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STREAMLINED SUMMARY DOCUMENT RELATED TO THE FLUORESCEIN LEAKAGE (FL) TEST METHOD FOR IDENTIFICATION OF OCULAR CORROSIVES AND SEVERE IRRITANTS (TG 460)

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IOMC

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FOREWORD

This streamlined summary document (SSD) was developed to address a request from the Working Group of National Coordinators of the Test Guidelines Programme (WNT) at its 2011 meeting. It was developed by a Secretariat consultant and submitted at the meeting of an expert group on eye irritation/corrosion, which was held on 29-30 September 2011 at the European Centre for Validation of Alternative Methods (ECVAM) (JRC, Italy). A first draft was submitted to the WNT in November 2011, for information, when approval of the draft Test Guideline for the Fluorescein Leakage Test Method was requested from the WNT by written procedure.

The draft document was approved with a few changes at the WNT meeting that was held on 24-27 April 2012; the Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology (hereafter Joint Meeting) agreed to its declassification on 7 August 2012.

This document is published under the responsibility of the Joint Meeting.

INTRODUCTION AND BACKGROUND

1. Throughout Europe and the USA, the Fluorescein Leakage test method (FL) assay has been used by industry, as a screening step to detect potential eye irritants, in the early developmental phase of product ingredients and formulations. EC-ECVAM conducted a retrospective validation study of the (FL), and evaluated several different INVITTOX protocols (1). The Fluorescein Leakage (FL) test method is an *in vitro* test method that can be used under certain circumstances and with specific limitations to classify chemicals (substances and mixtures) as ocular corrosives and severe irritants, as defined by the United Nations (UN) Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (Category 1), the European Union (EU) Regulation on Classification, Labelling and Packaging of Substances and Mixtures (CLP) (Category 1), and the U.S. Environmental Protection Agency (EPA) (Category I) (2) (3) (4). Severe irritants are defined as chemicals that cause tissue damage in the eye following test substance administration that is not reversible within 21 days or causes serious physical decay of vision, while ocular corrosives are chemicals that cause irreversible tissue damage to the eye. These chemicals are classified as UN GHS Cat. 1, EU CLP Cat. 1, or U.S. EPA Cat. I. While the FL test method is not considered valid as a complete replacement for the *in vivo* rabbit eye test (5), the FL is recommended for use as part of a tiered testing strategy for regulatory classification and labelling. Thus, the FL is recommended as an initial step within a Top-Down approach to identify ocular corrosives/severe irritants, specifically for limited types of chemicals (i.e. water soluble substances and mixtures) (1) (6). However, a chemical that is not predicted as ocular corrosive or severe irritant with the FL test method would need to be tested in one or more additional test methods (*in vitro* and/or *in vivo*) that are capable of accurately identifying i) chemicals that are *in vitro* false negative ocular corrosives/severe irritants in the FL (UN GHS Cat. 1; EU CLP Cat. 1; U.S. EPA Cat. I); ii) chemicals that are not classified for eye corrosion/irritation (UN GHS No Cat.; EU CLP No Cat.; U.S. EPA Cat. IV); and/or iii) chemicals that are moderate/mild eye irritants (UN GHS Cat. 2A and 2B; EU CLP Cat. 2; U.S. EPA Cat. II and III).

2. The comprehensive Background Review Document (BRD)(1) evaluates four different INVITTOX protocols (Nos. 71, 82, 86 and 120); however, the ECVAM Scientific Advisory Committee (ESAC) only recommended the use of INVITTOX protocol No. 71 (1) (7) and the performance presented in this document is based on results from the No. 71 protocol. However, for intra, and inter-laboratory reproducibility, also other protocols have been considered. The tables for chemical classes, performance and list of chemicals and formulations are based on the INVITTOX No. 71 protocol. In addition, several other studies not cited in this document are also evaluated by the BRD. Annex 1 is a list the 60 evaluated chemicals tested in 4 laboratories with comparisons of *in vivo* and *in vitro* ocular irritancy classifications.

SCIENTIFIC BASIS FOR THE FL TEST

3. The integrity of trans-epithelial permeability is a major function of an epithelium such as that found in the conjunctiva and the cornea. Trans-epithelial permeability is controlled by various tight junctions. Increasing the permeability of the corneal epithelium *in vivo* has been shown to correlate with the level of inflammation and surface damage observed as eye irritation develops. In the FL test method, toxic effects after a short exposure time to the test chemical are measured by an increase in permeability of sodium fluorescein through the epithelial monolayer of Madin-Darby Canine Kidney (MDCK) cells cultured on permeable inserts. The amount of fluorescein leakage that occurs is proportional to the chemical-induced damage to the tight junctions, desmosomal junctions and cell membranes, and can be used to estimate the ocular toxicity potential of a test chemical. The FL assay was developed by Tchao (1988) (8) as a model for detecting materials that are potentially irritating to the eye. *In vivo*, the tight junctions and desmosomes of the corneal epithelium prevent solutes and foreign materials moving into the cornea. Solutes in the cornea can induce water to move by osmosis into the cornea, thus causing oedema. Loss of trans-epithelial impermeability, due to damaged tight junctions and desmosomes, is one of the early events in chemical-induced ocular irritation. A confluent layer of MDCK cells consists of inter-cellular tight junctions and desmosomes. The

confluent monolayer used in the FL assay is non-proliferating, which models the non-proliferating state of the *in vivo* corneal epithelium. Whilst desmosomes maintain cell to cell adhesion, tight junctions form between adjacent cells and form a permeability barrier that can prevent the movement of molecules as small as 350 MW. Tight junctions are found at the apical surfaces of conjunctiva, corneal and skin epithelia. It is assumed that a significant part of ocular irritation is related to the state and ability of the corneal epithelium to act as a barrier against foreign and potentially irritant material. Increasing the permeability of the corneal epithelium *in vivo* has been found to accompany the inflammation and surface damage observed when eye irritation develops.

