**	2	1	0	0	
	Discharge	**F**	2	1	0	0	
EPA: Category III **EU:** Not labeled **GHS:** Not labeled **FHSA:** Irritant							
Notes: Corneal Opacity - 1 Hr - Dulling of the cornea							

NICEATM–ICCVAM
In Vivo
Myristyl myristate

[Wax base ingredient used in personal care products and cosmetics including cleansing and moisturizing creams, blushes, rouges, eye shadow, eyeliner, and eyebrow pencils, makeup, hair shampoos and conditioners, suntan products, bath products, cuticle softeners, shaving creams, skin and baby lotions, perfumes and deodorants/anti-perspirants. Myristyl myristate is an OECD High Production Volume (HPV) chemical, which indicates that the production volume is over 1,000 tons/year worldwide, although no specific information is available. However, it is not listed as an EPA HPV chemical indicating that production volume is not over 500 tons/year in the U.S.]

CASRN:	3234-85-3	**Number of Animals:**	3
Data Source:	ECETOC	**Data ID:**	Technical Report No. 48 (2); June 1998
Data Page:	117	**Study ID:**	162
Testing Lab:		**Study Date:**	
Species/Strain:	RABBIT	**Study Class:**	IN VIVO
Concentration:	100%	**Amount:**	0.1 ml (87 mg)
pH:		**Purity:**	
Substance Source:	DS Industries ApS	**MMAS:**	7.7
Product Class:		**Chemical Class:**	ESTER
EPA:	Category III	**EU:**	Not labeled
GHS:	Not labeled	**FHSA:**	Irritant (3/3 pos animals)
Physical Form:			

Animal Number 1

			HR 1	Day 1	Day 2	Day 3
Cornea	Opacity	**A**	0	0	0	0
	Area Involved	**B**	0	0	0	0
Iris		**C**	1	0	0	0
Conjunctiva	Redness	**D**	1	1	3	0
	Chemosis	**E**	1	0	1	0
	Discharge	**F**	0	0		0
EPA: Category III **EU:** Not labeled **GHS:** Not labeled **FHSA:** Irritant						
Notes:						

Animal Number 2

			HR 1	Day 1	Day 2	Day 3
Cornea	Opacity	**A**	0	0	0	0
	Area Involved	**B**	0	0	0	0
Iris		**C**	1	0	1	0
Conjunctiva	Redness	**D**	1	1		0
	Chemosis	**E**	1		0	0
	Discharge	**F**	0	0	0	0
EPA: Category III **EU:** Not labeled **GHS:** Not labeled **FHSA:** Irritant						
Notes:						

Animal Number 3

			HR 1	Day 1	Day 2	Day 3
Cornea	Opacity	**A**	0	1	0	0
	Area Involved	**B**	0	0		0
Iris		**C**	1	0	2	0
Conjunctiva	Redness	**D**	1	2	0	0
	Chemosis	**E**	1	0	0	0
	Discharge	**F**	1	0	0	0
EPA: Category III **EU:** Not labeled **GHS:** Not labeled **FHSA:** Irritant						
Notes:						

NICEATM–ICCVAM
In Vivo
Sodium lauryl sulfate

[Ingredient in personal care products including shampoos and conditioners, soaps, toothpastes, mouthwashes, hair colorants, skin powders and cleansers, body washes, and shaving creams and in cleaning products including floor cleaners, vegetable washes, tub, tile, shower and toilet bowl cleaners, fabric glues, silver cleaners, soap-scum removers, general purpose cleaning sprays, oven cleaners, carpet cleaners, stain removers, and adhesives. It is an OECD HPV chemical with over 10,000 tons/year produced in Germany.]

CASRN:	151-21-3	**Number of Animals:**	6
Data Source:	ECETOC	**Data ID:**	Technical Report No. 48 (2); June 1998
Data Page:	174	**Study ID:**	201
Testing Lab:		**Study Date:**	
Species/Strain:	RABBIT	**Study Class:**	IN VIVO
Concentration:	3.0%	**Amount:**	0.1 ml
pH:		**Purity:**	98 %
Substance Source:	Sigma	**MMAS:**	16
Product Class:		**Chemical Class:**	SALT, ORGANIC, CARBOXYLIC ACID, SALT
EPA:	Category III	**EU:**	Not labeled
GHS:	Not labeled	**FHSA:**	Irritant (5/6 pos animals)
Physical Form:			

Animal Number 1

			Day 1	Day 2	Day 3	Day 7
Cornea	Opacity	**A**	1	0	0	0
	Area Involved	**B**	1	0	0	0
Iris		**C**	0	0	0	0
Conjunctiva	Redness	**D**	2	2	1	0
	Chemosis	**E**	1	0	0	0
	Discharge	**F**	1	1	0	0

EPA: Category III **EU:** Not labeled **GHS:** Not labeled **FHSA:** Irritant

Notes:

