Reproductive toxicity – classification under CLP

(Regulation (EC) no 1272/2008 on **C**lassification, **L**abelling and **P**ackaging of chemicals)

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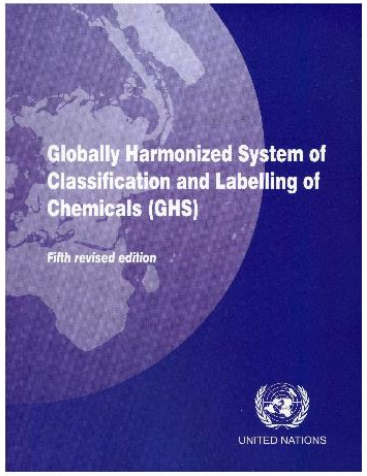
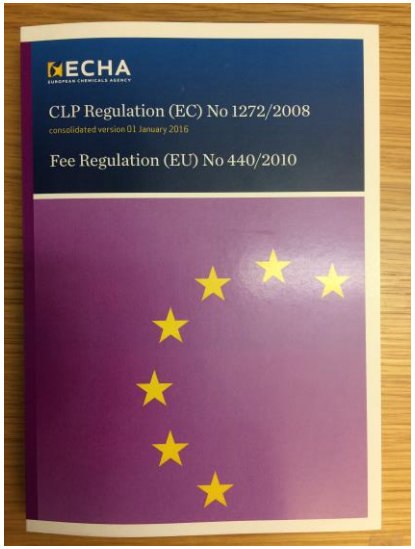
Legal framework for classification and labelling in the EU - CLP Regulation



- Harmonised criteria for C&L carefully developed over 12 years, adopted within the United Nations structure
  ⇨ the Globally Harmonised System of Classification and Labelling of Chemicals (GHS).

- CLP is based on GHS and implements GHS within the EU.



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REGULATION (EC) No 1272/2008 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 16 December 2008

on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission,

Having regard to the opinion of the European Economic and Social Committee [1],

Acting in accordance with the procedure laid down in Article 251 of the Treaty [2],

Hazard classification

- Aims to identify hazardous properties of chemicals
- Information about the **intrinsic properties** of a substance or mixture is evaluated by applying the criteria for classification in order to determine its potential to cause harm.
- Should not be confused with risk assessment.

➡ Does not take exposure into consideration.

hazard x exposure = risk (GHS 1.1.2.6.2.1)

Hazard classification

Decision to classify (Article 9(3), 13, and (33), CLP)