IDENTIFIED LIMITATIONS, WEAKNESSES AND STRENGTHS

4. The FL assay has predominately been used to test surfactant and surfactant-based materials. There is limited data regarding the predictive capacity of the FL assay for other chemical classes. In summary, the FL assay has many features rendering it suitable as an *in vitro* model for predicting *in vivo* ocular irritation, *e.g.,* relevant cell types, chemical concentrations, exposures, and endpoint. The FL assay is particularly advantageous in that it allows effects to be measured, which occur prior to, or even independent of cell death. Often, cell death does not occur in the cases of mild irritation and therefore a sensitive assay like the FL assay is essential (1).

Table 1: Physicochemical properties and compatibility with the FL test, from Table 2.1.3 of the FL BRD(1)

Physicochemical Property	**FL assay capable of testing materials with this physicochemical property?**
Alcohol	Yes
Fixative	No
Gases	No
Liquids	Yes (if aqueous soluble)
Solid materials	Yes (if aqueous soluble, but cannot be tested in its solid form)
Emulsions	Yes
Granular materials	Yes (if forms stable emulsion)
Suspensions	Impaired***
Coloured materials	Impaired**
Toxicity affected by dilution	No*
Highly viscous materials	Impaired
Volatile materials	Impaired
Reactive chemistries	No
Hydrophobic/lipophilic chemicals	No
Neat concentrations of chemicals	Yes
MW > 350	No

* the FL assay is unable to measure the toxicity of chemicals that have basic toxic mechanisms which are affected by dilution.

** the FL assay is able to measure coloured materials which can be fully removed from the insert following the chemical exposure and therefore do not interfere with OD readings.

*** solid materials suspended in liquid have the propensity to precipitate out and the final concentration exposed to cells can be difficult to determine.

5. The test method is not recommended for the identification of non-irritant (not classified) and mild/moderate irritant chemicals (substances and mixtures), strong acids and bases, cell fixatives, and highly volatile compounds. Due to the short exposure periods, the FL assay generally measures the effects of relatively high chemical concentrations. FL assay data differs from many other *in vitro* cytotoxicity assays which measure the effects of relatively low chemical concentrations and longer exposures on cell viability and replication rates. An advantage of the short incubation period used in the FL assay is that water-based ingredients and formulations can be tested neat if they can be easily removed after the short exposure period. This allows more direct comparisons of the FL assay results with the chemical effects *in vivo*.

6. A problem associated with the short exposure period of the FL assay is the difficulty of efficiently removing the test materials after the short exposure period. This is particularly true for viscous materials, such as gels and creams which are the type of materials often tested using the FL assay. Due to the short exposure period, the mild materials often need to be tested neat in order to produce a response which can be measured. Therefore the problems associated with viscous materials cannot be reduced by dilution. Test materials can also bind to the insert membrane, thus making their removal very difficult. Chemical binding to the insert membrane is more common for cationic materials, such as benzalkonium chloride, which are attracted to the positively charged membrane. Increased washing steps to remove the test material from the insert can also lead to insert membrane damage and thus erroneous results. Alternatively, if test materials are not removed fully and/or efficiently, they can potentially physically block the passage of the sodium-fluorescein through the insert, which would cause chemical effects to be under-estimated. In general, additional uncontrolled exposure time is a greater proportion of the short exposure period of the FL assay, than with assays with longer exposures. This leads to greater variability in results, and low assay reproducibility. As the FL assay can be repeated at multiple time-points, erroneous results due to ineffective removal of the test material would be more likely detected in comparison to cell viability assays which use single time-points. The efficient removal of test agents from the eye is also a concern of the *in vivo* test (1).

7. In conclusion, the FL assay is better suited to measure high concentrations of test materials that have low to mid-range toxicity and are soluble in water or HBSS. Test materials that are difficult to remove from the inserts due to viscosity or binding to the membrane are not accurately measured. Materials that have their basic toxic mechanism affected by dilution are not accurately measured by the FL assay (1).

USE OF THE FL TEST METHOD

Potential role in an ITS

8. The proposed FL test method is intended to be used in a Top-Down approach, as part of a tiered testing strategy, for classification of ocular severe irritants and corrosives (EU R41, GHS Cat. 1 and EPA Cat. I) for water-soluble chemicals (substances and mixtures) (1) (6). It can also be used to identify ocular corrosive and severe eye irritant chemicals like the validated and regulatory accepted organotypic assays BCOP (9) and ICE (10). The FL complements the applicability domain of BCOP and ICE, being able to correctly predict severe eye irritants within some of the chemical classes that are more problematic for the organotypic assays. Integration into test strategies of several *in vitro* test methods covering the full range of irritation as well as different physico-chemical classes, will be needed to achieve a full replacement of the *in vivo* eye test.

Categories of irritancy

9. The FL test method can be used for classification of ocular severe irritants and corrosives (EU R41, GHS Cat. 1 and EPA Cat. I) for water-soluble chemicals (substances and mixtures)(1)(6), and is not applicable for classification of chemicals as not irritating, nor for mild or moderate eye irritation.

APPLICABILITY DOMAIN

Mode of Action (MoA)

10. An Expert meeting held at EC-ECVAM in 2005 (6) recommended to expand the concept of defining the applicability domain as not only chemical classes, but also as a function of the mechanism of eye irritation. The four identified MoA that were discussed included: (i) cell membrane lysis (breakdown of membrane integrity as might occur from exposure to membrane active materials *e.g.,* surfactants), (ii) saponification (breakdown of lipids by alkaline action), (iii) coagulation (precipitation/denaturation of macromolecules), and (iv) actions of macromolecules (chemicals that react with cellular constituents/organelles). (1).

