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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.

**Table 1**
Specific target organ toxicity values (STOT-SE for single exposure and STOT-RE for repeat exposure).

| Dose (mg/kg/day) | STOT-SE and STOT-RE values for different study duration (oral dosing) | | |
|---|---|---|---|
| | 1 day | 28 days | 90 days |
| ⩽10 | | | Category 1 |
| ⩽30 | | Category 1 | |
| ⩽100 | | | Category 2 |
| ⩽300 | Category1 | Category 2 | No classification |
| ⩽2000 | Category 2 | No classification | |
| >2000 | No classification | | |

The classification of substances for carcinogenicity and reproductive toxicity differs in that classification is in general restricted to hazard identification. The EU criteria are based on the strength of scientific evidence that the substance causes cancer or reproductive toxicity in either humans or laboratory animals. No specific considerations are given to the potency of the substance, although there is a limit dose of 1000 mg/kg bwt/day set for most studies. The identification of individual substances on the basis of the strength of evidence for carcinogenicity or reproductive toxicity has resulted in the classification of a large number of substances as carcinogens or reproductive toxicants. However, classification for carcinogenicity and reproductive toxicity does not discriminate across the wide range of potencies seen (6 orders of magnitude) (Gold et al., 1989; Muller et al., 2012) and this limits the utility of the classification as a means of providing appropriate hazard labelling and information on safety measures.

## 3. Potency of chemicals to cause cancer and reproductive toxicity

It has been found that the potency of carcinogens and reproductive toxicants covers a wide range. Gold et al. (1989) examined the potency of 492 chemicals which had been tested in long term rodent bioassays for carcinogenicity by calculating the TD50, the dose calculated to cause an increased incidence of tumours of 50%. They found a range of TD50s which spanned 9 orders of magnitude ranging from 7 ng/kg bwt/day for 2,3,7,8-Tetrachlorodibenzo-p-dioxin to 24.5 g/kg bwt/day for SX Purple. In addition, the EPA's IRIS database includes chemicals with a range of 6 orders of magnitude (EPA). Muller et al. (2012) examined the LOAELs, NOAELs and ED10s (dose required to cause an increased incidence of 10%) of the effects which resulted in classification of 93 substances for developmental toxicity and effects on fertility. The range of values spanned 7 orders of magnitude for developmental toxicity (0.0002 to 2281 mg/kg bwt/day) and 5 orders of magnitude (0.032 mg/kg bwt/day to 940 mg/kg bwt/day) for fertility. Sanner and Dybing (2005) have a shown a correlation between the potency of chemicals to cause cancer in humans is related to their potency to cause cancer in rats and mice. Although there is no systematic review available for reproductive toxicity, many of the mechanisms involved such as effects on the endocrine system have been shown to occur in experimental animals which have been used in the development of such compounds for human therapeutic use which indicates that there must be a correlation of potency. It is clear that with such wide ranges of potency it is important to determine and communicate the degree of hazard as well as the nature of the hazard.

The importance of potency has been recognised in the framework of classification of mixtures that contain a hazardous ingredient with a cancer or reproductive toxicity classification. Whether or not such a classification of an ingredient will carry over to the mixture is governed by the concentration limit designated for that ingredient. The default procedure is to apply general concentration limits, which depend on the classification category of the substance. Category 1A (substances known to cause effects in humans) and 1B (substances presumed to cause effects in humans) substances are subjected to a limit of 0.1% for carcinogenicity and 0.3% for reproductive toxicity and Category 2 (suspected to cause effects in humans) substances are subjected to a limit of 1% for carcinogenicity and 3% for developmental/reproductive toxicity. However, due to the fact that the classification category does not take potency into account, the general concentration limits do not reflect the potency of a carcinogen or a developmental/reproductive toxicant in a mixture. As well as the need for a system to reflect this wide range of potencies, there are examples where the question of potency as such is of particular concern (EC, 1999). The high potency of the substances such as dimethylsulfate and hexylmethylphosphoramide or impurities such as TCDD and certain nitrosamines gives rise to concern and it is possible that a general limit of 0.1% does not adequately express the hazard of a mixture. In other cases, substances may be classified although relatively high doses are needed to induce tumours or reproductive toxicity. In such cases the general limit may inappropriately express the hazard of a mixture containing such substances, this time by over-estimating the carcinogenicity or reproductive toxicity of the mixture.

