

**DRAFT**

**Comparison between EU and GHS Criteria**

**Human Health and Environment**

**The comparison is based on the GHS ST/SG/AC.10/30/Rev2 2007**

This comparison of the current EU classification system and the GHS is a draft working document of the Commission Services. It is intended to serve as a first introduction and general orientation about consistency and differences between the two classification systems. Its aim is to give a first indication of where classification provisions differ. In case of any inconsistency in this document with the text of the GHS or the current Community legislation in force, the original texts alone shall be decisive. It does not supersede in any way the classification rules as set out in Community legislation currently in force. This document does not bind the Commission in any way.

**It does not include any opinion of the Commission Services on optionality.**

**Version December 2007**  
DG ENTR G1 REACH

# EU versus OECD Criteria for the Classification of Dangerous Substances and Mixtures

## 1. Acute Toxicity - Oral

<b>EU</b>	<b>T<sup>+</sup> R28</b>		<b>T R25</b>			<b>Xn R22</b>	
<b>LD<sub>50</sub> (*)</b>	≤ 5	5-25	25-50	50-200	200-300	300-2000	2000-5000
<b>GHS</b>	<b>Cat. 1</b>	<b>Category 2</b>	<b>Category 3</b>		<b>Category 4</b>	<b>Category 5</b>	

Remarks: (\*) : Alternative EU criteria when using the "Fixed Dose" procedure:  
 T+ R28 : oral, rat 5 mg/kg : < 100 % survival - T R25 : oral, rat 5 mg/kg : 100 % survival but evident toxicity  
 Xn R22 : oral, rat 50 mg/kg : 100 % survival but evident toxicity - 500 mg/kg : < 100 % survival

## 2. Acute Toxicity - Dermal

<b>EU</b>	<b>T<sup>+</sup> R27</b>	<b>T R24</b>			<b>Xn R21</b>	
<b>LD<sub>50</sub></b>	≤ 50	50-200	200-400	400-1000	1000-2000	2000-5000
<b>GHS</b>	<b>Category 1</b>	<b>Category 2</b>	<b>Category 3</b>		<b>Category 4</b>	<b>Category 5</b>

### 3. Acute Toxicity - Inhalation

#### 3.1 Aerosols & Particulates / Dusts and mists

<b>EU</b> Aerosols & particulates	T <sup>+</sup> R26		T R23		Xn R20	
<b>LC<sub>50</sub></b>	≤ 0.05	0.05-0.25	0.25-0.5	0.5-1	1-5	5-?
<b>GHS</b> Dust&Mist Mg/l	Category 1		Category 2		Category 3	
					Category 4	
					Category 5	

#### 3.2 Gases & Vapours

<b>EU</b>	T <sup>+</sup> R26		T R23		Xn R20	
<b>LC<sub>50</sub></b> (Vapours) mg/l/4hr	≤ 0.5	0.5-2		2-10	10-20	20-50
<b>GHS</b>	Category 1		Category 2		Category 3	
					Category 4	
					Category 5	
<b>LC<sub>50</sub>*</b> (gases) (ppm V)	≤ 100	100-500		500-2500	2500-20000	?

\*This criteria for gases are not defined in the current EU system and have only be defined in the frame of GHS

## 4. Aspiration Hazards

<b>EU</b>	<b>Xn R65 (May cause lung damage if swallowed)</b>	
<b>Criteria</b>	<p><b>Liquid substances and preparations presenting an aspiration hazard because of their low viscosity :</b></p> <p>(a) For substances and preparations containing aliphatic, alicyclic and aromatic hydrocarbons in a total concentration equal to or greater than 10% and having either</p> <ul style="list-style-type: none"> <li>- a flow time of less than 30 sec. in a 3 mm ISO cup according to ISO 2431 (April 1996/July 1999 edition) relating to "Paints and varnishes – Determination of flow time by use of flow cups",</li> <li>- a kinematic viscosity measured by a calibrated glass capillary viscometer in accordance with ISO 3104/3105 of less than <math>7 \times 10^{-6} \text{ m}^2/\text{sec}</math> at 40° C (ISO 3104, 1994 edition, relating to "Petroleum products – Transparent and opaque liquids – Determination of kinematic viscosity and calculation of dynamic viscosity" ; ISO 3105, 1994 edition, relating to "Glass capillary kinematic viscometers – Specifications and operating instructions"), or</li> <li>- a kinematic viscosity derived from measurements of rotational viscometry in accordance with ISO 3219 of less than <math>7 \times 10^{-6} \text{ m}^2/\text{sec}</math> at 40° C (ISO 3219, 1993 edition, relating to "Plastics – Polymers/resins in the liquid state or as emulsions or dispersions – Determination of viscosity using a rotational viscometer with defined shear rate").</li> </ul> <p>Note that substances and preparations meeting these criteria need not be classified if they have a mean surface tension greater than 33mN/m at 25° C as measured by the du Nouy tensiometer or by the test methods shown in Annex V Part A.5.</p> <p>(b) For substances and preparations, based on practical experience in humans.</p>	
<b>GHS</b>	<b>Category 1</b>	<b>Category 2</b>
<b>Criteria</b>	<p><b>Chemicals known to cause human aspiration toxicity hazards or to be regarded as if they cause human aspiration toxicity hazard.</b></p> <p>A substance is classified in Category 1:</p> <p>(a) Based on reliable and good quality human evidence; or</p> <p>(b) It is a hydrocarbons and has a kinematic viscosity of 20.5mm<sup>2</sup>/s or less, measured at 40° C.</p> <p>Note: Examples of substances included in Category 1 are certainly hydrocarbons, turpentine and pine oil</p> <p>A mixture is classified in Category 1:</p> <p>If it contains at least ≥10% of an ingredient Category 1 and has a kinematic viscosity of 20.5mm<sup>2</sup>/s or less, measured at 40° C.</p> <p>If a mixture with two layers, if one layers fulfils the criteria just above</p>	<p><b>Chemicals which cause concern owing to the presumption that they cause human aspiration toxicity hazard</b></p> <p><b>Substance classified Category 2:</b> on the basis of existing animal studies and expert judgment that takes into account surface tension, water solubility, boiling point, and volatility, substances with a kinematic viscosity of 14 mm<sup>2</sup>/s or less, measured at 40°C.</p> <p>Note: Taking this into account, some authorities would consider the following to be included in this Category: n-primary alcohols with a composition of at least 3 carbon atoms but not more than 13; isobutyl alcohol, and ketones with a composition of no more than 13 carbon atoms.</p> <p>Mixtures classified Category 2: If it contains at least ≥10% of an ingredient Category 2 and has a kinematic viscosity of 14 mm<sup>2</sup>/s or less, measured at 40° C.</p> <p>If a mixture with two layers, if one layers fulfils the criteria just above</p>