Table 2: Summary of the events involved in chemical-induced eye irritation *in vivo* which are (not) modelled by the FL assay. Text in italics indicates irreversible responses, from table 2.1.4.1 of the FL BRD (1).

Event involved in chemical-induced eye irritation	**Modelled by the FL assay**
Chemical interaction with tear film	No
Chemical binding to the conjunctival epithelium	No
Adhesion molecules compromised	Yes
Corneal epithelium damage	Yes
* inhibition of receptor-mediated membrane transport	Yes
* compromise of cell membrane integrity of upper corneal epithelium	Yes
* cell **membrane lysis** of all corneal epithelium layers	Yes
Hydration of corneal stroma	No
Cross-linking of proteins *in corneal stroma*	No
Erosion of corneal stroma	No
Cell damage to corneal epithelium and limbus	No
Dilation and increased lymphatic leakage from scleral vasculature (oedema and erythema)	No
Stimulation of nerve endings, i.e. enhanced blinking, tearing	No
Erosion of nerve endings in cornea and sclera	No
Duration of response, i.e. length of time cell responses deteriorate. Duration of response covers the effects of **reactive chemicals** which can cause **coagulation**, **saponification**, that are effects which develop and increase over time.	Yes
Recovery from response, i.e. length of time for cell responses to return to control levels	Yes

Chemical classes

11. A total of 60 chemicals and products have been evaluated in the test method evaluation, for a complete list see Annexes IVb, Vai and Vc of the FL BRD (1). Table 3 shows the performance of the FL test method with regard to false positives for the major chemical classes and physicochemical properties of interest, according the GHS classification system.

Table 3: False Positive and *False Negative Rates* of the FL Test Method, by Chemical Class and Properties of Interest, for the GHS Classification System.

Table 3: False Positive and False Negative Rates of the FL Test Method, by Chemical Class and Properties of Interest, for the GHS[1] Classification System

Category	N[2]	A[7]	False Positive Rate[3]		False Negative Rate[4]	
			%	No.[5]	%	No.
Overall	54	216	5.65	7/124	77.17	71/92
			Chemical Class[6]			
Acyl Halide	1	4	0	0/4	0	0/0
Alcohol	10	40	9.3	3/32	100	8/8
Alkali	2	8	0	0/4	0	0/4
Amine/Amidine	3	12	0	0/4	62.5	5/8
Carboxylic acid	9	36	25	3/12	79.2	19/24
Ester	7	28	3.6	1/28	0	0/0
Ether/Polyether	2	8	0	0/4	50	2/4
Heterocycle	7	28	0	0/8	85	17/20
Hydrocarbon	1	4	0	0/4	0	0/0
Inorganic salt	3	12	0	0/4	75	6/8
Ketone	5	20	0	0/20	0	0/0
Onium compound	2	8	0	0/0	75	6/8
Organic Sulfur compound	2	8	0	0/0	100	8/8
			Properties of Interest			
Liquids	38	152	5.5	6/108	65.9	15/44
Solids	16	64	6.3	1/16	87.5	42/48
Pesticides	3	12	0	0/0	100	0/12
Surfactants-anionic	2	8	75	3/4	0	0/4
Surfactants-cationic	5	20	0	0/4	75	12/16
Surfactants-nonionic	4	16	0	0/12	50	2/4

[1]GHS = Globally Harmonized System (UN 2003).
[2]N = Number of substances.
[3]False Positive Rate = the proportion of negative calls for substances that are falsely identified as positive *in vitro*.
[4]False Negative Rate = the proportion of all positive calls for substances that are falsely identified as negative *in vitro*.
[5]Data used to calculate the percentage.
[6]Chemical classes included in this table are assigned based on the MeSH categories (www.nlm.nih.gov/mesh)
[7]Total number of calls per category (4 calls per substance; substances for which study criteria were Not Met were excluded.)

SENSITIVITY, SPECIFICITY AND ACCURACY

Table 4: Evaluation of the performance of INVITTOX Protocol No. 71 for predicting ocular irritation according to the UN GHS, EU and US EPA classification systems – Severe irritants versus the rest (from table 6.2.4.2.3a, b, and c of the FL BRD (1))

Data Source	No*.	Concordance		Sensitivity		Specificity		False Positive Rate		False Negative Rate	
		%	No.	%	No.	%	No.	%	No.	%	No.
GHS	54	77-5	117/151	43.7	21/48	93.2	96/103	6.8	7/103	56.3	27/48
EU	50	77.9	113/145	45.7	21/46	92.9	92/99	7.1	7/99	54.3	25/46
US EPA**	48	81.1	103/127	46.4	13/28	90.9	90/99	9.1	9/99	53.6	15/28

* The reduced number of chemicals for the different classification schemes compared to the original dataset of 60 is due to the fact that not all chemicals met the classification criteria of each scheme.

**As the PM was not able to distinguish EPA Category III and Category IV materials, materials with these classifications were considered in the analyses concerning non-irritants. Refer to Annex V for the origins of the *in vitro* data and *in vivo* classification (1)

BETWEEN-LABORATORY RELIABILITY

12. Based on the data acquired in the validation study for 60 chemicals according to INVITTOX protocol 71, 43/60 materials (71.7%) had 100% agreement among all 4 participating laboratories. When concordance between 3 of the 4 laboratories was investigated, 59/60 materials (98.3%) had 100% agreement among 3 of the 4 laboratories. Moreover, data from INVITTOX protocol 120 were used as weight of evidence to further assess the Reproducibility of the FL test method. A good agreement of classification was obtained with 7/9 materials (77.8%) having 100% agreement among 3 laboratories, and 26/29 materials (89.7%) having 100% agreement among 2 laboratories.