The EU has addressed these issues by the option to derive specific concentration limits for carcinogens (EC, 1999) and for reproductive toxicity (ECHA, 2012b) in mixtures. These specific concentration limits are established on the basis of the determination of a dose descriptor for the relevant effect and the subsequent categorisation into high, medium or low potency. The categorisation can then be modified by a number of factors including the severity of the response. The concentration limits for the substance are then adjusted in accordance with the potency category. The limit for high potency substances is reduced by a factor of 10 and the limit for low potency substances is increased by a factor of 10. The limit for medium potency substances is not changed.

The concerns about the potential miscommunication of the degree of hazard remain for the overall classification because it does not include a consideration of potency. It has been argued that this is not part of the classification process as agreed under GHS, subsequently incorporated into the EU regulations, and therefore it should not be done. Closer examination of the GHS process for carcinogenicity can challenge this view. The current classification process uses 2 strands to consider the information:

- Strength of evidence
- Weight of evidence.

Strength of evidence – The GHS guidelines (GHS, 2013) for carcinogenicity describe the strength of evidence process as involving the enumeration of tumours in human and animal studies and determination of their level of statistical significance. Sufficient evidence in animals shows a causal relationship between the agent and an increased incidence of tumours.

Weight of evidence – The GHS guidelines (GHS, 2013) for carcinogenicity describe the weight of evidence as additional considerations, a number of other factors which should be considered that influence the overall likelihood that an agent may pose a carcinogenic hazard in humans. These factors include:

(a) Tumour type and background incidence.
(b) Multi-site responses.
(c) Progression of lesions to malignancy.
(d) Reduced tumour latency.
(e) Whether responses are in single or both sexes.
(f) Whether responses are in a single species or several species;
(g) Structural similarity to a substance(s) for which there is good evidence of carcinogenicity.

(h) Routes of exposure.
(i) Comparison of absorption, distribution, metabolism and excretion between test animals and humans.
(j) The possibility of a confounding effect of excessive toxicity at test doses.
(k) Mode of action and its relevance for humans, such as cytotoxicity with growth stimulation, mitogenesis, immunosuppression, mutagenicity.

The guidelines also suggest that methods for estimating potency should be developed.

ECETOC (McGregor et al., 2010) described a process for using the GHS guidelines for carcinogenicity which incorporates both strength of evidence and weight of evidence in deciding upon the classification for a chemical. It poses a series of 7 questions:

- Has the relevant form of the substance been tested? (strength of evidence)
- Is the study design relevant to human exposure, including dose and route of exposure? (strength of evidence)
- Is there a substance related response? (strength of evidence)
- Is the target tissue exposure relevant to humans? (weight of evidence)
- Can a Mode of Action be established and if so is it relevant to humans? (weight of evidence)
- What is the potency? (weight of evidence)

The guidelines for developmental/reproductive toxicity do not contain such a clear distinction between strength of evidence and weight of evidence; however it is a principle which can also be usefully be applied to these areas as well.

To summarise: strength of evidence = degree of association between chemical exposure and carcinogenicity or reproductive toxicity (integrity of the test system, strength of correlation based on comparison with concurrent and historic control values and clarity of dose response).

Weight of evidence = other factors which influence level of concern (human relevance, severity and dose response).

It is clear that an indication of the amount of chemical required to cause the adverse effects in classification for carcinogenicity and for developmental/reproductive toxicity would improve hazard communication.

## 4. Methodology for assessing potency

The methodology described in the EU Guidance for the derivation of specific concentration limits for carcinogens (EC, 1999) allows the derivation of carcinogen potency dose descriptors and the subsequent allocation of the chemical to high, medium or low potency groups. Potency is defined in the EU Guidance as the magnitude, with respect to dose, of the carcinogenic activity of a chemical in the species under consideration.

Several methods for deriving the dose descriptor were assessed. The T25 method was selected for potency ranking with several advantages in comparison to the TD50 and other methods being cited in the EU Guidance. First, it does not require (complex) computer modelling after establishment of a significant increase in tumour incidence. Also, T25 values are much more likely to be within the range of the experimental data and the use of data from the lowest dose giving a significant response, should in most instances reduce the problem of intercurrent mortality to an acceptable degree. Finally, the data profile needed for calculating a T25 value has to be less specific, e.g. time to tumour data are not needed. It is recognized that the potential loss of precision does not match the many order of magnitude differences in carcinogenic potencies which have been found between high and low potency substances in rodents. It is acknowledged that their are reservations about the use of the T25 for risk estimation as it does not explore the lower end of the dose response (EC, 1999; Roberts et al., 2001).