## 5. Skin Corrosion

<b>EU</b>	<b>C R35</b>		<b>C R34</b>	
	<p><b>Corrosion</b> = full thickness destruction of skin tissue on at least 1 animal during the <i>test for skin irritation</i> cited in Annex V or during an equivalent method or if the results are based on the results of a validated in vitro test or if the results can be predicted: for example from strong alkali or acid reactions indicated by a pH of <math>\leq 2</math> or <math>\geq 11,5</math> where extreme pH is the basis for classification, acid/alkali reserve may also be taken into consideration. If consideration of alkali/acid reserve suggests the substance or preparation may not be corrosive then further testing should be carried out to confirm this, preferably by use of an appropriate validated in vitro test.                  Consideration of acid/alkali reserve should not be used alone to exonerate substances or preparations from classification as corrosive.</p>			
<b>Exposure</b>	≤ 3 min	> 3 min - ≤ 1 hour	> 1 hour - ≤ 4 hours	
<b>GHS</b>	<b>Category 1</b>			
	<b>Category 1A</b> (Obs. ≤ 1 hour)	<b>Category 1B</b> (Observation period ≤ 14 days)		<b>Category 1C</b> (Observation period ≤ 14 days)
	<p><b>Corrosion</b> = destruction of skin tissue, namely visible necrosis through the epidermis and into the dermis in at least 1 of 3 tested animals after exposure up to 4 hours. Corrosive reactions are typified by ulcers, bleeding, bloody scabs and, by the end of observation at 14 days, by discoloration due to blanching of the skin, complete areas of alopecia and scars or if the results are based on the results of a validated in vitro test or if the results can be predicted: for example from strong alkali or acid reactions indicated by a pH of <math>\leq 2</math> or <math>\geq 11,5</math>                  Measurement of pH alone may be adequate but assessment of acidic or alkali reserve is preferable; methods are needed to assess buffering capacity.</p> <p>REM the text of the Regulation is the same as the text from 67/548 without the underlined sentence in yellow</p>			

Classification for eye effects

It is important to point out that the Category 1 corrosive to skin is carried over for the assessment of the corrosive effects to the eye, both in the EC Directives and in the GHS

## 6. Skin Irritation

<b>EU</b>	<b>Xi R38</b>	
<b>Criteria</b>	<p>- <b>Substances/preparations which when applied to intact skin of the rabbit cause significant inflammation of the skin which persists for at least 24 hours after an exposure period of up to 4 hours.</b></p> <p>Inflammation of the skin is significant if :</p> <p>(a) the mean value of the scores for either erythema and eschar formation or oedema formation, calculated over all the animals tested, is 2 or more; or</p> <p>(b) in the case where the Annex V test has been completed using three animals, either erythema and eschar formation or oedema formation equivalent to a mean value of 2 or more calculated for each animal separately has been observed in two or more animals.</p> <p>In both cases all scores at each of the reading times (24, 48 and 72 hr) for an effect should be used in calculating respective mean values.</p> <p>Inflammation of the skin is also significant if it persists in at least two animals at the end of the observation time, Particular effects e.g. hyperplasia, scaling, discoloration, fissures, scabs and alopecia should be taken into account. Relevant data may also be available from non-acute animal studies (see comments on R48, section 2.d). These are considered significant if the effects seen are comparable to those described above.</p> <p>- Substances and preparations which cause significant inflammation of the skin, based on practical observations in humans on immediate, prolonged or repeated contact.</p> <p>- Organic peroxides, except where evidence to the contrary is available.</p>	
<b>GHS</b>	<b>Category 2 (Irritant)</b>	<b>Category 3 (Mild Irritant) [OPTIONAL]</b>
<b>Criteria</b>	<p>(1) Mean value of <math>\geq 2.3</math> -<math>\leq 4.0</math> for erythema/eschar or for oedema in at least 2 of 3 test animals from gradings at 24, 48 and 72 hours after patch removal, or if reactions are delayed, from grades on 3 consecutive days after the onset of dermal reactions, or</p> <p>(2) Inflammation that persists to the end of the observation period normally 14 days in at least 2 animals, particularly taking into account alopecia (limited area) hyperkeratosis, hyperplasia, and scaling, or</p> <p>(3) In some cases where there is pronounced variability of response among animals, with very definite positive effects related to chemical exposure in a single animal but less than the criteria above</p>	<p>Mean value of <math>\geq 1.5</math> - <math>&lt; 2.3</math> for erythema/eschar or for oedema from gradings in at least 2 of 3 tested animals from grades at 24, 48 and 72 hours or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions (when not included in the irritant Category 2)</p>

It is important to point out that in the GHS the Category 2 irritant to skin is carried over for the assessment of the eye irritation effect.