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ANNEX 1

LIST OF THE 60 EVALUATED CHEMICALS TESTED IN 4 LABORATORIES AND COMPARISONS OF IN VIVO AND IN VITRO OCULAR IRRITANCY CLASSIFICATIONS: SORTED BY SUBSTANCE (1)

Chemical	CASRN [1]	Conc. Causing 20% Fl. leakeage (FL20)	In vitro predicted EU [2,3]	In vitro predicted GHS [4,5]	In vitro predicted EPA [6,7]	In vivo EU class [2,3]	In vivo GHS class [4,5]	In vivo EPA class [6,7]
1-naphthalene acetic acid	86-87-3	>100	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R41	Cat 1	Cat I
1-naphthalene acetic acid	86-87-3	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R41	Cat 1	Cat I
1-naphthalene acetic acid	86-87-3	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R41	Cat 1	Cat I
1-naphthalene acetic acid	86-87-3	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R41	Cat 1	Cat I
1-naphthalene acetic acid, Na salt	61-31-4	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R41	Cat 1	Cat I
1-naphthalene acetic acid, Na salt	61-31-4	>500	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R41	Cat 1	Cat I
1-naphthalene acetic acid, Na salt	61-31-4	171	R36	Cat 2	Cat II	R41	Cat 1	Cat I
1-naphthalene acetic acid, Na salt	61-31-4	245	R36	Cat 2	Cat II	R41	Cat 1	Cat I
2,2-dimethylbutanoic acid	595-37-9	>810	NC	No Cat	Cat III/IV	SCNM	SCNM	SCNM
2,2-dimethylbutanoic acid	595-37-9	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	SCNM	SCNM	SCNM
2,2-dimethylbutanoic acid	595-37-9	>100	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	SCNM	SCNM	SCNM
2,2-dimethylbutanoic acid	595-37-9	172	R36	Cat 2	Cat II	SCNM	SCNM	SCNM
2,5-dimethylhexanediol	110-03-2	>750	NC	No Cat	Cat III/IV	R41	Cat 1	Cat I
2,5-dimethylhexanediol	110-03-2	>750	NC	No Cat	Cat III/IV	R41	Cat 1	Cat I
2,5-dimethylhexanediol	110-03-2	>750	NC	No Cat	Cat III/IV	R41	Cat 1	Cat I
2,5-dimethylhexanediol	110-03-2	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R41	Cat 1	Cat I
2,6-dichlorobenzoyl chloride	4659-45-4	>1500	NC	No Cat	Cat III/IV	R36	Cat 2A	Cat II
2,6-dichlorobenzoyl chloride	4659-45-4	>1448	NC	No Cat	Cat III/IV	R36	Cat 2A	Cat II
2,6-dichlorobenzoyl chloride	4659-45-4	>1400	NC	No Cat	Cat III/IV	R36	Cat 2A	Cat II
2,6-dichlorobenzoyl chloride	4659-45-4	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R36	Cat 2A	Cat II
2-ethyl-1-hexanol	104-76-7	>1000	NC	No Cat	Cat III/IV	NC	Cat 2A	Cat II
2-ethyl-1-hexanol	104-76-7	>730	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	NC	Cat 2A	Cat II
2-ethyl-1-hexanol	104-76-7	230	R36	Cat 2	Cat II	NC	Cat 2A	Cat II
2-ethyl-1-hexanol	104-76-7	78,4	R41	Cat 1	Cat I	NC	Cat 2A	Cat II
4-carboxybenzaldehyde	619-66-9	>100	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R36	Cat 2A	Cat II
4-carboxybenzaldehyde	619-66-9	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R36	Cat 2A	Cat II
4-carboxybenzaldehyde	619-66-9	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R36	Cat 2A	Cat II
4-carboxybenzaldehyde	619-66-9	>100	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R36	Cat 2A	Cat II