The EU guidance states: "The subdivision into the three potency groups is performed based on a tumorigenic dose descriptor. Among several possible descriptors, T25 is selected, the dose giving a tumour incidence of 25% in experimental animals after correction for the spontaneous incidence. Carcinogens of high potency are those with a T25 value which is: $\leqslant$1 mg/kg bodyweight/day, those of medium potency when: 1 mg/kg bw/day < T25 value $\leqslant$ 100 mg/kg bw/day, and those of low potency when the T25 value is: >100 mg/kg bw/day. In addition to subdividing carcinogens by the use of the tumorigenic dose descriptor, T25, several other elements bearing on tumorigenic potency (dose–response relationships, site/species/strain/gender activity, mechanism including genotoxicity, mechanistic relevance to humans, toxicokinetics and other elements relevant to potency classification) are taken into consideration, which thereby may modify the potency preliminary evaluation."

The purpose of the modifying factors is to bring a structured way of applying expert judgment to the process of assigning chemicals to the potency categories by considering a number aspects which could mean that the chemical should be considered to be either more potent or less potent than indicated by the T25. The use of the modifying factors process is especially important when the T25 value falls close to a boundary between categories. These process and the modifying factors described in detail in the guidance document (EC, 1999), and they are summarized here.

### 4.1. Dose–response relationships

A supralinear dose–response relationship may indicate higher relative potency at lower doses than for a linear dose response. This could move chemicals near potency borders into a higher potency group. A related problem arises when the tumour frequency is very high at the lowest dose tested. In such cases a maximal tumour response may already have been reached and the calculated T25 might be higher than that which would have been found if lower experimental doses had been used. In such cases substances near the potency borders may likewise be moved into a higher potency group.

A sublinear relationship may indicate lower relative potency at lower doses than at higher doses. This could move chemicals near the potency borders into a lower potency group.

### 4.2. Site/species/strain/gender activity

Potent carcinogens tend to be effective in common, multiple tissue sites and across species and genders. Thus, chemicals near the potency borders may be moved to a higher potency group for carcinogens expressing this behaviour.

Low potency carcinogens tend to only be active in a single specific tissue site in a single gender of a single species or only at a single site with a high spontaneous tumour incidence.

Thus, chemicals near the potency borders may be moved to a lower potency group for carcinogens expressing this behaviour.

### 4.3. Mechanisms including genotoxicity

It is recommended to use information on mechanism including genotoxic activity as one element in conjunction with the other elements. Genotoxic chemicals are defined in the EU Guidance (EC, 1999) as chemicals that fulfill the criteria as EU Category 2 mutagens (positive evidence obtained from experiments in

mammals and/or in some cases from in vitro experiments, obtained from somatic cell mutagenicity tests *in vivo*, in mammals or other *in vivo* somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays).

Lack of genotoxic activity in appropriate, well-performed tests may indicate a lower carcinogenic potency and may thus move a chemical near the potency borders to the next lower potency group, normally from intermediate to low.

### 4.4. Mechanistic relevance to humans

For experimental carcinogenic chemicals where the available studies of mechanisms are so convincing that the chemical obviously does not represent a cancer hazard for humans, the chemical should not be classified for carcinogenic properties and would not be subjected to this process. The WHO/IPCS Human Relevance Framework gives guidance on how relevance to humans should be assessed (Meek et al., 2014).

### 4.5. Toxicokinetics

In most instances, data will not be available allowing a comparison of the toxicokinetic behaviour of a carcinogen between humans and the test animal. However where this information is available it can be used to determine whether a chemical close to the border should be moved because of knowledge that the test animal is either exposed to a higher or lower internal dose of the relevant metabolite. Thus, in the absence of comparative data, it is assumed that the carcinogen shows similar toxicokinetic behaviour in humans and in test animals.

### 4.6. Other elements relevant to potency evaluation

Other types of information may be utilized in deriving a final allocation of a carcinogen to a potency group. Structure–activity considerations may give important indications on the potency, by examining the potency of structurally related carcinogens.

As described above, the categorisation into high, medium or low potency is then used to ascribe a specific concentration limit for the concentration of the chemical above which the mixture containing the chemical must be labelled for carcinogenicity. These specific concentration limits vary by a factor of 10 depending on the potency category.

Guidance on the derivation of specific concentration limits for developmental/reproductive toxicity has been included in the EC Guidance version 3.0 (ECHA, 2012b). An approach similar to that for carcinogenicity has been adopted and it is based largely on the work of Muller et al. (2012). The guidelines provide a definition and a commentary:

"Reproductive toxicity potency is defined as the dose which induces reproductive toxic effects with a specific type, incidence and magnitude, considering the study design in terms of species and strain, exposure route, exposure duration, exposure window in the life cycle, and possible concomitant parental toxicity.