## 7. Eye Irritation

<b>EU</b>	<b>Xi R41</b>	<b>Xi R36</b>	
<b>Criteria</b>	<p><b>Substances/preparations when applied to the eye of an animal cause severe ocular lesions within 72 hours after exposure which persist for at least 24 hours.</b></p> <p>Ocular lesions are severe if the means of the scores of the eye irritation test in Annex V have any of the values:</p> <ul style="list-style-type: none"> <li>- cornea opacity equal to or greater than 3,</li> <li>- iris lesion greater than 1.5,</li> </ul> <p>The same shall be the case where the test has been completed using three animals if these lesions, on two or more animals, have any of the values :</p> <ul style="list-style-type: none"> <li>- cornea opacity equal to or greater than 3,</li> <li>- iris lesion equal to 2.</li> </ul> <p>In both cases all scores at each of the reading times (24, 48 and 72 hours) for an effect should be used in calculating the respective mean values.</p> <p>Ocular lesions are also severe when they are still present at the end of the observation time.</p> <p>Ocular lesions are also severe if the substance or preparation causes irreversible colouration of the eyes</p> <ul style="list-style-type: none"> <li>- Substances and preparations which cause severe ocular lesions based on practical experience in humans.</li> </ul> <p>Note : When a substance or preparation is classified as corrosive and assigned R34 or R35, the risk of severe damage to eyes is considered implicit and R41 is not included in the label.</p>	<p><b>Substances/preparations when applied to the eye of an animal, cause <i>significant</i> ocular lesions within 72 hours after exposure which persist for at least 24 hours.</b></p> <p>Ocular lesions are significant if the mean score of the eye irritation test cited in Annex V have any of the following values :</p> <ul style="list-style-type: none"> <li>- cornea opacity equal to or greater than 2 but less than 3,</li> <li>- iris lesion equal to or greater that 1 but not greater than 1.5,</li> <li>- redness of the conjunctivae equal to or greater than 2.5,</li> <li>- oedema of the conjunctiva (chemosis) equal to or greater than 2,</li> </ul> <p>or, in the case where the Annex V test has been completed using three animals if the lesions, on two or more animals, are equivalent to any of the above values except that for iris lesion the value should be equal to or greater than 1 but less than 2 and for redness of the conjunctivae the value should be equal to or greater than 2.5.</p> <p>In both cases all scores at each of the reading times (24, 48 and 72 hours) for an effect should be used in calculating the respective mean values.</p> <ul style="list-style-type: none"> <li>- Substances or preparations which cause significant ocular lesions, based on practical experience in humans.</li> <li>- Organic peroxides except where evidence to the contrary is available.</li> </ul>	
<b>Correlation</b>	Irreversible effects	Reversible effects	
<b>GHS</b>	<b>Category 1</b> (irreversible effects on the eye)	<b>Category 2 A</b> (irritating to eyes)	<b>Category 2B</b> (mildly irritating to eyes)  OPTIONAL
<b>Description</b>	At least in 1 animal effects on the cornea, iris or conjunctiva not expected to, or have not fully reversed within an observation period of 21 days and/or at least in 2 of 3 test animals a positive response of: corneal opacity $\geq 3$ and/or iritis $> 1.5$ calculated on the mean scores following grading at 24, 48 and 72 hours after installation of the test material.	At least in 2 of 3 tested animals a positive response of: corneal opacity $\geq 1$ and/or iritis $\geq 1$ and/or conjunctival redness $\geq 2$ , and/or conjunctival oedema (chemosis) $\geq 2$ calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days.	When the effects listed in Category 2 A fully reverse within 7 days of observation

## 8. Respiratory Sensitisation

<b>EU</b>	<b>Xn R42</b>
-----------	---------------

<b>Criteria</b>	Human evidence that the substance/preparation can induce specific respiratory hypersensitive - normally seen as asthma, rhinitis and alveolitis - or where there are positive results from appropriate animal tests, or in case the substance is an isocyanate unless there is evidence that the specific isocyanate does not cause respiratory hypersensitivity.
-----------------	---

<b>GHS</b>	<b>Category 1</b>
------------	-------------------

<b>Criteria</b>	<ul style="list-style-type: none"><li>- If there is evidence in humans that the substance can induce specific respiratory hypersensitivity and/or</li><li>- if there are positive results from an appropriate animal test.</li></ul>
-----------------	--

## 9. Skin Sensitisation

<b>EU</b>	<b>Xi R43</b>
-----------	---------------

<b>Criteria</b>	If practical experience shows that the substance/preparation may be capable of inducing sensitisation by skin contact in a <i>substantial number</i> of persons, or where there are positive results from an appropriate animal test
-----------------	--

<b>GHS</b>	<b>Category 1</b>
------------	-------------------

<b>Criteria</b>	<ul style="list-style-type: none"><li>- If there is evidence in humans that the substance can induce sensitization by skin contact in a substantial number of persons or</li><li>- if there are positive results from an appropriate animal test.</li></ul>
-----------------	---

## 10. Mutagenic Substances

<b>EU</b>	<b>Category 1 T R46</b>	<b>Category 2 T R46</b>	<b>Category 3 Xn R68</b>
<b>Criteria</b>	<p><b>Substances <i>known to be mutagenic to man.</i></b></p> <p>There is sufficient evidence to establish a causal association between human exposure to a substance and heritable genetic damage.</p>	<p><b>Substances which <i>should be regarded as if they are mutagenic to man.</i></b></p> <p>There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in the development of heritable genetic damage, generally on the basis of :</p> <ul style="list-style-type: none"> <li>- appropriate animal studies,</li> <li>- other relevant information.</li> </ul>	<p><b>Substances which <i>cause concern for man owing to possible mutagenic effects.</i></b></p> <p>There is evidence from appropriate mutagenicity studies, but this is insufficient to place the substance in Category 2.</p>