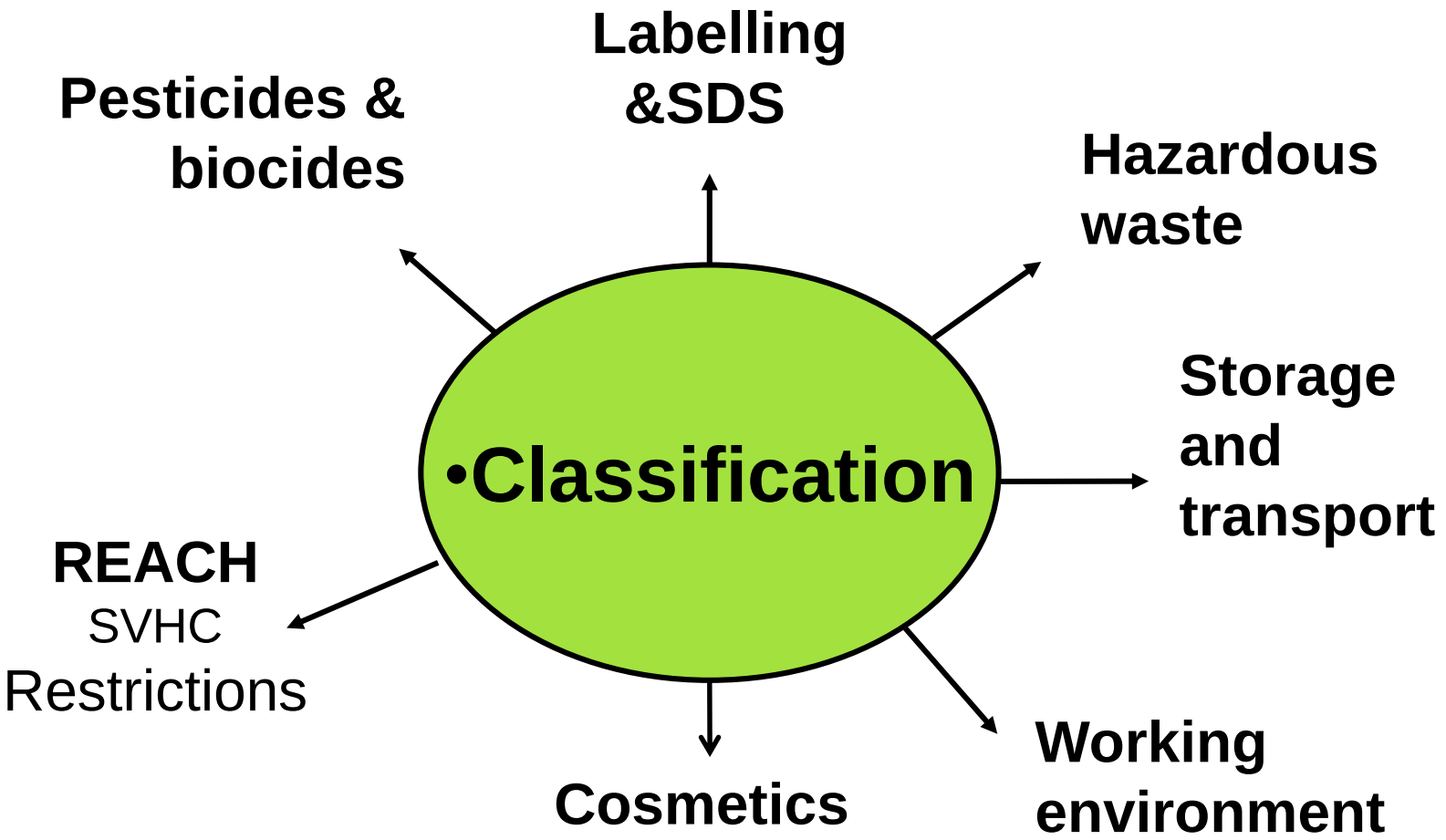
- If the evaluation shows that the physical, human health and environmental hazards associated with the substance or mixture **meet the criteria** for classification, manufacturers/importers/downstream users shall classify the substance or mixture by assigning:

  - hazard category or categories for each hazard class or differentiation, and

  - hazard statement(s)

- Where the criteria cannot be applied directly to available identified information (e.g. when the application is not straightforward or simple), the **weight of evidence** determination using **expert judgement** shall be applied when evaluating if the criteria are met.

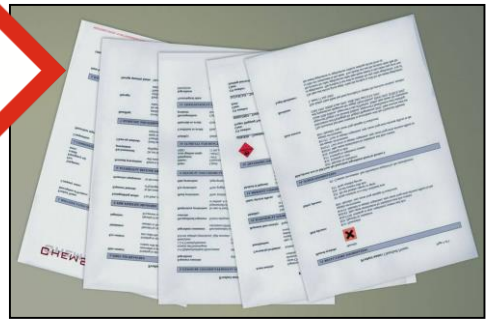
Risk management measures based on classification - other legislations



Why to label?

- The user has the need and right to know the hazards (i.e. classification) in order to protect him/herself and others (e.g. a child), and the environment.

- Thus, anyone who places a substance or mixture on the market* needs to classify and label with hazard information.



⇨ communication of hazard(s)!

*or makes available to a third party

Classification

- A supplier must classify and label a substance or mixture before placing it on the market

- A supplier must him/herself classify a substance or mixture according to the CLP criteria *except when the substance has an EU harmonised classification and labelling (CLH)*

EU harmonised classification and labelling (CLH)

For the following cases, an EU harmonised legally binding classification should normally be agreed upon and included in Annex VI, CLP:

- active substances in PPP (pesticide) or BP (biocide) Regulation.

- other substances
  - fulfilling the CLP criteria for
    - respiratory sensitisation, category 1
    - germ cell mutagenicity, category 1A, 1B or 2
    - carcinogenicity, category 1A, 1B or 2 and/or
    - **reproductive toxicity, category 1A, 1B or 2**
  - case-by-case for other hazards, when justification is provided demonstrating the need for a harmonised action at Community level.

CLH process overview (CLP Art. 37)

Main actors:

- Dossier submitter **(Member states Competent Authority (CA) or Industry)** - submits their intention for a CLH proposal to ECHA's Registry of Intentions (RoI)
- Dossier submitter
- Parties Concerned including IND, other MSCAs, individuals and NGOs
- **ECHA/Committee for Risk Assessment (RAC)**
- European Commission
- ECHA Secretariat support

Stakeholders are observers.