According to this definition 'Potency' is primarily based on applied *dose* and can be modified by consideration of 'severity'. Within this definition the dose is defined as the amount of chemical to which the animals or humans that showed the effect (meaning type, incidence and magnitude) were exposed on an mg/kg bw/day basis. The incidence is the proportion of animals or humans that showed the effect. The type of effect describes which property of an organ or system of the animal or human is affected and the magnitude describes the level of change compared to the control. Together, the incidence, type and magnitude describe the 'severity' of the effect, meaning how adverse the effect or combination of effects is. With specific incidence, type and magnitude (together specific severity) a comparable level of severity is indicated for different effects. The working definition above allows potency to be defined at different levels of specific severity, for example at the ED10 and the LOAEL (Lowest Observed Adverse Effect Level), and for different type of effects. Therefore, several possible estimates for potency were investigated" (ECHA, 2012b).

Muller et al. (2012) suggested the use of the ED10 as a measure of potency for developmental/reproductive toxicity effects which lead to classification on strength of evidence in a similar way to the use of the T25 value for tumours. They applied the principle that the majority of chemicals being classified should fall into the medium range and this principle led them to use 4 mg/kg/day as their boundary between high and medium potency, and 400 mg/kg/day as the boundary between medium and low potency. There is also provision to reduce the specific concentration limit for chemicals where the ED10 is 10 or 100 times lower than the 4 mg/kg/day boundary for high potency. There is a similar process of considering the application of modifying factors especially when the ED10 is close to a boundary between potency categories. The factors are:

- Type of effect/severity
- Data availability
- Dose–response relationship
- Mode or mechanism of action
- Toxicokinetics
- Bio-accumulation of chemicals

While most modifying factors would result in a higher potency group than the preliminary one, also the opposite could occur.

Some modifying factors are of a more qualitative nature. When applied, they will simply point to a potency group different from the one resulting from the preliminary assessment.

Other modifying factors might be quantifiable, at least on a semi-quantitative scale. In such cases, a potency group higher (or lower) than the preliminary one should be chosen if the estimated size of the modifying factor exceeds the distance of the preliminary ED10 to the border of the relevant (higher or lower) adjacent potency group. There is detailed guidance on the application of the modifying factors in the CLP Guidance (ECHA, 2012b), the main points from the guidance are:

### 4.7. Type of effect/severity

The type of effect(s) resulting in the same classification as reproductive toxicant differs between chemicals. Some effects could be considered as more severe than others, however, ranking different effects based on their severity is controversial and it is difficult to establish criteria. In addition the effects can become more severe as the dose levels are increased e.g. from variations to malformations or small changes in testes histopathology through effects on fertility to an irreversible and complete absence of fertility. However, the full spectrum of effects usually lies within a range of doses which is smaller than the range of the potency groups. The classification is usually based on the most severe effects and the most severe effects are usually observed at the lowest dose with reproductive effects (Muller et al., 2012). Therefore, a differentiation between types of effects is considered to have limited added value. Exceptions can be dealt with on a case by case basis.

### 4.8. Data availability

There are several aspects to this modifying factor, some of which are:

- limited data availability where certain test protocols are lacking and therefore certain parameters have not been evaluated,
- limited data availability where the spectrum of evaluated parameters is sufficient, but only studies with limited duration are available, and
- limited data availability where only a LOAEL, but no NOAEL could be identified.

### 4.9. Dose–response relationship

The ED10 will in most cases probably be in the same range as the NOAEL and LOAEL.

However, in cases of a shallow dose effect relationship curve, the LOAEL may sometimes be clearly below the ED10. In such situations, if a chemical would fall into a lower potency group based on the ED10 but into a higher potency group based on the LOAEL then the higher potency group should be used for that chemical.

### 4.10. Mode or mechanism of action

It is assumed that effects observed in animal studies are relevant to humans. Where it is known that the mode or mechanism of action is not relevant for humans or is of doubtful relevance to humans, this should have been taken into account in the classification and should not be used again as a modifying factor for potency.

However, quantitative differences in toxicodynamics can be taken into account when not already taken into account in the classification. In cases where mechanistic information shows a lower sensitivity in humans than in experimental animals, this may move chemicals which are close to the potency boundaries to a lower potency group. In cases where mechanistic information indicates a higher sensitivity in humans than in experimental animals, this may move chemicals near the potency boundaries to a higher potency group.

### 4.11. Toxicokinetics

The toxicokinetics of a chemical can differ between the tested animal species and humans. Where a difference in toxicokinetics is known between the test animal and humans this should be taken into account when determining the potency group of a substance.