R46 May cause heritable genetic damage

R68 Possible risk of irreversible effects

	<b>Category 1</b>		<b>Category 2</b>
<b>GHS</b>	<b>Category 1A</b>	<b>Category 1B</b>	
<b>Criteria</b>	<p><b>Chemicals <i>known to induce heritable mutations in germ cells of humans.</i></b></p> <p>Positive evidence from human epidemiological studies.</p>	<p><b>Chemicals which <i>should be regarded as if they induce heritable mutations in germ cells of humans.</i></b></p> <ul style="list-style-type: none"> <li>- Positive result(s) from <i>in vivo</i> heritable germ cell mutagenicity tests in mammals; or</li> <li>- Positive result(s) from <i>in vivo</i> somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. This supporting evidence may, for example, be derived from mutagenicity/genotoxicity tests in germ cells <i>in vivo</i>, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or</li> <li>- Positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people.</li> </ul>	<p><b>Chemicals which <i>cause concern for man owing to the possibility that they may induce heritable mutations in germ cells of humans</i></b></p> <p>Positive evidence obtained from experiments in mammals and/or in some cases from <i>in vitro</i> experiments, obtained from:</p> <ul style="list-style-type: none"> <li>- Somatic cell mutagenicity tests <i>in vivo</i>, in mammals; or</li> <li>- Other <i>in vivo</i> somatic cell genotoxicity tests which are supported by positive results from <i>in vitro</i> mutagenicity assays.</li> </ul> <p><b>Note :</b></p> <ul style="list-style-type: none"> <li>- Chemicals which are positive in <i>in vitro</i> mammalian mutagenicity assays, and which also show chemical structure activity relationship to known germ cell mutagens, should be considered for classification as Category 2 mutagens.</li> </ul>

## 11. Carcinogenic Substances

<b>EU</b>	<b>Category 1 T R45 &amp; T R49</b>	<b>Category 2 T R45 &amp; T R49</b>	<b>Category 3 Xn R40</b>
-----------	-------------------------------------	-------------------------------------	--------------------------

<b>Criteria</b>	<p><b>Substances <i>known</i> to be carcinogenic to man.</b></p> <p>There is sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer.</p>	<p><b>Substances <i>which should be regarded as if they are</i> carcinogenic to man.</b></p> <p>There is sufficient evidence to provide a strong presumption that human exposure to a substance may result in the development of cancer, generally on the basis of:</p> <ul style="list-style-type: none"> <li>- appropriate long-term animal studies,</li> <li>- other relevant information.</li> </ul>	<p><b>Substances which <i>cause concern</i> for man owing to possible carcinogenic effects.</b></p> <p>Substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment. There is some evidence from appropriate animal studies, but this is insufficient to place the substance in Category 2.</p>
-----------------	---	--	---

R45 = may cause cancer -

R49 = may cause cancer by inhalation

R40 Limited evidence of a carcinogenic effect

<b>GHS</b>	<b>Category 1</b>		<b>Category 2</b>
	<b>Category 1A</b>	<b>Category 1B</b>	

<b>Criteria</b>	<p><b>Chemicals <i>known</i> to have carcinogenic potential for humans.; the placing of a chemical is largely based on human evidence</b></p>	<p><b>Chemicals <i>presumed</i> to have carcinogenic potential for humans; the placing of a chemical is largely based on animal evidence</b></p> <p>Based on strength of evidence together with additional considerations, such evidence may be derived from human studies that establish a causal relationship between human exposure to a chemical and the development of cancer (known human carcinogen). Alternatively, evidence may be derived from animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen). In addition, on a case by case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals.</p>	<p><b>Suspected human carcinogens</b></p> <p>The placing of a chemical in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the chemical in Category 1. Based on strength of evidence together with additional considerations, such evidence may be from either limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.</p>
-----------------	---	---	--

## 12. Substances Toxic for Reproduction

EU	Category 1 T R60 & T R61	Category 2 T R60 & T R61	Category 3 Xn R62 & R63
Criteria	<p><b>Substances <i>known</i> to impair fertility in humans or to cause developmental toxicity in humans. (Sufficient evidence from human exposure)</b></p> <p>There is sufficient evidence to establish a causal relationship between human exposure to the substance and impaired fertility or</p> <p>There is sufficient evidence to establish a causal relationship between human exposure to the substance and subsequent developmental toxic effects in the progeny.</p>	<p><b>Substances which <i>should be regarded as if they impair fertility to humans or cause developmental toxicity in humans.</i></b></p> <ul style="list-style-type: none"> <li>- <i>Substances which should be regarded as if they impair fertility in humans.</i> There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in impaired fertility on the basis of:               <ul style="list-style-type: none"> <li>- clear evidence in animal studies of impaired fertility in the absence of toxic effects, or, evidence of impaired fertility occurring at around the same dose levels as other toxic effects but which is not a secondary non-specific consequence of the other toxic effects.</li> <li>- other relevant information.</li> </ul> </li> <li>- <i>Substances which should be regarded as if they cause developmental toxicity to humans</i></li> </ul> <p>There is sufficient evidence to provide a strong presumption that human exposure to the substance may result developmental toxicity, generally on the basis of:</p> <ul style="list-style-type: none"> <li>- clear results in appropriate animal studies where effects have been observed in the absence of signs of marked maternal toxicity, or at around the same dose levels as other toxic effects but which are not a secondary non-specific consequence of the other toxic effects.</li> <li>- other relevant information.</li> </ul>	<p><b>Substances which <i>cause concern</i> for human fertility or to possible developmental toxic effects</b></p> <ul style="list-style-type: none"> <li>- <i>Substances which cause concern for human fertility</i></li> </ul> <p>Generally on the basis of:</p> <ul style="list-style-type: none"> <li>- results in appropriate animal studies which provide sufficient evidence to cause a strong suspicion of impaired fertility in the absence of toxic effects, or evidence of impaired fertility occurring at around the same dose levels as other toxic effects, but which is not a secondary non-specific consequence of the other toxic effects, but where the evidence is insufficient to place the substance in Category 2.</li> <li>- other relevant information.</li> </ul> <p>- <i>Substances which cause concern for humans owing to possible developmental toxic effects</i></p> <p>Generally on the basis of:</p> <ul style="list-style-type: none"> <li>- results in appropriate animal studies which provide sufficient evidence to cause a strong suspicion of developmental toxicity in the absence of signs of marked maternal toxicity, or at around the same dose levels as other toxic effects but which are not a secondary non-specific consequence of the other toxic effects, but where the evidence is insufficient to place the substance in Category 2,</li> <li>- other relevant information.</li> </ul>