18 months legally binding deadline to adopt a RAC opinion

ECHA's Committee for Risk Assessment = RAC

The RAC members

- are appointed by ECHA's Management Board based on candidates nominated by the Members States for a renewable term of three years. (REACH Art. 85)
- make a declaration of commitment to fulfil their duties and a declaration of interests. (REACH Art. 88)
- may be accompanied by advisers.

What is Reproductive toxicity under CLP?
(CLP Annex I, 3.7)

Reproductive toxicity is divided into two main types of effects:

- **Adverse effects on sexual function and fertility** in adult males and females
- **Adverse effects on development** of the offspring (non-inheritable effects)

In addition:

- Effects on or via **lactation**

Adverse effects on sexual function and fertility

(CLP Annex I, 3.7.1.3)

Any effect that has the potential to interfere with sexual function and fertility including:

- alterations to the female and male reproductive system

- adverse effects on
  - onset of puberty
  - gamete production and transport
  - reproductive cycle normality
  - sexual behaviour
  - fertility
  - parturition
  - pregnancy outcomes
  - premature reproductive senescence, or
  - modifications in other functions that are dependent on the integrity of the reproductive systems

Adverse effects on development of the offspring

(CLP Annex I, 3.7.1.4)

- In its widest sense any effect interfering with normal development of the conceptus, before or after birth, resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, to the time of sexual maturation. These effects can be manifested at any time point in the life span.
- Major manifestations:
  - **death of the developing organism**
  - **structural abnormality**
  - **altered growth**
  - **functional deficiency**.

- Primarily intended to provide a hazard warning for pregnant women, and for men and women of reproductive capacity.

Basis of classification for reproductive toxicity

(CLP Annex I, 3.7.2.2)

- Assessment of the total weight of evidence in order to make a comparison with the criteria.
- Intended to be used for substances which have an intrinsic, specific property to produce an adverse effect on reproduction.
- In the evaluation of toxic effects on the developing offspring, important to consider the possible influence of maternal toxicity.
- No classification if reproductive toxicity is produced solely as a non-specific secondary consequence of other toxic effects.

Hazard categories for reproductive toxicants (CLP Annex I, 3.7.2.1.1, 3.7.2.2)

- Reproductive toxicants are allocated to one of two categories: Category 1 (1A or 1B) or 2.

- Within each category, effects on sexual function and fertility, and on development, are considered separately.

- If the substance meets the CLP criteria for both Cat. 1A/1B (e.g. sexual function and fertility) and 2 (e.g. developmental toxicity), the substance should be classified in Cat. 1A/1B and both types of hazards shall be communicated in the hazard statement.

E.g. Repr. 1B; H360**Fd** ('**May** damage fertility. **Suspected of** damaging the unborn child.')

- Effects on or via lactation are allocated to a separate hazard category irrespective if the substance is classified in any other category for reproductive toxicity or not.

Reproductive toxicity Cat. 1: known or presumed human reproductive toxicant (CLP Annex I, Table 3.7.1(a))

- **Category 1A: Known** human reproductive toxicant
  - Largely based on evidence from humans.
  - Known to have produced an adverse effect on sexual function and fertility, or on development in humans.

Reproductive toxicity Cat. 1: known or presumed human reproductive toxicant (CLP Annex I, Table 3.7.1(a))

Category 1B: Presumed human reproductive toxicant

- Largely based on data from animal studies.
- **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.
- When there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.

Reproductive toxicity Cat. 2: suspected human reproductive toxicant (CLP Annex I, Table 3.7.1(a))

- **Some evidence** from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development.

- Where the evidence is not sufficiently convincing to place the substance in Category 1.

- If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification.

- Such effects shall have been observed in the absence of other toxic effects, or <u>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</u>.

CLP criteria for effects on or via lactation (CLP Annex I, 3.7.1.5, Table 3.7.1(b))

Substances

- absorbed by women and 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.

Can be based on

- human evidence indicating a hazard to babies during the lactation period; and/or

- 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

- absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk.

Classification may not necessarily be the outcome (CLP Annex I, 3.7.2.3.3.)

- when the only effects recorded are considered to be of low or minimal toxicological significance.

- e.g. **small changes** in
  - semen parameters
  - incidence of spontaneous defects in the foetus
  - proportions of common foetal variants (such as are observed in skeletal examinations)
  - foetal weights
  - postnatal developmental assessments

Weight of evidence (WoE) assessment for reproductive toxicity (CLP Annex I, 1.1.1., 3.7.2.3.)

