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Incorporating potency into EU classification for carcinogenicity and reproductive toxicity

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ABSTRACT

Although risk assessment, assessing the potential harm of each particular exposure of a substance, is desirable, it is not feasible in many situations. Risk assessment uses a process of hazard identification, hazard characterisation, and exposure assessment as its components. In the absence of risk assessment, the purpose of classification is to give broad guidance (through the label) on the suitability of a chemical in a range of use situations. Hazard classification in the EU is a process involving identification of the hazards of a substance, followed by comparison of those hazards (including *degree of hazard*) with defined criteria. Classification should therefore give guidance on degree of hazard as well as hazard identification. Potency is the most important indicator of degree of hazard and should therefore be included in classification. This is done for acute lethality and general toxicity by classifying on dose required to cause the effect. The classification in the EU for carcinogenicity and reproductive toxicity does not discriminate across the wide range of potencies seen (6 orders of magnitude) for carcinogenicity and for developmental toxicity and fertility. Therefore potency should be included in the classification process. The methodology in the EU guidelines for classification for deriving specific concentration limits is a rigorous process for assigning substances which cause tumours or developmental toxicity and infertility in experimental animals to high, medium or low degree of hazard categories by incorporating potency. Methods are suggested on how the degree of hazard so derived could be used in the EU classification process to improve hazard communication and in downstream risk management.

Abbreviations: C&L, Classification and Labelling; CLP, Classification and Labelling and Packaging Regulations; CMR, carcinogenicity, mutagenicity and reproductive toxicity; D/RT, developmental/reproductive toxicity; EC, European Community; ECETOC, European Centre for Ecotoxicology and Toxicology of Chemicals; ECHA, European Chemicals Agency; ED10, dose calculated to cause an increase incidence of 10% of a response; EPA, United States Environmental Protection Agency; EU, European Union; GHS, United Nations Globally Harmonized System of Classification and Labelling of Chemicals; IRIS, EPA's Integrated Risk Information System; LOAEL, Lowest Observable Adverse Effect Level; NOAEL, No Observable Adverse Effect Level; SCL, specific concentration limit for presence of a CMR in a mixture; STOT, specific target organ toxicity; STOT-RE, specific target organ toxicity for repeat exposure; STOT-SE, specific target organ toxicity for single exposure; T25, the dose giving a tumour incidence of 25% in experimental animals after correction for the spontaneous incidence; TCDD, 2,3,7,8-tetrachlorodibenzodioxin; TD50, the dose calculated to cause an increased incidence of tumours over background of 50%.

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1. Introduction

There has been a debate for many years about the relative merits of regulation by hazard or by risk (Lofstedt, 2011). Much of the debate seems to focus on Classification and Labelling (C&L) and what is meant by the term "intrinsic hazard" and by the assertion that C&L is hazard based and does not take into account exposure. In contrast, risk assessment takes exposure into account. However, the source of the controversy which continues to fuel the debate lies in the downstream consequences of either classification or of risk assessment and that is risk management, more particularly those aspects of risk management which find their way into regulation and legislation in the form of restrictions on use.

There is a well recognised process for assessing the potential adverse effects of chemicals on health which has been described in detail by van Leeuwen and Vermieire (2007). The first step is hazard identification, identifying the adverse effects a chemical has the inherent capacity to cause. The next step, effects assessment or hazard characterisation, is the estimation of the response between dose or level of exposure to a substance and the incidence and severity of an effect. Exposure assessment is the estimation of the doses/exposure levels to which human populations are exposed. Risk assessment or risk characterisation brings together hazard characterisation and exposure assessment in an estimate of the incidence and severity of the adverse effects likely to occur in a human population due to the predicted exposure. Risk management then follows which is a decision making process that entails weighing political, social, economic and engineering information against risk related information to develop and select the appropriate response to a potential health hazard.

The full process of chemical risk assessment and risk management requires an assessment of the use or uses of the chemical which relies on detailed knowledge of the use patterns (both industrial and consumer), emissions, pathways and rates of movement and degradation. It is the use of the substance in the particular situation or situations which is being assessed. The classification of substances offers a quick and uncomplicated means of communicating to potential users the potential health hazard to humans, wildlife or the environment, and therefore is a valuable tool especially for managing the risk of accidental exposure. Also, in situations where risk assessment is not possible due to the lack of reliable exposure information, hazard classification can help in the risk management of chemicals.