R60 = may impair fertility - R62 = possible risk of impaired fertility  
 R61 = may cause harm to the unborn child - R63 = possible risk of harm to unborn child

GHS	Category 1		Category 2
	Category 1A	Category 1B	
Criteria	<p><b>Chemicals <i>known</i> human reproductive toxicant</b></p> <p>The placing of the substance in this category is largely based on evidence that the substance produced an adverse effect on sexual function and fertility or on development in humans.</p>	<p><b>Chemicals <i>presumed</i> human reproductive toxicant</b></p> <p>The placing of substances in this category is largely based on evidence from experimental animals. Data from animal studies should provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.</p>	<p><b>Chemicals <i>suspected</i> human reproductive toxicant</b></p> <p>This category includes substances for which there is some evidence from humans or experimental animals, - possibly supplemented with other information – of an adverse effect on sexual function and fertility, or on development, in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects, and where the evidence is not sufficiently convincing to place the substance in Category 1. For instance, deficiencies in the study may make the quality of evidence less convincing, and in view of this Category 2 be the more appropriate classification.</p>

### 13. Effect during Lactation

EU

R64

**Criteria**

Substances which are classified as toxic to reproduction and which also cause concern due to their effects on lactation should in addition be labelled with R64 .

For the purpose of classification, toxic effects on offspring resulting only from exposure via the breast milk, or toxic effects resulting from direct exposure of children will not be regarded as "Toxic to reproduction", unless such effects result in impaired development of the offspring.

Substances which are not classified as toxic to reproduction but which cause concern due to toxicity when transferred to the baby during the period of lactation should be labelled with R64. This R-phrase may also be appropriate for substances which affect the quantity or quality of the milk.

For substances and preparations which are absorbed by women and may interfere with lactation or which may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of the breastfed child.

R64 would normally be assigned on the basis of:

- (a) toxicokinetic studies that would indicate the likelihood that the substance would be present in potentially toxic levels in breast milk; and/or
- (b) on the basis of results of one or two generation studies in animals which indicate the presence of adverse effects on the offspring due to transfer in the milk; and/or
- (c) on the basis of evidence in humans indicating a risk to babies during the lactational period.

Substances which are known to accumulate in the body and which subsequently may be released into milk during lactation may be labelled with R33 and R64.

R64 May cause harm to breastfed babies

GHS

Effects on or via lactation.

**Criteria**

Effects on or via lactation are allocated to a separate single category. It is appreciated that for many substances there is no information on the potential to cause adverse effects on the offspring via lactation.

However substances which are absorbed by women and have been shown to interfere with lactation, or which may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child, should be classified to indicate this property hazardous to breastfed babies.

This classification can be assigned on the basis of:

- (a) absorption, metabolism, distribution and excretion studies that would indicate the likelihood the substances would be present in potentially toxic levels in breast milk; and/or
- (b) results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or
- (c) human evidence indicating a hazard to babies during the lactation period.