- All available information that bears on the determination of reproductive toxicity are considered together, e.g.:
  - epidemiological studies and case reports in humans
  - animal studies providing information regarding toxicity to reproductive and related endocrine organs
  - data on chemically related substances, particularly when information on the substance is scarce

- The weight given influenced by e.g.:
  - quality of the studies
  - consistency of results
  - nature and severity of effects
  - the presence of maternal toxicity in experimental animal studies
  - level of statistical significance for inter-group differences
  - number of endpoints affected
  - relevance of route of administration to humans
  - freedom from bias

WoE assessment for reproductive toxicity

(CLP Annex I, 1.1.1., 3.7.2.3.)

- Both positive and negative results assembled together.
- *A single, positive study* performed according to good scientific principles and with statistically or biologically significant positive results *may justify classification*.

WoE –human vs. animal data

(CLP Annex I, 1.1.1.4)

- The quality and reliability of the evidence from both sources shall be evaluated.

- Generally, **adequate, reliable and representative data** on humans shall have precedence over other data.

- However, even well-designed and conducted epidemiological studies may lack a sufficient number of subjects to detect relatively rare but still significant effects, to assess potentially confounding factors.

- Therefore, **positive results from well-conducted animal studies are not necessarily negated by the lack of positive human experience** but require an assessment of the robustness, quality and statistical power of both the human and animal data.

WoE – in vitro assays, structure-activity relationsip (SAR) (CLP Annex I, 3.7.2.5.4.)

- Evidence from *in vitro* assays, structure analogues, or non mammalian tests *can contribute* to classification.

- Evaluation of substances chemically related to the substance under study may also be included (in a WoE assessment), particularly when information on the substance is scarce. **(CLP Annex I, 3.7.2.3.1)**

WoE – Human relevance

(CLP Annex I, 1.1.1.5 and 3.7.2.1.1, 3.7.2.3.2.)

- *Toxicokinetic, site of action and mechanism or mode of action* study results may reduce or increase concerns about the hazard to human health.

- Classification in category 2 may be more appropriate (than Cat. 1B) when *mechanistic information* raises doubt about relevance in humans, as far as there is reassurance about the robustness and quality of the data.

- Should not classify:
  - if it is **conclusively demonstrated** that the clearly identified *mechanism or mode of action* has no relevance for humans (other mechanisms or MoAs must be excluded).
  - when the *toxicokinetic* differences are so marked that **it is certain** that the hazardous property expressed in experimental animals will not be expressed in humans.
- *Note:* No requirement to show the mechanism or MoA and relevance to humans in order to classify.

Parental toxicity

(CLP Guidance 3.7.2.2.1)

- Associations between parental and offspring effects do not by default prove a causal relationship.

- A comparison between the ***severity*** of the effects on fertility/development and the ***severity*** of other toxicological findings (e.g. in the mother) *must* be performed.
  - The developing organism can be more susceptible and long-term consequences can be more severe than in the adult.
  - The mother might recover while the offspring could be permanently affected.

- When **effects on the offspring can be proved to be secondary to maternal toxicity, they may still be relevant for developmental classification, dependent on the *severity* of the effects**.

Parental toxicity

(CLP Guidance 3.7.2.2.1)

- Adverse effects on sexual function and fertility seen **only** at dose levels causing **marked** systemic toxity (e.g. lethality, dramatic reduction in absolute bw, coma) are not relevant for classification.

- **Parental toxicity that is less than marked should not influence the classification for reproductive toxicity.**

- In order to determine whether a reproductive toxic effect is independent or secondary to a parental effect, it would be most appropriate to **correlate individual data for offspring and their parents**. *(See example on slide 29)*

WoE –maternal toxicity

(CLP Annex I, 3.7.2.3.4-5, 3.7.2.4.)

- Effects in embryo/foetus considered first, then maternal toxicity and other factors.
- **Maternal toxicity shall not be used to negate findings of embryo/foetal effects** unless it can be **clearly demonstrated** that the effects are **secondary non-specific** effects. This is especially the case when the effects in the offspring are significant e.g. irreversible effects such as structural malformations.

- The calculation of an adjusted (corrected) mean maternal body weight change, may indicate whether the effect is maternal or intrauterine.

See example, next slide →

- In rabbits, the body weight gain may <u>not</u> be useful indicators of maternal toxicity because of normal fluctuations in body weight during pregnancy.

