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COMMITTEE OF EXPERTS ON THE TRANSPORT OF DANGEROUS GOODS AND ON THE GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELLING OF CHEMICALS
Sub-Committee of Experts on the
Globally Harmonized System of Classification
and Labelling of Chemicals
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agenda item 2)

GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELLING OF CHEMICALS (GHS)

Submitted by the GHS Editorial Group

Annex 7

AN EXAMPLE OF CLASSIFICATION IN THE GLOBALLY HARMONIZED SYSTEM

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Annex 7

An example of classification in the Globally Harmonized System

A7.1 CLASSIFICATION PROPOSAL

The following classification proposal draws on the GHS criteria. The document includes both brief statements about the proposal for each health hazard endpoint and details of all the available scientific evidence.

Classification is proposed for both the acute toxicity and the corrosivity of this substance based on standard and non-standard animal studies. It should be noted that the current absence of GHS criteria for respiratory tract irritation is an issue for this substance.

Proposed classification	GHS:	Acute oral toxicity Category 4 Acute dermal (skin) toxicity Category 3 Skin irritation/corrosion Category 1C Eye irritation/serious eye damage Category 1 Flammable liquid Category 4

A7.2 IDENTIFICATION OF THE SUBSTANCE

1.1 EINECS Name If not in EINECS IUPAC Name	Globalene Hazexyl Systemol
	CAS No. 999-99-9 EINECS No. 222-222-2
1.2 Synonyms (state ISO name if available)	2-Hazanol Globalethylene
1.3 Molecular formula	$C_xH_yO_z$
1.4 Structural formula	
1.5 Purity (w/w)	
1.6 Significant impurities or additives	
1.7 Known uses	*Industrial:* Solvent for surface coatings and cleaning solutions. Chemical intermediate for Globalexyl UNoxy ILOate. *General public:* Toilet cleaner

A7.3 PHYSICO-CHEMICAL CHARACTERISTICS

Classification as a category 4 flammable liquid is proposed for the physico-chemical endpoints*

2.1	**Physical form**	Liquid
2.2	**Molecular weight**	146.2
2.3	**Melting point/range (°C)**	-45
2.4	**Initial Boiling point/ boiling range (°C)**	208.3
2.5	**Decomposition temperature**	
2.6	**Vapour pressure (Pa(°C))**	7
2.7	**Relative density (g/cm3)**	0.887 - 0.890
2.8	**Vapour density (air = 1)**	5.04
2.9	**Fat solubility (mg/kg, °C)**	
2.10	**Water solubility (mg/kg, °C)**	Slightly soluble (0.99% w/w)
2.11	**Partition coefficient (log Pow)**	
2.12	**Flammability** **flash point (°C)** **explosivity limits (%,v/v)** **auto-flammability temp. (°C)**	**closed cup:** 81.7 **open cup:** 90.6 **lower limit:** 1.2 **upper limit:** 8.4
2.13	**Explosivity**	No data available
2.14	**Oxidising properties**	
2.15	**Other physico-chemical properties**	

A.7.4 HEALTH AND ENVIRONMENTAL CHARACTERISTICS

A.7.4.1. Acute toxicity

There is no reliable information available about the potential of this substance to produce specific, non-lethal target organ/systemic toxicity arising from a single exposure. Therefore, under GHS, no classification for target organ/systemic toxicity (TOST) is proposed.

A7.4.1.1 *Oral*

Classification under GHS Category 4 (300-2000 mg/kg) are justified.

Species	LD_{50} (mg/kg)	Observations and remarks	Ref.
Rat	1480	No further details were available.	2
Rat	1500 (males) 740 (females)	The LD_{50} values in mg/kg were calculated from ml/kg using the known density for EGHE of 0.89 g/cm^3.	8

A7.4.1.2 *Inhalation*

There were no deaths or signs of overt toxicity in animals exposed to the saturated vapour concentration of approximately 0.5 mg/L and therefore, the available data do not support classification.

Species	LC_{50} (mg/l)	Exposure time (h)	Observations and remarks	Ref.
Rat	> 83 ppm. (approx equal to 0.5 mg/l).	4	No deaths, clinical signs or gross lesions occurred at 83 ppm (85 ppm is stated to be the saturated vapour concentration at room temperature).	3
Rat	Not stated	6	The animals were exposed to the saturated vapour concentration at room temperature (assumed to be 85 ppm). No deaths occurred and no signs of gross pathology were observed.	8
Rat	Not stated	8	No deaths occurred with exposure to the “saturated vapour concentration” at room temperature (assumed to be 85 ppm).	2

A7.4.1.3 ***Skin***

Classification under GHS Category 3 (200-1000 mg/kg) is justified.