## 14. Specific Target Organ Systemic Toxicity - Single Exposure

EU	T <sup>+</sup> , R39	T, R39	Xn, R68	R37, R67
<b>Criteria</b>	<p><b>R39 Danger of very serious irreversible effects</b></p> <ul style="list-style-type: none"> <li>- Strong evidence that irreversible damage other than the effects than CMR is likely to be caused by a single exposure by an appropriate route, generally in the below mentioned dose range.</li> <li>- oral, rat <math>\leq 25</math> mg/kg (bodyweight)/day,</li> <li>- dermal, rat or rabbit <math>\leq 50</math> mg/kg (bodyweight)/day,</li> <li>- inhalation, rat (gas, vapour) <math>\leq 0.5</math> mg/litre/4 hr,</li> <li>- inhalation, rat (aerosols or particulates) <math>\leq 0.25</math> mg/litre/4 hr.</li> </ul>	<p><b>R39 Danger of very serious irreversible effects</b></p> <ul style="list-style-type: none"> <li>- Strong evidence that irreversible damage other than the effects than CMR is likely to be caused by a single exposure by an appropriate route, generally in the below mentioned dose range.</li> <li>- oral, rat <math>&gt;25 - \leq 200</math> mg/kg (bodyweight)/day,</li> <li>- dermal, rat or rabbit <math>&gt;50 - \leq 400</math> mg/kg (bodyweight)/day,</li> <li>- inhalation, rat (gas, vapour) <math>&gt; 0.5 - \leq 2</math> mg/litre/4 hr,</li> <li>- inhalation, rat (aerosols or particulates) <math>&gt; 0.25 - \leq 1</math> mg/litre/4 hr.</li> </ul>	<p><b>R68 Possible risk of irreversible effects</b></p> <ul style="list-style-type: none"> <li>- Strong evidence that irreversible damage other than the CMR effects is likely to be caused by a single exposure by an appropriate route, generally in the below mentioned dose range.</li> <li>- oral, rat <math>&gt; 200 - \leq 2000</math> mg/kg (bodyweight)/day,</li> <li>- dermal, rat or rabbit <math>&gt; 400 - \leq 2000</math> mg/kg (bodyweight)/day,</li> <li>- inhalation, rat (gas, vapour) <math>&gt; 2 - \leq 20</math> mg/litre/4 hr,</li> <li>- inhalation, rat (aerosols or particulates) <math>&gt; 1 - \leq 5</math> mg/litre/4 hr.</li> </ul>	<p><b>R37 Irritating to respiratory system.</b></p> <p><b>Substances and preparations which cause serious irritation to the respiratory system</b> based on:</p> <ul style="list-style-type: none"> <li>- practical observation in humans</li> <li>- positive results from appropriate animal tests.</li> </ul> <p>Comments regarding the use of R37</p> <p>In interpreting practical observations in humans, care should be taken to distinguish between effects which lead to classification with R48 from those leading to classification with R37. Conditions normally leading to classification with R37 are reversible and usually limited to the upper airways.</p> <p>Positive results from appropriate animal tests may include data obtained in a general toxicity test, including histopathological data from the respiratory system. Data from the measurement of experimental bradypnea may also be used to assess airway irritation.</p> <p><b>R67 Vapours may cause drowsiness and dizziness.</b></p> <p><b>For volatile substances and preparations containing such substances which cause clear symptoms of central nervous system depression by inhalation and which are not already classified with respect to acute inhalation toxicity (R20, R23, R26, R68/20, R39/23 or R39/26).</b></p> <p>The following evidence may be used:</p> <p>(a) Data from animal studies showing clear signs of CNS depression such as narcotic effects, lethargy, lack of coordination (including loss of righting reflex) and ataxia either:</p> <ul style="list-style-type: none"> <li>- at concentrations/exposure times not exceeding 20 mg/l/4 h or,</li> <li>- for which the ratio of the effect concentration at = 4 h to the saturated vapour concentration (SVC) at 20°C is =1/10.</li> </ul> <p>(b) Practical experience in humans (e.g. narcosis, drowsiness, reduced alertness, loss of reflexes, lack of coordination, vertigo) from well documented reports under comparable exposure conditions to the effects specified above for animals.</p>

GHS	Category 1	Category 2	Category 3
Criteria	<p><b>Substances that have produced significant toxicity in humans, or that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to produce significant toxicity in humans following single exposure.</b></p> <p>Placing a substance in Category 1 is done on the basis of:</p> <ul style="list-style-type: none"> <li>- reliable and good quality evidence from human cases or epidemiological studies;</li> </ul> <p>or,</p> <ul style="list-style-type: none"> <li>- observations from appropriate studies in experimental animals in which significant and/or severe toxic effects of relevance to human health were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below to be used as part of weight-of-evidence evaluation.</li> <li>- oral, rat <math>\leq 300</math> mg/kg (bodyweight)/day,</li> <li>- dermal, rat or rabbit <math>\leq 1000</math> mg/kg (bodyweight)/day,</li> <li>- inhalation, rat (gas) <math>\leq 2500</math> ppm,</li> <li>- inhalation, rat (vapour) <math>\leq 10</math> mg/litre,</li> <li>- inhalation, rat (dust/mist/fume) <math>\leq 1</math> mg/litre/4hr</li> </ul>	<p><b>Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following single exposure.</b></p> <p>Placing a substance in Category 2 is done on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below in order to help in classification.</p> <ul style="list-style-type: none"> <li>- oral, rat <math>&gt; 300 - \leq 2000</math> mg/kg (bodyweight)/day,</li> <li>- dermal, rat or rabbit <math>&gt; 1000 - \leq 2000</math> mg/kg (bodyweight)/day,</li> <li>- inhalation, rat (gas) <math>&gt; 2500 - \leq 5000</math> ppm,</li> <li>- inhalation, rat (vapour) <math>&gt; 10 - &lt; 20</math> mg/litre,</li> <li>- inhalation, rat (dust/mist/fume) <math>&gt; 1 - &lt; 5</math> mg/litre/4hr</li> </ul> <p>In exceptional cases, human evidence can also be used to place a substance in Category 2.</p>	<p><b>Transient target organ effects.</b></p> <p>There are target organ effects for which a substance/mixture may not meet the criteria to be classified in Categories 1 or 2 indicated above. These effects which adversely alter human function for a short duration after exposure and from which humans may recover in a reasonable period without leaving significant alteration of structure or function. This category only includes narcotic effects and respiratory tract irritation.</p> <p>Note : Guidance values are not provided since this classification is primarily based on human data. Animal data may be included in the weight of evidence evaluation.</p>