Chemical	CASRN [1]	Conc. Causing 20% Fl. leakeage (FL20)	In vitro predicted EU [2,3]	In vitro predicted GHS [4,5]	In vitro predicted EPA [6,7]	In vivo EU class [2,3]	In vivo GHS class [4,5]	In vivo EPA class [6,7]
Acetone	67-64-1	839	NC	No Cat	Cat III/IV	R36	Cat 2A	Cat II
Acetone	67-64-1	523	R36	Cat 2	Cat II	R36	Cat 2A	Cat II
Acetone	67-64-1	709,25	R36	Cat 2	Cat II	R36	Cat 2A	Cat II
Acetone	67-64-1	678	R36	Cat 2	Cat II	R36	Cat 2A	Cat II
ammonium nitrate	6484-52-2	>750	NC	No Cat	Cat III/IV	R36	Cat 2A	Cat III
ammonium nitrate	6484-52-2	>750	NC	No Cat	Cat III/IV	R36	Cat 2A	Cat III
ammonium nitrate	6484-52-2	>750	NC	No Cat	Cat III/IV	R36	Cat 2A	Cat III
ammonium nitrate	6484-52-2	551	R36	Cat 2	Cat II	R36	Cat 2A	Cat III
benzalkonium chloride (1 %)	63449-41-2	>960	NC	No Cat	Cat III/IV	R41	Cat 1	Cat I
benzalkonium chloride (1 %)	63449-41-2	>100	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R41	Cat 1	Cat I
benzalkonium chloride (1 %)	63449-41-2	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R41	Cat 1	Cat I
benzalkonium chloride (1 %)	63449-41-2	91	R41	Cat 1	Cat I	R41	Cat 1	Cat I
benzalkonium chloride (10%)	63449-41-2	>1000	NC	No Cat	Cat III/IV	R41	Cat 1	Cat I
benzalkonium chloride (10%)	63449-41-2	19	R41	Cat 1	Cat I	R41	Cat 1	Cat I
benzalkonium chloride (10%)	63449-41-2	>25	unknown	unknown	unknown	R41	Cat 1	Cat I
benzalkonium chloride (10%)	63449-41-2	>25	unknown	unknown	unknown	R41	Cat 1	Cat I
benzalkonium chloride (5%)	63449-41-2	>1000	NC	No Cat	Cat III/IV	R41	Cat 1	Cat I
benzalkonium chloride (5%)	63449-41-2	18	R41	Cat 1	Cat I	R41	Cat 1	Cat I
benzalkonium chloride (5%)	63449-41-2	>25	unknown	unknown	unknown	R41	Cat 1	Cat I
benzalkonium chloride (5%)	63449-41-2	>25	unknown	unknown	unknown	R41	Cat 1	Cat I
benzoyl-L-tartaric acid	2743-38-6	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R41	Cat 1	SCNM
benzoyl-L-tartaric acid	2743-38-6	>100	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R41	Cat 1	SCNM
benzoyl-L-tartaric acid	2743-38-6	49,5	R41	Cat 1	Cat I	R41	Cat 1	SCNM
benzoyl-L-tartaric acid	2743-38-6	>25	unknown	unknown	unknown	R41	Cat 1	SCNM
butyl acetate	123-86-4	>940	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
butyl acetate	123-86-4	>874	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
butyl acetate	123-86-4	>860	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
butyl acetate	123-86-4	>100	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	NC	No Cat	Cat III
captan 90 concentrate	133-06-2	>100	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R41	Cat 1	Cat I
captan 90 concentrate	133-06-2	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R41	Cat 1	Cat I
captan 90 concentrate	133-06-2	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R41	Cat 1	Cat I
captan 90 concentrate	133-06-2	>100	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R41	Cat 1	Cat I
cetylpyridinium bromide (0.1%)	140-72-7	>900	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
cetylpyridinium bromide (0.1%)	140-72-7	>984	NC	No Cat	Cat III/IV	NC	No Cat	Cat III

Chemical	CASRN [1]	Conc. Causing 20% Fl. leakeage (FL20)	In vitro predicted EU [2,3]	In vitro predicted GHS [4,5]	In vitro predicted EPA [6,7]	In vivo EU class [2,3]	In vivo GHS class [4,5]	In vivo EPA class [6,7]
cetylpyridinium bromide (0.1%)	140-72-7	>960	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
cetylpyridinium bromide (0.1%)	140-72-7	>1000	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
cetylpyridinium bromide (10%)	140-72-7	>960	NC	No Cat	Cat III/IV	R41	Cat 1	Cat I
cetylpyridinium bromide (10%)	140-72-7	27	R41	Cat 1	Cat I	R41	Cat 1	Cat I
cetylpyridinium bromide (10%)	140-72-7	>25	unknown	unknown	unknown	R41	Cat 1	Cat I
cetylpyridinium bromide (10%)	140-72-7	>25	unknown	unknown	unknown	R41	Cat 1	Cat I
cetylpyridinium bromide (6%)	140-72-7	>810	NC	No Cat	Cat III/IV	R41	Cat 1	SCNM
cetylpyridinium bromide (6%)	140-72-7	>100	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R41	Cat 1	SCNM
cetylpyridinium bromide (6%)	140-72-7	93	R41	Cat 1	Cat I	R41	Cat 1	SCNM
cetylpyridinium bromide (6%)	140-72-7	>25	unknown	unknown	unknown	R41	Cat 1	SCNM
chlorhexidine	55-56-1	>100	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	SCNM	Cat 1	SCNM
chlorhexidine	55-56-1	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	SCNM	Cat 1	SCNM
chlorhexidine	55-56-1	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	SCNM	Cat 1	SCNM
chlorhexidine	55-56-1	>100	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	SCNM	Cat 1	SCNM
cyclohexanol	108-93-0	>938	NC	No Cat	Cat III/IV	R41	Cat 1	Cat I
cyclohexanol	108-93-0	>1000	NC	No Cat	Cat III/IV	R41	Cat 1	Cat I
cyclohexanol	108-93-0	473	R36	Cat 2	Cat II	R41	Cat 1	Cat I
cyclohexanol	108-93-0	741	R36	Cat 2	Cat II	R41	Cat 1	Cat I
dibenzyl phosphate	1623-08-1	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R36	Cat 2A	Cat II
dibenzyl phosphate	1623-08-1	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R36	Cat 2A	Cat II
dibenzyl phosphate	1623-08-1	21	R41	Cat 1	Cat I	R36	Cat 2A	Cat II
dibenzyl phosphate	1623-08-1	>25	unknown	unknown	unknown	R36	Cat 2A	Cat II
ethanol	64-17-5	>1000	NC	No Cat	Cat III/IV	NC	Cat 2A	Cat III
ethanol	64-17-5	516	R36	Cat 2	Cat II	NC	Cat 2A	Cat III
ethanol	64-17-5	698,64	R36	Cat 2	Cat II	NC	Cat 2A	Cat III
ethanol	64-17-5	590	R36	Cat 2	Cat II	NC	Cat 2A	Cat III
ethyl acetate	141-78-6	>887	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
ethyl acetate	141-78-6	>1000	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
ethyl acetate	141-78-6	231	R36	Cat 2	Cat II	NC	No Cat	Cat III
ethyl acetate	141-78-6	746	R36	Cat 2	Cat II	NC	No Cat	Cat III
ethyl trimethyl acetate	3938-95-2	>850	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
ethyl trimethyl acetate	3938-95-2	>844	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
ethyl trimethyl acetate	3938-95-2	>800	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
ethyl trimethyl acetate	3938-95-2	>1000	NC	No Cat	Cat III/IV	NC	No Cat	Cat III