Species	LD_{50} (mg/kg)	Observations and remarks	Ref.
Rat	790	No further details were available.	2
Rabbit (5/sex/ group)	720 (males) 830 (females)	Animals were exposed to up to 3560 mg/kg for 24 hours. All but 2 of the animals that died did so during the application period. Following the exposure period, local toxicity (erythema, oedema, necrosis and ecchymoses) was reported in an unstated number of animals, and persisted throughout the 14 day post-application observation period. Ulceration was also noted in an unstated number of animals at the end of the observation period.	8

A7.4.2 Skin irritation/corrosion

There are conflicting reports concerning the irritant nature of this substance. In a dedicated skin irritation study reported in the same paper as the acute dermal study, the author states that “necrosis” was observed in 3 of 6 treated rabbits which was still present on the last day of observation (day 7), along with mild to moderate erythema. Mild to marked oedema was also observed during the course of the study but had resolved within the 7-day observation period. Given that one animal showed no evidence of any skin response in this study and that only slight to moderate skin irritation was observed in the other animals the observation of “necrosis” in three of the animals is somewhat surprising. An acute dermal (skin) toxicity study in rabbits also reported signs of skin irritation including the description 'necrosis' and ulceration but did not quantify the number of animals affected. In contrast to these findings, an old and briefly reported study indicated that there was little or no indication of skin irritation in rabbits.

Similarly mixed skin irritation findings have been observed with a closely related substance, for which both necrosis and no skin irritation has been reported. In addition a secondary source indicates that some other similar substances cause 'moderate' skin irritation, and that prolonged exposure to these group of substances may cause burns. However, much shorter chain similar substances are not considered to be skin irritants.

It was considered that the reported necrosis in both the acute dermal and skin irritation studies cannot be dismissed and, taken together with the findings seen with structurally similar substances, this justifies classification. There are 3 Categories under the GHS for classification as corrosive. The data do not match the criteria readily, but Category 1C would be appropriate since the necrotic lesions observed occurred after an exposure period of 4 hours. There is no evidence to suggest that significantly shorter exposures would produce skin corrosion.

Species	No. of animals	Exposure time (h)	Conc. (w/w)	Dressing: (occlusive, semi-occlusive, open)	Observations and remarks (specify degree and nature of irritation and reversibility)	Ref.
Rabbit	6	4	0.5 ml of 100%	Occlusive	No signs of irritation was observed in one animal, and only slight erythema (grade 1) in another on day 1, which had resolved by day 7. Four animals showed a mild to moderate erythema (grade 1-2) and a mild to marked oedema (grade 1-3) after removal of the dressing. The oedema had resolved by day 7 post-exposure. "Necrosis" at the application site was reported in 3/6 rabbits from day 1 until the end of the observation period on day 7. Desquamation was observed in 4/6 rabbits on day 7.	8
Rabbit (albino)	5	24	100% (volume not stated)	Not stated	Little or no signs of skin irritation were found in this poorly reported study.	2

A7.4.3 Serious damage to eyes/eye irritation

The only available study involved exposure of rabbits to considerably lower amounts of the test substance than the standard protocols for this endpoint recommend. Relatively severe (eg. conjunctival redness grade 3) but reversible effects were seen. It is predictable that under standard test conditions, the effects on the eye would be very severe and consequently GHS Category 1 (irreversible effects on the eye) would be justified.

Species	No. of animals	Conc. (w/w)	Observations and remarks (specify degree and nature if irritation, any serious lesions, reversibility)	Ref.
Rabbit	6	0.005 ml of 100%	One hour post-instillation conjunctival redness (grade 3) and discharge (grade 2.8) observed. The mean scores for the 24, 48 and 72 hour readings for corneal opacity, iris, conjunctival redness, chemosis and discharge were all approx 0.5. All lesions had resolved by day 7. This study did not conform to the EU Annex V protocol in that only a very small amount of substance was used in the test.	8
Rabbit	60	1 and 5%.	A report in the secondary literature of severe eye injury observed in rabbits associated with instillation of an unstated amount of 5%, could not be substantiated as the information was not found in the reference stated.	1

A7.4.4 Irritation of the respiratory tract

It is noted that irritant effects on the upper respiratory tract have not been reported in either single and repeat exposure studies in rats exposed to saturated vapour concentrations of the substance.