## 15. Specific Target Organ Systemic Toxicity-Repeated Exposure

<b>EU</b>	<b>T R48</b>	<b>Xn R48</b>
<b>Criteria</b>	<p>Serious damage (clear functional disturbance or morphological change which have toxicological significance) is likely to be caused by repeated or prolonged exposure by an appropriate route.</p> <p>Substances and preparations are classified at least as Toxic when these effects are observed at levels of the order of :</p> <ul style="list-style-type: none"> <li>- oral, rat <math>\leq 5</math> mg/kg (bodyweight)/day,</li> <li>- dermal, rat or rabbit <math>\leq 10</math> mg/kg (bodyweight)/day,</li> <li>- inhalation, rat <math>\leq 0.025</math> mg/l, 6hr/day.</li> </ul> <p>These guide values can apply directly when severe lesions have been observed in a sub-chronic (90 day) toxicity test. When interpreting the results of a sub-acute (28 day) toxicity test these figures should be increased approximately three fold.</p>	<p>Serious damage (clear functional disturbance or morphological change which has toxicological significance) is likely to be caused by repeated or prolonged exposure by an appropriate route.</p> <p>Substances and preparations are classified at least as harmful when these effects are observed at levels of the order of :</p> <ul style="list-style-type: none"> <li>- oral, rat <math>&gt; 5 - \leq 50</math> mg/kg (bodyweight)/day,</li> <li>- dermal, rat or rabbit <math>&gt; 10 - \leq 100</math> mg/kg (bodyweight)/day,</li> <li>- inhalation, rat <math>&gt; 0.025 - \leq 0.25</math> mg/l, 6hr/day.</li> </ul> <p>These guide values can apply directly when severe lesions have been observed in a sub-chronic (90 day) toxicity test. When interpreting the results of a sub-acute (28 day) toxicity test these figures should be increased approximately three fold</p>
<b>GHS</b>	<b>Category 1</b>	<b>Category 2</b>
<b>Criteria</b>	<p><b>Substances that have produced significant toxicity in humans, or that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to produce significant toxicity in humans following repeated exposure</b></p> <p>Placing a substance in Category 1 is done on the basis of :</p> <ul style="list-style-type: none"> <li>- reliable and good quality evidence from human cases or epidemiological studies; or,</li> <li>- observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below to be used as part of weight-of-evidence evaluation.</li> <li>- oral, rat <math>\leq 10</math> mg/kg (bodyweight)/day,</li> <li>- dermal, rat or rabbit <math>\leq 20</math> mg/kg (bodyweight)/day,</li> <li>- inhalation, rat (gas) <math>\leq 50</math> ppm/6 hr/day,</li> <li>- inhalation, rat (vapour) <math>\leq 0.2</math> mg/litre/6 hr/day,</li> <li>- inhalation, rat (dust/mist/fume) <math>\leq 0.02</math> mg/litre/6 hr/day,</li> </ul>	<p><b>Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated exposure.</b></p> <p>Placing a substance in Category 2 is done on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration range values are provided below in order to help in classification.</p> <ul style="list-style-type: none"> <li>- oral, rat <math>&gt; 10 - \leq 100</math> mg/kg (bodyweight)/day,</li> <li>- dermal, rat or rabbit <math>&gt; 20 - \leq 200</math> mg/kg (bodyweight)/day,</li> <li>- inhalation, rat (gas) <math>&gt; 50 - \leq 250</math> ppm/6 hr/day,</li> <li>- inhalation, rat (vapour) <math>&gt; 0.2 - \leq 1</math> mg/litre/6 hr/day,</li> <li>- inhalation, rat (dust/mist/fume) <math>&gt; 0.02 - \leq 0.2</math> mg/litre/6 hr/day,</li> </ul> <p>In exceptional cases human evidence can also be used to place a substance in Category 2.</p>

## 16. Effects on the aquatic Environment

### Acute hazard categories toxicity

EU	N; R50	[N, R51 Does not exist individual]	[R52 based on specified cut-offs for acute toxicity does not exist individual]
GHS	Category : Acute I	Category : Acute II	Category : Acute III
96 hr LC <sub>50</sub> (fish) 48 hr EC <sub>50</sub> (crustacea/daphnia) 72 hr or 96 hr ErC <sub>50</sub> (algae/aquatic plants)	≤ 1 mg/L	> 1 - ≤ 10 mg/L	>10 - ≤ 100 mg/L

### Chronic hazard categories toxicity

EU	N; R50-53	N; R51-53	R52-53	
96 hr LC <sub>50</sub> (fish) 48 hr EC <sub>50</sub> (daphnia) 72 hr IC <sub>50</sub> (algae)	≤ 1 mg/L	> 1 - ≤ 10 mg/L	> 10 - ≤ 100 mg/L	
<ul style="list-style-type: none"> <li>- <b>Readily</b> degradability, or</li> <li>- Potential to bioaccumulate:                             <ul style="list-style-type: none"> <li>- log <b>Pow</b>, unless</li> <li>- BCF</li> </ul> </li> <li>- Unless chronic toxicity NOEC</li> </ul>	No  ≥ 3 ≤ 100	No  ≥ 3 ≤ 100	No   > 1 mg/L	
GHS	Category : Chronic I	Category : Chronic II	Category : Chronic III	
96 hr LC <sub>50</sub> (fish) 48 hr EC <sub>50</sub> ( <b>crustacea</b> ) 72 hr or 96 hr ErC <sub>50</sub> (algae/aquatic plants)	≤ 1 mg/L	> 1 - ≤ 10 mg/L	> 10 - ≤ 100 mg/L	
<ul style="list-style-type: none"> <li>- <b>Rapidly</b> degradability, and/or</li> <li>- Potential to bioaccumulate:                             <ul style="list-style-type: none"> <li>- log <b>Kow</b>, unless</li> <li>- BCF</li> </ul> </li> <li>- Unless chronic toxicity NOECs</li> </ul>	No  ≥ 4 ≤ 500 -	No  ≥ 4 ≤ 500 > 1 mg/L	No  ≥ 4 ≤ 500 > 1 mg/L	



### 'Safety net'

Substances not falling under the criteria listed above, but which, on the basis of the available evidence concerning their toxicity (R52), persistence to accumulate, and predicted or observed environmental fate and behaviour (R53) may nevertheless present a danger to the structure and/or functioning of aquatic ecosystems.