Chemical	CASRN [1]	Conc. Causing 20% Fl. leakeage (FL20)	In vitro predicted EU [2,3]	In vitro predicted GHS [4,5]	In vitro predicted EPA [6,7]	In vivo EU class [2,3]	In vivo GHS class [4,5]	In vivo EPA class [6,7]
ethyl-2-methylacetoacetate	609-14-3	>990	NC	No Cat	Cat III/IV	NC	Cat 2B	Cat III
ethyl-2-methylacetoacetate	609-14-3	>1000	NC	No Cat	Cat III/IV	NC	Cat 2B	Cat III
ethyl-2-methylacetoacetate	609-14-3	369	R36	Cat 2	Cat II	NC	Cat 2B	Cat III
ethyl-2-methylacetoacetate	609-14-3	*				NC	Cat 2B	Cat III
fomesafen	72128-02-0	>750	NC	No Cat	Cat III/IV	SCNM	SCNM	Cat III
fomesafen	72128-02-0	>100	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	SCNM	SCNM	Cat III
fomesafen	72128-02-0	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	SCNM	SCNM	Cat III
fomesafen	72128-02-0	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	SCNM	SCNM	Cat III
gammabutyrolactone	96-48-0	133	R36	Cat 2	Cat II	R36	Cat 2A	Cat II
gammabutyrolactone	96-48-0	160,69	R36	Cat 2	Cat II	R36	Cat 2A	Cat II
gammabutyrolactone	96-48-0	482	R36	Cat 2	Cat II	R36	Cat 2A	Cat II
gammabutyrolactone	96-48-0	152	R36	Cat 2	Cat II	R36	Cat 2A	Cat II
glycerol	56-81-5	>1200	NC	No Cat	Cat III/IV	NC	No Cat	Cat IV
glycerol	56-81-5	>1254	NC	No Cat	Cat III/IV	NC	No Cat	Cat IV
glycerol	56-81-5	>1000	NC	No Cat	Cat III/IV	NC	No Cat	Cat IV
glycerol	56-81-5	>1000	NC	No Cat	Cat III/IV	NC	No Cat	Cat IV
hexanol	111-27-3	>750	NC	No Cat	Cat III/IV	R36	Cat 2A	Cat II
hexanol	111-27-3	>1000	NC	No Cat	Cat III/IV	R36	Cat 2A	Cat II
hexanol	111-27-3	270	R36	Cat 2	Cat II	R36	Cat 2A	Cat II
hexanol	111-27-3	12,67	R41	Cat 1	Cat I	R36	Cat 2A	Cat II
imidazole	288-32-4	135	R36	Cat 2	Cat II	R41	Cat 1	SCNM
imidazole	288-32-4	185	R36	Cat 2	Cat II	R41	Cat 1	SCNM
imidazole	288-32-4	185	R36	Cat 2	Cat II	R41	Cat 1	SCNM
imidazole	288-32-4	86,33	R41	Cat 1	Cat I	R41	Cat 1	SCNM
isobutanol	78-83-1	>770	NC	No Cat	Cat III/IV	R36	Cat 2A	Cat II
isobutanol	78-83-1	>1000	NC	No Cat	Cat III/IV	R36	Cat 2A	Cat II
isobutanol	78-83-1	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R36	Cat 2A	Cat II
isobutanol	78-83-1	369	R36	Cat 2	Cat II	R36	Cat 2A	Cat II
isopropanol	67-63-0	992	NC	No Cat	Cat III/IV	NC	Cat 2A	Cat III
isopropanol	67-63-0	549	R36	Cat 2	Cat II	NC	Cat 2A	Cat III
isopropanol	67-63-0	714,96	R36	Cat 2	Cat II	NC	Cat 2A	Cat III
isopropanol	67-63-0	618	R36	Cat 2	Cat II	NC	Cat 2A	Cat III
L-aspartic acid	70-47-3	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	SCNM	SCNM	SCNM
L-aspartic acid	70-47-3	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	SCNM	SCNM	SCNM
L-aspartic acid	70-47-3	>100	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	SCNM	SCNM	SCNM
L-aspartic acid	70-47-3	16	R41	Cat 1	Cat I	SCNM	SCNM	SCNM
maneb	12427-38-2	>750	NC	No Cat	Cat III/IV	SCNM	SCNM	Cat III
maneb	12427-38-2	>100	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	SCNM	SCNM	Cat III
maneb	12427-38-2	>250	NC/R36	No Cat/	Cat II/	SCNM	SCNM	Cat III