### 4.12. Bio-accumulation of substances

The study design of, for example, developmental studies is aimed at exposure only during development. For chemicals which bio-accumulate, the actual exposure in the time window of sensitivity for some developmental effects may therefore be much lower than when exposure at the same external dose level would have started long before the sensitivity window.

## 5. Classification for mutagenicity

The classification of chemicals for mutagenicity also does not take into account potency. Classification is done on a strength of evidence basis from the results of a range of in vitro and *in vivo* assays. In addition there is no provision for the derivation of specific concentration limits for mixtures. The EU CLP Guidance (ECHA, 2012a) explains that "There are several reasons why it is considered impossible to set SCLs for mutagens without a comprehensive guidance, one of them being that mutagenicity tests have not been specifically developed for the derivation of a quantitative response. Moreover, different mutagenicity tests have different sensitivities in detecting mutagens. Thus, it is very difficult to describe the minimum data requirements which would allow a standardized SCL derivation. Another drawback in practice is that the results obtained for the most part do not offer sufficient information on dose–response, especially in the case for *in vivo* tests. In conclusion, the possibility to set SCL for germ cell mutagenicity is therefore not considered possible in the process of self-classification as there is no standardized methodical approach available which adequately takes into account all relevant information." It is therefore not possible to bring potency consideration into the classification of chemicals for mutagenicity at this point in time.

## 6. Bringing degree of hazard into classification

The C&L potency categorisations for carcinogenicity and for developmental and reproductive toxicity as developed and described in the ECHA Guidelines (EC, 1999; ECHA, 2012a,b) represent a rigorous and well thought process for assessing the degree of hazard of chemicals which cause cancer or reproductive toxicity in laboratory animals. The potency categories which are derived from this process could be used as an aid to improving hazard communication in overall classification of the chemical in addition to their primary purpose in the derivation of specific concentration limits.

A short verbal description which incorporates both the hazard identification and the degree of hazard can be derived quite simply:

- Presumed human with high potency
- Presumed human with medium potency
- Presumed human with low potency
- Suspected human with high potency
- Suspected human with medium potency
- Suspected human with low potency.

These short verbal descriptions provide a transparent and concise means of communicating the hazard. It is recommended that these verbal descriptions should be used wherever possible, including in downstream risk management and communication processes.

However there may be situations where a coded categorisation is required. This could be done in 2 ways:

- By adding a potency suffix to the existing classification categories ("Supplementary classification category")
- By adding potency as additional classification criterion and keeping the existing classification categories ("Integration into overall classification category").

*Degree of hazard as a supplementary classification category* could be achieved in a similar manner. The chemical would first be classified in the current way using a strength of evidence approach based on the strength of the association between the chemical and the incidence of tumours or developmental/reproductive effects and an assessment of human relevance. No further assessment would be required for chemicals which are not classified, including those considered to be non-relevant to humans. Then those chemicals in categories 1A, 1B or 2 would be assessed as described for the derivation of specific concentration limits and assigned to a potency category. This potency categorisation would then be added as a subscript as shown in Table 3. This method would recognise the two components which give rise to concern for adverse health effects; the strength of evidence that the effect could be caused by the chemical and the weight of evidence on its degree of hazard or potency recognising that higher potency increases concern. It would allow both hazard identification and

hazard characterisation to be communicated by the classification, the primary classification indicating the hazard identification and the suffix indicating the hazard characterisation as it is a codified version of the verbal two part descriptor.

*Integration of degree of hazard into the overall classification* is similar to the method proposed by ECETOC (McGregor et al., 2010). The chemical would first be the subject of a strength of evidence assessment as in the current system and placed tentatively into the categories of presumed, suspected or none. This would include an assessment of relevance. There would be no requirement for further assessment if a human non-relevance has been established and the chemical would be classified as a non-carcinogen. For those chemicals where non-relevance cannot be established, an assessment of potency as described in the CLP Guidance (ECHA, 2012a) would be carried out. Bringing in the potency determination as described by the EU into the overall classification would then be derived as shown in Table 2. The resulting classification would recognise that there are 2 major components contributing to concern for adverse health effects; the strength of evidence that the effect could be caused by the chemical and the weight of evidence on its degree of hazard or potency recognising that higher potency increases concern. This process results in a classification which is an integration of both hazard identification and hazard characterisation and incorporates the degree of hazard which is called for in the definition of classification. However, it involves the loss of some transparency in communication because the classification integrates the two components which give rise to concern for adverse health effects; the strength of evidence that the effect could be caused by the chemical and the weight of evidence on its degree of hazard or potency recognising that higher potency increases concern (see table 4).