- Classification shall not automatically be discounted for substances that produce developmental toxicity only in association with maternal toxicity, even if a **specific maternally-mediated mechanism** has been **demonstrated**. In such a case, classification in Category 2 <u>may</u> be considered more appropriate than Category 1.

EXAMPLE: Is the effect on post-implantation loss related to maternal toxicity (as revealed by effects on body weight)? (rat, TG 414 study)

Individual data for the high dose (HD)

Female*	Corpora lutea	Implan-tations	Embryonic deaths	Live fetuses	Corr. bw gain (GR)	
1	14	11	2	9	40,5	
2	14	14	0	14	36,6	
3	14	14	0	14	23,7	
4	9	9	3	6	37,2	
5	11	11	2	9	30,3	
6	13	13	0	13	19,9	
7	16	14	11	3	26,0	
8	15	15	9	6	18,1	
9	13	13	0	13	11,2	
10	16	14	2	12	19,0	
11	15	13	0	13	-5,5	←
12	13	13	4	9	9,3	
13	14	12	0	12	-25,6	←
14	16	16	13	3	20,2	
15	16	12	1	11	24,0	
16	14	14	0	14	-30,5	←
17	16	16	7	9	19,5	
18	14	14	9	5	22,2	
19	14	13	5	8	31,5	
20	15	14	12	2	10,2	
TOTAL			80,0	185,0		
MEAN			4,0*	9,3*	16,9	
ST.DEV.			4,5	4,0	18,8	

2 additional females were not pregnant

GROUP level (high dose vs controls):

- ↑ embryonic resorptions: 30.2% in HD vs 2.6% controls
- ↓maternal food consumption: 10% less as compared to controls
- ↓ maternal body weight gain (days 6-21 p.c., gram): 79 in HD as compared to 112 in controls, i.e. **30% lower** than the bw gain in controls (stat.analysis not done)
- ↓ corrected body weight gain (days 6–21 p.c., gram): 16.9±18.8 in HD as compared to 27.2±12.3 g in the controls, not stat.sign. i.e. **38% lower corr. bw gain in HD than in controls**

INDIVIDUAL level (high dose):

- ***No correlation*** *between effects on maternal corrected body weight gain and embryonic viability*.
- The increase in post-implantation loss should not be viewed as being a nonspecific secondary consequence of the maternal toxicity recorded in this study.

WoE – maternal toxicity

(CLP Annex I, 3.7.2.3.5, 3.7.2.4)

- Classification is not necessarily the outcome when there is/are:
  - minor developmental changes
  - only a small reduction in foetal/pup body weight or retardation of ossification

  in association with maternal toxicity

- When a substance is so toxic that maternal death or severe inanition results, or the dams are prostrate and incapable of nursing the pups, it is reasonable to assume that developmental toxicity is produced solely as a secondary (non-specific) consequence of maternal toxicity and discount the developmental effects.

- Maternal mortality greater than 10 % is considered excessive and the data for that dose level shall not normally be considered for further evaluation.

Is there a limit dose in the criteria above which no classification?

(CLP Annex I, 3.7.2.5.7-9)

- **Not included** in the CLP criteria for reproductive toxicity
  - no general agreement; may not be adequate where humans are more sensitive than the animal model due to species differences in TKs.

- A ”limit dose” is specified in some OECD test guidelines
  - Meaning *that a full study with 3 or several dose levels may not be considered necessary* if a dose of 1000 mg/kg bw/day (oral) does not produce any observable toxic effects and if toxicity would not be expected. This applies only when human exposure does not indicate the need for a higher dose level to be used. For other routes such as dermal or inhalation, phycial chemical properties of test substance may dictate maximum attainable test exposure.

- (But) *adverse effects* on reproduction *only at very high dose levels* in animal studies (e.g. that induce prostration, severe inappetence, excessive mortality) would not normally lead to classification unless indications that humans may be more susceptible.

Potency and classification

• Potency is *not* stated in the CLP criteria for distinguishing between different hazard categories for reproductive toxicants (1A,1B or 2).

• However, potency is considered for setting SCLs for a substance. **(CLP guidance 3.7.2.6 and Annex VI)**

- primarily based on *dose* causing the reproductive toxic effect. **(CLP guidance Annex VI)**

•Mixtures are classified for reproductive toxicity if they contain reproductive toxic substances at or above a generic (0.3% for Cat. 1A or 1B and 3% for Cat. 2 substances) or specific concentration limit (SCL).

Thank you!

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