Chemical	CASRN [1]	Conc. Causing 20% Fl. leakeage (FL20)	In vitro predicted EU [2,3]	In vitro predicted GHS [4,5]	In vitro predicted EPA [6,7]	In vivo EU class [2,3]	In vivo GHS class [4,5]	In vivo EPA class [6,7]
				Cat 2	III/IV			
maneb	12427-38-2	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	SCNM	SCNM	Cat III
methyl acetate	79-20-9	>870	NC	No Cat	Cat III/IV	R36	Cat 2A	Cat II
methyl acetate	79-20-9	>1000	NC	No Cat	Cat III/IV	R36	Cat 2A	Cat II
methyl acetate	79-20-9	361	R36	Cat 2	Cat II	R36	Cat 2A	Cat II
methyl acetate	79-20-9	518,8	R36	Cat 2	Cat II	R36	Cat 2A	Cat II
methyl cyanoacetate	105-34-0	>1100	NC	No Cat	Cat III/IV	R36	Cat 2A	Cat II
methyl cyanoacetate	105-34-0	>1115	NC	No Cat	Cat III/IV	R36	Cat 2A	Cat II
methyl cyanoacetate	105-34-0	>750	NC	No Cat	Cat III/IV	R36	Cat 2A	Cat II
methyl cyanoacetate	105-34-0	>100	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R36	Cat 2A	Cat II
methyl ethyl ketone	78-93-3	>1000	NC	No Cat	Cat III/IV	R36	Cat 2A	Cat III
methyl ethyl ketone	78-93-3	256	R36	Cat 2	Cat II	R36	Cat 2A	Cat III
methyl ethyl ketone	78-93-3	273,25	R36	Cat 2	Cat II	R36	Cat 2A	Cat III
methyl ethyl ketone	78-93-3	235	R36	Cat 2	Cat II	R36	Cat 2A	Cat III
methyl isobutyl ketone	108-10-1	>800	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
methyl isobutyl ketone	108-10-1	>792	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
methyl isobutyl ketone	108-10-1	>770	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
methyl isobutyl ketone	108-10-1	>1000	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
methylcyclopentane	96-37-7	>750	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
methylcyclopentane	96-37-7	>1000	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
methylcyclopentane	96-37-7	>741	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	NC	No Cat	Cat III
methylcyclopentane	96-37-7	>670	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	NC	No Cat	Cat III
octanol	111-87-5	>770	NC	No Cat	Cat III/IV	R36	Cat 2A	Cat II
octanol	111-87-5	>1000	NC	No Cat	Cat III/IV	R36	Cat 2A	Cat II
octanol	111-87-5	198,5	R36	Cat 2	Cat II	R36	Cat 2A	Cat II
octanol	111-87-5	82,4	R41	Cat 1	Cat I	R36	Cat 2A	Cat II
parafluoraniline	371-40-4	>1146	NC	No Cat	Cat III/IV	SCNM	SCNM	SCNM
parafluoraniline	371-40-4	>1120	NC	No Cat	Cat III/IV	SCNM	SCNM	SCNM
parafluoraniline	371-40-4	55	R41	Cat 1	Cat I	SCNM	SCNM	SCNM
parafluoraniline	371-40-4	*				SCNM	SCNM	SCNM
polyethylene glycol 400	25322-68-3	>1200	NC	No Cat	Cat III/IV	NC	No Cat	Cat IV
polyethylene glycol 400	25322-68-3	>1110	NC	No Cat	Cat III/IV	NC	No Cat	Cat IV
polyethylene glycol 400	25322-68-3	>1100	NC	No Cat	Cat III/IV	NC	No Cat	Cat IV
polyethylene glycol 400	25322-68-3	>1	unknown	unknown	unknown	NC	No Cat	Cat IV
potassium cyanate	590-28-3	>750	NC	No Cat	Cat III/IV	SCNM	SCNM	SCNM
potassium cyanate	590-28-3	>750	NC	No Cat	Cat III/IV	SCNM	SCNM	SCNM
potassium cyanate	590-28-3	>500	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	SCNM	SCNM	SCNM
potassium cyanate	590-28-3	>500	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	SCNM	SCNM	SCNM
promethazine HCl	58-33-3	12	R41	Cat 1	Cat I	R41	Cat 1	SCNM
promethazine HCl	58-33-3	53,01	R41	Cat 1	Cat I	R41	Cat 1	SCNM

Chemical	CASRN [1]	Conc. Causing 20% Fl. leakeage (FL20)	In vitro predicted EU [2,3]	In vitro predicted GHS [4,5]	In vitro predicted EPA [6,7]	In vivo EU class [2,3]	In vivo GHS class [4,5]	In vivo EPA class [6,7]
promethazine HCl	58-33-3	65,1	R41	Cat 1	Cat I	R41	Cat 1	SCNM
promethazine HCl	58-33-3	>25	unknown	unknown	unknown	R41	Cat 1	SCNM
pyridine	110-86-1	989	NC	No Cat	Cat III/IV	R41	Cat 1	SCNM
pyridine	110-86-1	176	R36	Cat 2	Cat II	R41	Cat 1	SCNM
pyridine	110-86-1	315,83	R36	Cat 2	Cat II	R41	Cat 1	SCNM
pyridine	110-86-1	371	R36	Cat 2	Cat II	R41	Cat 1	SCNM
quiniacrine	69-05-6	>750	NC	No Cat	Cat III/IV	SCNM	Cat 1	SCNM
quiniacrine	69-05-6	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	SCNM	Cat 1	SCNM
quiniacrine	69-05-6	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	SCNM	Cat 1	SCNM
quiniacrine	69-05-6	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	SCNM	Cat 1	SCNM
sodium hydroxide (1%)	1310-73-2	132	R36	Cat 2	Cat II	R36	Cat 2B	Cat III
sodium hydroxide (1%)	1310-73-2	125,17	R36	Cat 2	Cat II	R36	Cat 2B	Cat III
sodium hydroxide (1%)	1310-73-2	127	R36	Cat 2	Cat II	R36	Cat 2B	Cat III
sodium hydroxide (1%)	1310-73-2	133	R36	Cat 2	Cat II	R36	Cat 2B	Cat III
sodium hydroxide (10%)	1310-73-2	6,3	R41	Cat 1	Cat I	R41	Cat 1	Cat I
sodium hydroxide (10%)	1310-73-2	13,26	R41	Cat 1	Cat I	R41	Cat 1	Cat I
sodium hydroxide (10%)	1310-73-2	5,8	R41	Cat 1	Cat I	R41	Cat 1	Cat I
sodium hydroxide (10%)	1310-73-2	10	R41	Cat 1	Cat I	R41	Cat 1	Cat I
sodium lauryl sulfate (3 %)	151-21-3	317	R36	Cat 2	Cat II	NC	No Cat	Cat III
sodium lauryl sulfate (3 %)	151-21-3	25	R41	Cat 1	Cat I	NC	No Cat	Cat III
sodium lauryl sulfate (3 %)	151-21-3	14,7	R41	Cat 1	Cat I	NC	No Cat	Cat III
sodium lauryl sulfate (3 %)	151-21-3	73	R41	Cat 1	Cat I	NC	No Cat	Cat III
sodium lauryl sulphate (15 %)	151-21-3	12	R41	Cat 1	Cat I	R41	Cat 1	Cat I
sodium lauryl sulphate (15 %)	151-21-3	8,87	R41	Cat 1	Cat I	R41	Cat 1	Cat I
sodium lauryl sulphate (15 %)	151-21-3	24	R41	Cat 1	Cat I	R41	Cat 1	Cat I
sodium lauryl sulphate (15 %)	151-21-3	70	R41	Cat 1	Cat I	R41	Cat 1	Cat I
sodium oxalate	62-76-0	>750	NC	No Cat	Cat III/IV	SCNM	Cat 1	SCNM
sodium oxalate	62-76-0	>100	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	SCNM	Cat 1	SCNM
sodium oxalate	62-76-0	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	SCNM	Cat 1	SCNM
sodium oxalate	62-76-0	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	SCNM	Cat 1	SCNM
sodium perborate	10486-00-7	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R41	Cat 1	Cat I
sodium perborate	10486-00-7	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R41	Cat 1	Cat I
sodium perborate	10486-00-7	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R41	Cat 1	Cat I
sodium perborate	10486-00-7	50,5	R41	Cat 1	Cat I	R41	Cat 1	Cat I
tetraaminopyrimidine sulphate	5392-28-9	>100	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	NC	No Cat	Cat III