Fig. 1 is a flow diagram of how these processes would operate. It shows a two step process in which first the strength of evidence for hazard identification is assessed and then the degree of hazard is assessed for presumed or suspected carcinogens or reproductive toxicants. The process is primarily focused on carcinogenicity or reproductive toxicity identified by the use of experimental animals, however it could also be applied to known human carcinogens or reproductive toxicants where laboratory animal studies have also been carried out. Accurate and reliable potency estimates based upon human data have preference above those based on animal data. However, there are several difficulties in establishing reliable human exposure doses (Allen et al., 1988). In spite of the obvious species relevance, significant human epidemiological data are not available for most chemicals. (See table 5)

The impact of these proposed classification schemes has been explored by the use of examples. The examples are based on those described in the EU guidance notes for setting SCLs for carcinogenicity (EC, 1999) and for developmental/reproductive toxicity (ECHA, 2012b). The examples are summarised in Tables 6 and 7 and they are described in more detail in Appendices 1 and 2. In the guidance document for carcinogenicity no strength of evidence categorisation was given for the examples, however the examples have been given a categorisation based on EU guidance. The categorisation for degree of hazard and potency provided in the examples has not been changed. In the examples for developmental/reproductive toxicity, categorisation for hazard identification by strength if evidence is shown and this has not been changed. The categorisation for degree of hazard by weight of evidence assessment provided in the examples has also not been changed. For examples 3b for carcinogenicity and examples 4b and 4c for developmental/reproductive toxicity, the dose levels for the examples have been changed to illustrate the impact of higher or lower potency with the same effects, i.e. only the potency has changed.

Tables 6 and 7 show the comparison of the three classification methods: the *current* method which does not take into account degree of hazard; the *integrated* method which adjusts the category by taking into account the degree of hazard; and the *supplemental* method which assigns a suffix to indicate the degree of hazard.

It will be seen that the current method assigns the same category to chemicals regardless of their degree of hazard or potency, and thus does not communicate the overall hazard. The *integrated* method offers some improvement in providing a better indication of the degree of hazard. However using this method, it is not possible to distinguish between chemicals with the following full hazard descriptions which would all be categorised as 1B:

- Presumed human with high potency
- Presumed human with medium potency
- Suspected human with low potency.

**Table 2**
Proposed categorisation to allow communication of both hazard identification based on strength of evidence and degree of hazard based on weight of evidence using EU potency determination.

| Hazard identification assessment categorisation | Degree of hazard categorisation | | |
|---|---|---|---|
| | High<br>Carc < 1 mg/kg<br>Repr < 4 mg/kg | Medium<br>Carc 1 < 100 mg/kg<br>Repr 4 < 400 mg/kg | Low<br>Carc > 100 mg/kg<br>Repr > 400 mg/kg |
| Known | $1A_{High}$ | $1A_{Med}$ | $1A_{Low}$ |
| Presumed | $1B_{High}$ | $1B_{Med}$ | $1B_{Low}$ |
| Suspected | $2_{High}$ | $2_{Med}$ | $2_{Low}$ |

**Table 3**
Proposed categorisation integrating hazard identification based on strength of evidence and degree of hazard based on weight of evidence using EU potency determination.

| Hazard identification assessment categorisation | Degree of hazard categorisation | | |
|---|---|---|---|
| | High<br>Carc < 1 mg/kg<br>Repr < 4 mg/kg | Medium<br>Carc 1 < 100 mg/kg<br>Repr 4 < 400 mg/kg | Low<br>Carc > 100 mg/kg<br>Repr > 400 mg/kg |
| Known | 1A | 1A | 1B |
| Presumed | 1B | 1B | 2 |
| Suspected | 1B | 2 | No class'n |

Similarly it would not be possible to distinguish chemicals categorised as 2 with the full hazard descriptions of:

- Suspected human with medium potency
- Presumed human with low potency.

The *supplemental* method provides a categorisation which allows both the strength of evidence about hazard identification and the degree of hazard to be communicated. Chemicals which differ in hazard identification and/or degree of hazard do not end up in the same category as is the case with the *current* method and with the *integrated* method.

The *supplemental* method provides a means to communicate both the hazard and identification and degree of hazard and therefore would be the better method of communication. The *integrated* method does offer some improvement over the *current* system in that it is better at highlighting chemicals of high concern than the *current* method. As it uses the same category nomenclature as the present system it could be used as a transition towards transparency and better communication of the hazards of chemicals.