A7.4.5 Skin and respiratory sensitization

No data are available. There are no additional grounds for concern (eg. structure activity relationships) and no classification proposed.

A7.4.6 Toxicity following repeated exposure

A7.4.6.1 *Oral*

No oral repeat dose studies are available and therefore no classification is proposed.

A7.4.6.2 *Inhalation*

There was no evidence of adverse toxicity in a 13-week rat inhalation study at 0.43 mg/l (approx. 72 ppm), an exposure level close to the saturated vapour concentration. No classification is justified according to GHS criteria.

Species	conc. mg/l	Exposure time (h)	Duration of treatment	Observations and remarks (specify group size, NOEL, effects of major toxicological significance)	Ref.
Rat (F344) 20/sex / group (plus 10/ sex/group - 4 week recovery groups)	0.12, 0.24 & 0.425	6	5 d/wk for 13 weeks	No deaths occurred. Decreased weight gain was observed in high dose animals of both sexes and medium dose females. There were no toxicologically significant changes in haematological or urinalysis parameters. High dose females showed an increase in alkaline phosphatase. High and medium dose males showed a statistically significant increase in absolute and relative kidney weight. A small increase in absolute liver weight (12%) was observed in high dose females. However, there were no gross or histopathological changes in any organs examined.	3

A7.4.6.3 ***Dermal***

Unquantified haematological changes were reported in rabbits exposed to 444 mg/kg dermally for 11 days. However, due to the limited information provided, no conclusions can be drawn from this study and no classification is proposed.

Species	Dose mg/kg	Exposure time (h)	Duration of treatment	Observations and remarks (specify group size, NOEL, effects of major toxicological significance)	Ref.
Rabbit	0, 44, 222 & 444	6	9 doses applied over 11 days	This is an unpublished study reported in the secondary literature. Unquantified decreases in haematological parameters were noted in top dose animals. No description of local effects was provided.	1

A7.4.7 Carcinogenicity (including chronic toxicity studies)

No data available – no classification proposed.

A7.4.8 Mutation in germ cells

Negative results have been reported *in vitro* from Ames, cytogenetics, and gene mutation tests reported in the secondary literature. There are no *in vivo* data available. These data do not support classification.

In vitro **studies**

Test	Cell type	Conc. range	Observations and remarks	Ref.
Ames	Salmonella (strains unstated)	0.3-15 mg/plate	**Negative**, in the presence and absence of metabolic activation. This is an unpublished study described in a secondary source and no further information is available.	5
IVC	CHO	0.1-0.8 mg/ml (-S9), 0.08-0.4 mg/ml (+S9)	**Negative**, in the presence and absence of metabolic activation. This is an unpublished study described in a secondary source and no further information is available.	6
Gene mutation	CHO	Not stated	**Negative**. This is an unpublished study described in a secondary source and no further information is available.	7
SCE	CHO	Not stated	**Negative**. This is an unpublished study described in a secondary source and no further information is available.	7

A7.4.9 Reproductive toxicity-Fertility

No data available – no classification proposed.

A7.4.10 Reproductive toxicity-developmental toxicity

There was no evidence of developmental toxicity in rats or rabbits following inhalation exposure to levels inducing slight maternal toxicity. It is noted that although shorter chain related substances are classified for developmental toxicity, this toxicity decreases with increasing chain length such that there is no evidence of this hazard. No classification is proposed.

Species	Route	Dose	Exposure	Observations and remarks	Ref.
Rat	Inhalation	21, 41 & 80 ppm (0.12, 0.24 & 0.48 mg/L)	days 6-15 of gestation	The substance was tested up to approximately the saturated vapour concentration. Decreases in dam body weight gain, associated with decreases in food consumption, were observed in the medium and high dose groups during the exposure period. There was no evidence of developmental toxicity.	4
Rabbit	Inhalation	21, 41 & 80 ppm (0.12, 0.24 & 0.48 mg/L)	days 6-18 of gestation	The substance was tested up to approximately the saturated vapour concentration. Decrease in absolute body weight during the exposure period was observed in the high dose animals. There was no evidence of developmental toxicity.	4

A.7.5 REFERENCES

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