Chemical	CASRN [1]	Conc. Causing 20% Fl. leakeage (FL20)	In vitro predicted EU [2,3]	In vitro predicted GHS [4,5]	In vitro predicted EPA [6,7]	In vivo EU class [2,3]	In vivo GHS class [4,5]	In vivo EPA class [6,7]
tetraaminopyrimidine sulphate	5392-28-9	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	NC	No Cat	Cat III
tetraaminopyrimidine sulphate	5392-28-9	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	NC	No Cat	Cat III
tetraaminopyrimidine sulphate	5392-28-9	>100	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	NC	No Cat	Cat III
thiourea	62-56-6	>100	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	Animal died	Animal died	Animal died
thiourea	62-56-6	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	Animal died	Animal died	Animal died
thiourea	62-56-6	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	Animal died	Animal died	Animal died
thiourea	62-56-6	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	Animal died	Animal died	Animal died
toluene	108-88-3	>860	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
toluene	108-88-3	>800	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
toluene	108-88-3	>830	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
toluene	108-88-3	>1000	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
trichloroacetic acid (3%)	76-03-9	803	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
trichloroacetic acid (3%)	76-03-9	>1006	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
trichloroacetic acid (3%)	76-03-9	>1000	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
trichloroacetic acid (3%)	76-03-9	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	NC	No Cat	Cat III
trichloroacetic acid (30%)	76-03-9	>1000	NC	No Cat	Cat III/IV	R41	Cat 1	Cat I
trichloroacetic acid (30%)	76-03-9	>250	NC/R36	No Cat/ Cat 2	Cat II/ III/IV	R41	Cat 1	Cat I
trichloroacetic acid (30%)	76-03-9	120	R36	Cat 2	Cat II	R41	Cat 1	Cat I
trichloroacetic acid (30%)	76-03-9	>25	unknown	unknown	unknown	R41	Cat 1	Cat I
triton X-100 (10 %)	9002-93-1	339	R36	Cat 2	Cat II	R41	Cat 1	Cat II
triton X-100 (10 %)	9002-93-1	665	R36	Cat 2	Cat II	R41	Cat 1	Cat II
triton X-100 (10 %)	9002-93-1	90	R41	Cat 1	Cat I	R41	Cat 1	Cat II
triton X-100 (10 %)	9002-93-1	99,44	R41	Cat 1	Cat I	R41	Cat 1	Cat II
triton X-100 (5 %)	9002-93-1	167	R36	Cat 2	Cat II	SCNM	Cat 2A	Cat III
triton X-100 (5 %)	9002-93-1	163,72	R36	Cat 2	Cat II	SCNM	Cat 2A	Cat III
triton X-100 (5 %)	9002-93-1	625	R36	Cat 2	Cat II	SCNM	Cat 2A	Cat III
triton X-100 (5 %)	9002-93-1	715	R36	Cat 2	Cat II	SCNM	Cat 2A	Cat III
tween 20	9005-64-5	653	R36	Cat 2	Cat II	NC	No Cat	Cat III
tween 20	9005-64-5	>1101	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
tween 20	9005-64-5	>750	NC	No Cat	Cat III/IV	NC	No Cat	Cat III
tween 20	9005-64-5	>1000	NC	No Cat	Cat III/IV	NC	No Cat	Cat III

[1]CASRN=Chemical Abstract Services Registry Number

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

[3]Risk phrase R41 = risk of serious damage to the eyes; R36 = irritating to the eyes; not classified.

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

[5]Eye Irritant Category 1 = irreversible effects on the eye/serious damage to the eye; Category 2A = reversible effects on the eye/irritating to the eyes; Category 2B = reversible effects on the eye/mildly irritating to the eyes; No category

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

[7]Toxicity Category I for the Primary Eye Irritation Study = Corrosive, or corneal involvement or irritation not reversible within 21 days; Category II = Corneal involvement or irritation clearing in 8-21 days; Category III = Corneal involvement or irritation clearing in 1-7 daysl; Category IV: minimal effects clearing in less than 24 hr

Abbreviations: MMAS scores reported in Balls et al. (1995) and in the ECETOC Technical Report n. 48 (1998), SCNM=Study Crtieria Not Met, n.p.=not provided