However, it is suggested that more use is made in hazard communication and downstream risk management of the short verbal descriptor than of the overall category assignment. The short verbal descriptor has an element which indicates the strength of evidence that the chemical is capable of causing the adverse effect of concern: "Presumed" or "Suspected" and an element which reflects the degree of hazard "with high potency", "with medium potency" or "with low potency". The supplemental method provides a code to represent the verbal descriptors. Bringing degree of hazard into the process has already been used to overcome the difficulties of hazard communication in the setting of limits for chemicals in mixtures and it could also be used to overcome difficulties in other aspects of hazard communication and risk management.

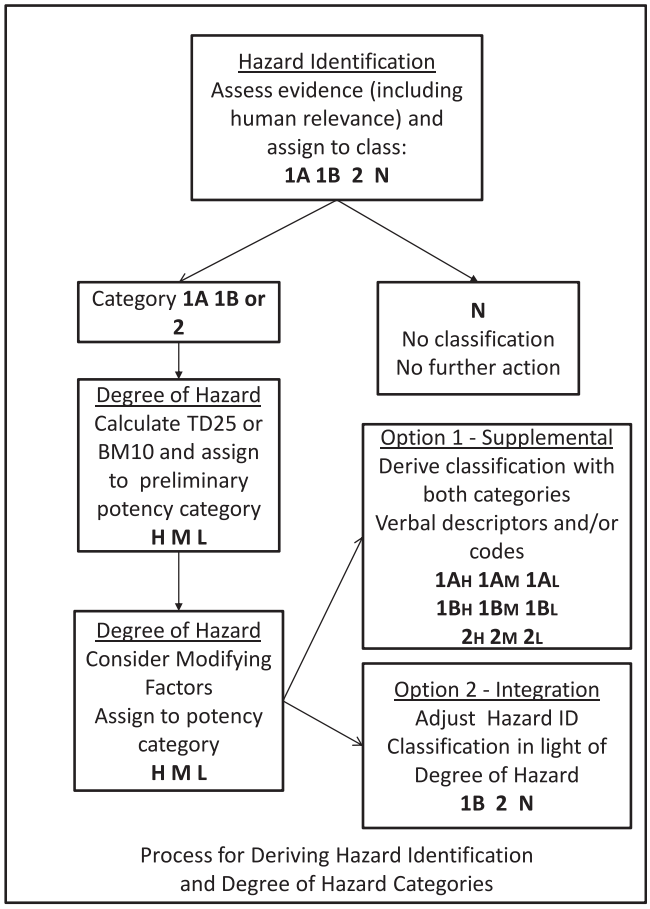


**Fig. 1.** Process for deriving hazard identification and degree of hazard categories.

**Table 4**
Examples of classification for carcinogenicity.

| Example | Results | Hazard identification category | T25 or $ED10_{mg/kg/day}$ | Modification | Degree of hazard category | Overall classification |
|---|---|---|---|---|---|---|
| 1 | Lung carcinomas, Hemangioendothelioma, mammary tumours in mice at 9.5 mg/kg/day | Presumed | 2.4 Medium | Mode of action, lack of lower dose, tumour type – modify | High | *Current:* presumed human carcinogen: **1B** *Integrated:* presumed human carcinogen with high potency: **1B** *Supplemental:* presumed human carcinogen with high potency: **$1B_{HIGH}$** |
| 2 | Brain gliomas at 2.5 mg/kg/day rats | Presumed | 1.9 Medium | Mode of action, lack of lower dose, tumour type – modify | High | *Current:* presumed human carcinogen: **1B** *Integrated:* presumed human carcinogen with high potency: **1B** *Supplemental:* presumed human carcinogen with high potency: **$1B_{HIGH}$** |
| 3 | Liver carcinomas rats and mice at 50–200 mg/kg/day | Suspected | 74.4 Medium | Lack of genotox, presence of toxicity, comparative metabolism – Modify | Low | *Current:* suspected human carcinogen: **2** *Integrated:* suspected human carcinogen with low potency: **N** *Supplemental:* suspected human carcinogen with low potency: **$2_{LOW}$** |
| 3b | Liver carcinomas kidney tumours rats at 0.1 mg/kg/day | Suspected | 0.074 High | Lack of genotox, presence of toxicity, comparative metabolism suggest modification but very low T25 leads to – no grounds to modify | High | *Current:* suspected human carcinogen: **2** *Integrated:* suspected human carcinogen with high potency: **1B** *Supplemental:* suspected human carcinogen with high potency: **$2_{HIGH}$** |