Animal Number 2

			Day 1	Day 2	Day 3	Day 7
Cornea	Opacity	**A**	2	0	0	
	Area Involved	**B**	1	0	0	
Iris		**C**	1	0	0	
Conjunctiva	Redness	**D**	2	1	0	
	Chemosis	**E**	2	0	0	
	Discharge	**F**	2	1	0	
EPA: Category III **EU:** Not labeled **GHS:** Not labeled **FHSA:** Irritant						
Notes:						

Animal Number 3

			Day 1	Day 2	Day 3	Day 7
Cornea	Opacity	**A**	2	0	0	0
	Area Involved	**B**	1	0	0	0
Iris		**C**	0	0	0	0
Conjunctiva	Redness	**D**	2	1	1	0
	Chemosis	**E**	2	0	0	0
	Discharge	**F**	2	1	0	0
EPA: Category III **EU:** Not labeled **GHS:** Not labeled **FHSA:** Irritant						
Notes:						

Animal Number 4

			Day 1	Day 2	Day 3	Day 7
Cornea	Opacity	**A**	0	0	0	
	Area Involved	**B**	0	0	0	
Iris		**C**	0	0	0	
Conjunctiva	Redness	**D**	2	0	0	
	Chemosis	**E**	1	0	0	
	Discharge	**F**	1	0	0	
EPA: Category III **EU:** Not labeled **GHS:** Not labeled **FHSA:** Irritant						
Notes:						

Animal Number 5

			Day 1	Day 2	Day 3	Day 7
Cornea	Opacity	**A**	2	2	0	0
	Area Involved	**B**	1	1	0	0
Iris		**C**	0	0	0	0
Conjunctiva	Redness	**D**	2	2	1	0
	Chemosis	**E**	2	2	0	0
	Discharge	**F**	1	1	0	0
EPA: Category III **EU:** Not labeled **GHS:** Cat2B **FHSA:** Irritant						
Notes:						

Animal Number 6

			Day 1	Day 2	Day 3	Day 7
Cornea	Opacity	**A**	0	0	0	
	Area Involved	**B**	0	0	0	
Iris		**C**	0	0	0	
Conjunctiva	Redness	**D**	1	0	0	
	Chemosis	**E**	1	0	0	
	Discharge	**F**	1	0	0	
EPA: Category IV **EU:** Not labeled **GHS:** Not labeled **FHSA:** Not labeled						
Notes:						

NICEATM–ICCVAM
In Vivo
Tetraaminopyrimidine sulfate

[Raw material used in the preparation of hair dyes and as a chemical intermediate. Tetraaminopyrimidine sulfate is not on the OECD HPV chemical list.]

CASRN:	5392-28-9	**Number of Animals:**	3
Data Source:	ECETOC	**Data ID:**	Technical Report No. 48 (2); June 1998
Data Page:	122	**Study ID:**	167
Testing Lab:		**Study Date:**	
Species/Strain:	RABBIT	**Study Class:**	IN VIVO
Concentration:	100%	**Amount:**	100 mg
pH:		**Purity:**	97%
Substance Source:	Aldrich	**MMAS:**	10.3
Product Class:		**Chemical Class:**	AMINE, HETEROCYCLE, SULFUR COMPOUND, ORGANIC
EPA:	Category III	**EU:**	Not labeled
GHS:	Not labeled	**FHSA:**	Irritant (2/3 pos animals)
Physical Form:			

Animal Number 1

			HR 1	Day 1	Day 2	Day 3	Day 4	Day 7	Day 14
Cornea	Opacity	**A**	1	2	0	0	0	0	0
	Area Involved	**B**	1	1	0	0	0	0	0
Iris		**C**	0	0	0	0	0	0	0
Conjunctiva	Redness	**D**	2	2	1	1	0	0	0
	Chemosis	**E**	2	1	0	0	0	0	0
	Discharge	**F**	1	0	0	0	0	0	0

EPA: Category III **EU:** Not labeled **GHS:** Not labeled **FHSA:** Irritant

Notes:

Animal Number 2

			HR 1	Day 1	Day 2	Day 3	Day 4	Day 7	Day 14
Cornea	Opacity	**A**	1	1	0	0	0	0	0
	Area Involved	**B**	1	1	0	0	0	0	0
Iris		**C**	0	0	0	0	0	0	0
Conjunctiva	Redness	**D**	2	2	1	1	0	0	0
	Chemosis	**E**	2	1	0	0	0	0	0
	Discharge	**F**	1	0	0	0	0	0	0
EPA: Category III **EU:** Not labeled **GHS:** Not labeled **FHSA:** Irritant									
Notes:									

Animal Number 3

			HR 1	Day 1	Day 2	Day 3	Day 4	Day 7	Day 14
Cornea	Opacity	**A**	1	0	0	0	0	0	0
	Area Involved	**B**	1	0	0	0	0	0	0
Iris		**C**	0	0	0	0	0	0	0
Conjunctiva	Redness	**D**	1	1	1	1	0	0	0
	Chemosis	**E**	2	1	0	0	0	0	0
	Discharge	**F**	1	0	0	0	0	0	0
EPA: Category IV **EU:** Not labeled **GHS:** Not labeled **FHSA:** Not labeled									
Notes:									

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