EU	R52	R53
<ul style="list-style-type: none"><li>- Water solubility (<math>S_w</math>) and</li><li>- <b>Readily</b> degradability, and</li><li>- Potential to bioaccumulate:<ul style="list-style-type: none"><li>- log <b>Pow</b>, unless</li><li>- BCF</li></ul></li><li>- Unless chronic toxicity NOEC</li></ul>	The precise criteria are not defined.	The precise criteria are not defined with one exception:  $< 1 \text{ mg/l}$ <u>No</u>  $\geq 3$ $\leq 100$ $> 1 \text{ mg/l}$

The system introduces as "safety net" classification for use when the data available do not allow classification under the formal criteria but there are nevertheless some grounds for concern (Chronic IV).

GHS	Category : Chronic IV
<ul style="list-style-type: none"><li>- Water solubility (<math>S_w</math>)</li><li>- <b>Rapidly</b> degradability, and/or</li><li>- Potential to bioaccumulate:<ul style="list-style-type: none"><li>- log <b>Kow</b>, unless</li><li>- BCF</li></ul></li><li>- Unless chronic toxicity NOECs</li></ul>	The precise criteria are not defined with one exception:  $< 1 \text{ mg/l}$ No  $\geq 4$ $\leq 500$ $> 1 \text{ mg/l}$

## Remarks on the Aquatic Environment hazards:

1. The boxes above are presented in a way that will show the main difference between the current EU system and GHS. However, in order to make a good comparison between the two systems it is necessary to go beyond the tables (given in Annex VI of the current substance directive and Chapter 4.1 in GHS) and actually compare the whole Chapter 5 of Annex VI in the current legislation with Chapter 4.1 of GHS. To fully understand the criteria and how they are meant to be applied it is even necessary to take notice of the guidance given in Annex 9 of GHS.
2. Despite what the tables given in figure 4.1.1 (GHS) says it should be emphasised that we are dealing with hazard classification systems and not toxicity classification systems.
3. The Acute Category I (GHS) may be further sub-divided to include an additional category for acute toxicity  $L(E)C_{50} < 0.1 \text{ mg/L}$ . However, as explained in para 4.1.2.4 it is anticipated that their use would be restricted to regulatory systems concerning bulk transport. It is equally explained in para A9.2.1 that Acute Categories II and III are not normally used when considering packaged goods, which leaves us regarding Supply and Use with to very similar systems.
4. Although the EU and GHS criteria for the hazards on the aquatic environment are practically the same ( 3 classes of acute toxicity, based on the 96 hr  $LC_{50}$ , 48 hr  $EC_{50}$  and 72-96 hr  $ER_{50}$  values) therethere are some small differences:
  - EU criteria refer to uses Daphnia whereas for the 48 hr Medium Lethal Concentration  $EC_{50}$ , whereas GHS refer to uses cCrustacea as test organisms.
  - EU criteria refer to “readily” v whereass. GHS refer to “rapidly” degradability. However, the definition for both terms is for classification purposes identical. (\*)
  - The potential for bioaccumulation - determined by using the octanol/water partition coefficient - is reported as log “Pow” by the EU, whereas the GHS criteria refer to log “Kow”. Again, the definition for both terms is for classification purposes identical. More important is the change from 3 to 4, i.e. (EU criteria refer to “log Pow  $\geq 3$ ” whereas GHS refer tovs. “log Kow  $\geq 4$ ”.)
  - EU criteria refer to a BCF of 100 whereas GHS refer to a BCF of 500. Here it is important to notice that the tables in both system only refer to BCF as an escape clause (i.e. unless BCF  $< 100$  vs.  $< 500$ ). Regarding industrial self-classification, this has in EU sometimes been interpreted in a way that the criteria for bioaccumulation are not fulfilled by a BCF above this cut off level when log Pow is below 3. It can be concluded from the guidance given in A9.5.2.3 that this is a miss interpretation of the criteria and could easily be clarified in any of the systems by reversing the phrase related to BCF, e.g.:
    - “and
    - the substance is not rapidly degradable
    - and/or
    - the experimentally determined BCF  $\geq 500$  or, if absent, the log  $K_{ow} \geq 4$  (unless the experimentally determined BCF  $< 500$ ).”
  - As safety net classification, EU criteria refer to two different risk-phrases whereas GHS refers only to one hazard category.

(The hazard category “Chronic IV” in GHS could be seen as covering both safety net classifications in the EU system (R52 as well as R53). Furthermore, the safety net classifications in any of the systems can not be directly compared with any of the categories presented in the formal criteria. E.g. It is not possible to say that substances falling under these criteria are less (or more) hazardous than substances falling in any of the categories under the formal criteria.)

Generally the EU system combines the acute with the chronic toxicity; the GHS puts them in separate classes.

The EU has no individual class for R51. As this class seems to correspond with the GHS “Class: Acute II”, the EU class “R51” was put in square brackets in the GHS column “Class: Acute II”.

### EU Risk-phrases:

R50: Very toxic to aquatic organisms.

R51: Toxic to aquatic organisms.

R52: Harmful to aquatic organisms.

R53: May cause long-term adverse effects in the aquatic environment.

### Comparable Hazard statements given in GHS:

• Very toxic to aquatic life.

• Toxic to aquatic life.

• Harmful to aquatic life.

• May cause long lasting harmful effects to aquatic life.

(<sup>1</sup>) See Dir.92/32/EEC of 30 April 1992, Annex VI Sect. 5.2.1.3 and OECD Document "Harmonized Integrated Hazard Classification System for Human Health and Environmental Effects of Chemical Substances" endorsed by the 28<sup>th</sup> Joint Meeting of the Chemicals Committee and the Working Party on Chemicals in November 1998