National Institute for Public Health
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Classification & Labelling Introduction

Aldert H. Piersma

Center for Health Protection
RIVM Bilthoven-NL

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The European Community Classification and Labelling of Chemicals for Reproductive Toxicity

- First introduced in 1967 in the European Community with Council Directive 67/548/EEC known as the “**Dangerous Substances Directive”**.
- The Sixth Amendment to this directive in 1979 introduced a notification procedure and a requirement for labelling chemicals for toxicity.
- Three special categories for labelling were for "Carcinogenicity, Mutagenicity and Teratogenicity“ (**CMT**).

Classification and Labelling of Chemicals for Reproductive Toxicity in The European Community

- In the Seventh Amendment to the “Dangerous Substances Directive”, 1992 the classification of “Teratogenicity” was changed and expanded to "Toxic to Reproduction".
- This includes adverse effects on fertility, pre- and postnatal development and encompasses not only structural malformations but also functional deficits.
- **CMT** was changed to **CMR**
- In 1992 a warning for danger from Lactation was added: R64 “May cause harm to breast-fed babies”

REACH

- In 2007 a new chemicals control system, REACH (Registration, Evaluation, Authorisation and Restriction of CHemicals) was introduced in the EU (based on 67/548/EEC)
- Onus for safe use transferred to Industry
- Since June 2008 the European Chemicals Agency (ECHA) based in Helsinki is responsible for REACH.

GHS & CLP

- A new classification system GHS (Globally Harmonised System for Classification and Labelling of Chemicals) has been introduced by United Nations.
- GHS is integrated into REACH
- Is being implemented in EU by Regulation on Classification Labelling and Packaging (CLP) broadly similar to present system

- This classification has two major subdivisions:
  - **Effects on Male or Female Fertility**
  - **Developmental Toxicity**

CLP and Effects on Male or Female Fertility

This includes adverse effects on libido, sexual behaviour, any aspect of spermatogenesis or oogenesis, hormonal activity or physiological response which would interfere with the capacity to fertilise, fertilisation itself or the development of the fertilised ovum up to and including implantation.

CLP and Developmental Toxicity

This is taken in its widest sense to include any effect interfering with normal development which is induced prenatally and may be manifest either pre- or postnatally. This includes embryo-fetal toxicity, death, abortion, retarded development, structural (teratogenic) effects, functional defects, impaired postnatal mental and physical development up to and including normal pubertal development.

Classification of chemicals Toxic to Reproduction

- Chemicals are only classified as toxic to reproduction when they have specific intrinsic toxic potential to adversely affect reproduction.
- That is, the effects should not merely be secondary to other toxic effects.
- i.e. Hazard (not Risk) based classification

Classification of chemicals as Toxic for Reproduction

Categorisation of Classification:

- **Category 1a** is based of human data, with evidence of reproductive toxicity to humans.
- **Category 1b** is usually on the basis of animal studies, with results suggesting that adverse effects would be likely with human exposure.
- **Category 2** (**or no classification**) is given based on less convincing data, or if there is the possibility of nonspecific effects, or with only small changes in common variants or in postnatal developmental tests.

Use of Hazard Phrases on labels for classified chemicals under CLP

H phrases under REACH/CLP

- Category 1a and 1b:
  - H360 “May damage fertility or the unborn child.”
  - H360F “May damage fertility”
  - H360D “May damage the unborn child”.
  - H360FD; H360Fd; H360Df.
- Category 2:
  - H361 “Suspected of damaging fertility or the unborn child.”
  - H361f; H361d; H361fd.

Some Downstream Consequences of Classification

- **76/769/EEC Restriction of Marketing and Use:** CMR substances which are Category 1 or 2 may not be sold to the general public.
- **88/379/EEC Preparations Directive**: Limits the percentage of CMR substances which may be sold to the general public (C/M 0.1-1%, R 0.5-5%). (**GD EC1272/2008**: 0.03, 0.3, 3, 10%, July 2017)
- **98/8/EC Biocidal Products (Pesticides) Directive:** Category 1 or 2 CMR substances may not be sold for use by the general public, and may soon be banned altogether.
- **2003/15/EC Cosmetics Directive 7th Amend**: Bans the use of substances classified as CMR, with a risk assessment being permitted only for Category 3 substances.

Issues with the Classification System

- Hazard (not risk) based – direct link to risk management
- Downstream consequences – ban on uses

- Consideration of ratio of reproductive toxic dose to expected exposure levels
- Consider route of administration as related to ‘normal handling and use’
- Parental general toxicity versus reproductive and developmental toxicity
- Weight of minor changes, and consistency in application

Dutch Health Council interpretation of CLP (1/3)

The guideline necessarily leaves room for interpretation, dependent on the specific data set under consideration. In the process of using the regulation, the Committee has agreed upon a number of additional considerations:

- If there is sufficient evidence to establish a causal relationship between human exposure to the substance and impaired fertility or subsequent developmental toxic effects in the offspring, the compound will be classified in category 1A, irrespective of the general toxic effects (see Annex D, 3.7.2.2.1.).

Dutch Health Council interpretation of CLP (2/3)

- Adverse effects in a reproductive study, occurring without reporting the parental or maternal toxicity, may lead to a classification other than category 1B, when the effects occur at dose levels which cause severe toxicity in *general* toxicity studies.
- Clear adverse reproductive effects will not be disregarded on the basis of reversibility per se.
- The Committee does not only use guideline studies (studies performed according to OECD standard protocols) for the classification of compounds, but non-guideline studies are taken into consideration as well.

Dutch Health Council interpretation of CLP (3/3)

- The classification of compounds is based on hazard evaluation only, which is one of a series of elements guiding the risk evaluation process. The Committee emphasizes that for derivation of health-based occupational exposure limits, these classifications should be placed in a wider context. For a comprehensive risk evaluation, hazard evaluation should be combined with dose-response assessment, human risk characterization, human exposure assessment and recommendations of other organizations.

HESI-DART CLP Satellite Workshop Programme

1300 Introduction *Aldert Piersma (RIVM)*

1330 Reproductive toxicity under CLP *Kati Hellsten (ECHA)*

1400 Considerations of maternal toxicity in classification *George Daston (Proctor & Gamble)*

1430 Case Studies

- Boric acid *Leonello Attias (ISS)*
- Azoles *Nina Hallmark (Bayer)*
- Phthalates *Jennifer Foreman (ExxonMobil)*

1530 Breakout groups to discuss case studies

1630 Plenary & panel discussion of case studies

1725 Concluding remarks

Thank you