The aim of this paper is to explore ways in which the outcome of the classification process for cancer and for reproductive toxicity could be improved to better communicate the degree of hazard which substances may pose.

2. Classification in the EU

The Globally Harmonised System of Classification and Labelling of Chemicals (GHS, 2013) provides a harmonised basis for globally uniform physical, environmental and health and safety information on hazardous chemical substances and mixtures. The European Commission, the EU Member States and the European Parliament endorsed the UN recommendation to implement the GHS in domestic law. In practice the implementation of GHS in the EU resulted in very little change from the previous process.

Classification as defined in the EU Guidance on CLP (ECHA, 2012a) is essentially a process of hazard identification and effects assessment: "Hazard classification is a process involving identification of the physical, health and environmental hazards of a substance or a mixture, followed by comparison of those hazards (including *degree of hazard*) with defined criteria in order to arrive at a *classification* of the substance or mixture." The aim is to provide information which can then be used in risk management, the EU Guidance states: "The aim of classification and labelling is to identify the hazardous properties of a substance or a mixture by applying specific criteria to the available hazard data (classification), and then to provide any appropriate hazard labelling and information on safety measures."

The EU guidance emphasises that: "Classification according to CLP is based on *intrinsic* hazards, i.e. the basic properties of a substance as determined in standard tests or by other means designed to identify hazards. As C&L is hazard-based, it does not take exposure into consideration in arriving at either a classification or appropriate labelling, unless for specific exceptions when a substance can be considered as not being biologically available, such as the derogation not to label a metal in the massive form." The controversy lies in the interpretation of whether "intrinsic hazard" means identifying the potential to cause adverse effects and nothing else or whether it includes hazard characterisation. The definition of the hazard classification process provided by ECHA is unequivocal in specifying a two part process including hazard characterisation: "Hazard classification is a process involving identification of the physical, health and environmental hazards of a substance or a mixture, followed by comparison of those hazards (including *degree of hazard*)." In order to be meaningful classification has to provide guidance to determine if a substance or mixture is suitable for specific downstream uses. Therefore it must take into account the degree of the hazard as well as the nature of the hazard. The degree of hazard is determined by potency, which is primarily based on the dose causing a specific toxic effect (type of hazard). In addition degree of hazard takes into account the severity of the effect. The incidence, type and magnitude describe the 'severity', meaning how adverse the effect is (ECHA, 2012a). Chemicals are then placed into categories reflecting their degree of hazard.

This concept has been incorporated into the classification of most toxic effects. Acute toxicity, irritation and corrosivity have used an estimate of potency to assign a substance to a category. With acute toxicity, the end point, death, is fixed and the dose required to cause death is determined and then the substance is ascribed to one of 4 categories on the basis of its acute lethal potency. For skin and eye irritation the dose is fixed, but the consequences are scored according to their severity and the substance assigned to one of three categories as a result based on its irritant potency. In corrosivity, the dose is fixed, but the duration that the substance is in contact with the skin or the eye is varied. The effects are then assessed and the substance is ascribed to a category based on the length of exposure required to cause corrosion, the corrosivity potency.

The classification system also incorporates potency in the way it deals with other types of toxicity, the so-called specific target organ toxicity (STOT). The system recognises that many substances are capable of the hazard of causing damage or adverse effects to specific organs or systems. STOT means specific, target organ toxicity arising from a single or repeated exposure to a substance or mixture. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed are included. However, other specific toxic effects that are specifically addressed (acute toxicity, skin corrosion/irritation, serious eye damage/irritation, respiratory or skin sensitisation, germ cell mutagenicity, carcinogenicity, reproductive toxicity) are not included (ECHA, 2012a). The distinction between the categories in specific target organ toxicity is based on the dose level used in the animal studies in which the adverse effects were seen, with the Category 1 being reserved for the substances which cause adverse effects at low doses. The distinguishing dose levels are adjusted using Haber's Rule to take into account the duration of dosing as shown in Table 1.