**Table 5**
Examples of classification for reproductive toxicity.

| Example | Results | Hazard identification category | T25 or $ED10_{mg/kg/day}$ | Modification | Degree of hazard category | Overall classification |
|---|---|---|---|---|---|---|
| 1 | Post implantation loss, malformations in rats dose range 20–180 mg/kg/day | Presumed | 89.8 Medium | No grounds to modify | Medium | *Current:* presumed human reproductive toxicant: **1B** *Integrated:* presumed human reproductive toxicant with medium potency**: 1B** *Supplemental:* presumed human reproductive toxicantreproductive toxicant with medium potency**: $1B_{MED}$** |
| 2 | Skeletal malformations in rabbits dose range 25–50 mg/kg/day | Presumed | 33 Medium | No grounds to modify | Medium | *Current:* presumed human reproductive toxicantreproductive toxicant: **1B** *Integrated:* presumed human reproductive toxicantreproductive toxicant with medium potency**: 1B** *Supplemental:* presumed human reproductive toxicantreproductive toxicant with medium potency**: $1B_{MED}$** |
| 3 | Developmental delay and testicular in male rats dose range 50–750 mg/kg/day | Presumed | 416 Low | No grounds to modify | Low | *Current:* presumed human reproductive toxicantreproductive toxicant: **1B** *Integrated:* presumed human reproductive toxicantreproductive toxicant with low potency**: 2** *Supplemental:* presumed human reproductive toxicantreproductive toxicant with medium potency**: $1B_{LOW}$** |
| 4 | Repeat dose studies, testicular lesions – single dose 660 mg/kg/day also seen in inhalation study at 2.9 mg/l | Suspected | 132 Medium | No grounds to modify | Medium | *Current:* suspected human reproductive toxicantreproductive toxicant: **2** *Integrated:* suspected human reproductive toxicantreproductive toxicant with medium potency**: 2** *Supplemental:* suspected human reproductive toxicantreproductive toxicant with medium potency**: $2_{MED}$** |
| 4b | Repeat dose studies, testicular lesions at 1000 mg/kg NOAEL 500 mg/kg | Suspected | 750 Low | No Grounds to modify | Low | *Current:* suspected human reproductive toxicantreproductive toxicant: **2** *Integrated:* suspected human reproductive toxicant with low potency**: N** *Supplemental:* suspected human reproductive toxicant with low potency**: $2_{LOW}$** |
| 4c | Repeat dose studies, testicular lesions at 1 mg/kg NOAEL 0.5 mg/kg | Suspected | 0.75 High | No Grounds to modify | High | *Current:* suspected human reproductive toxicant: **2** *Integrated:* suspected human reproductive toxicant with high potency**: 1B** *Supplemental:* suspected human reproductive toxicant with high potency**: $2_{HIGH}$** |

**Table 6**
Comparison of classification using three methods for carcinogenicity.

| Example | Hazard identification category | Degree of hazard category | Overall classification |
|---|---|---|---|
| Carc 1 | Presumed | High | *Current:* **1B** *Integrated:* **1B** *Supplemental:* **$1B_{HIGH}$** |
| Carc 2 | Presumed | High | *Current:* **1B** *Integrated:* **1B** *Supplemental:* **$1B_{HIGH}$** |
| Carc 3 | Suspected | Low | *Current:* **2** *Integrated:* **N** *Supplemental:* **$2_{LOW}$** |
| Carc 3b | Suspected | High | *Current:* **2** *Integrated:* **1B** *Supplemental:* **$2_{HIGH}$** |

There is a problem with labelling in that it does not communicate the hazard well. The same hazard statement "May Cause Cancer" is used for all Category 1B carcinogens regardless of their degree of hazard or potency. This is in contrast to those chemicals which can cause death after a single dose where the dose required is reflected in the hazard statement which describes them as "Fatal if Swallowed" for those of high potency, "Toxic if Swallowed" for those of medium potency or "Harmful if Swallowed" for those with low potency. All of these categories are determined by the dose at which the chemical causes fatality in laboratory animals. The current scheme derived from GHS and adopted by the EU for carcinogenicity and for reproductive toxicity does not allow this differential communication. This issue would be improved by the adoption of either the integrated scheme or the supplemental scheme for incorporating degree of hazard.

Adopting the supplemental scheme would require the introduction of new hazard phrases which would indicate the potency of the chemical. The existing hazard phrases could be used with a supplement, for example "Limited Exposure May Cause Cancer" for 1B with high potency, "May Cause Cancer" for 1B with medium potency and "Prolonged High Exposure May Cause Cancer" for 1B

**Table 7**
Comparison of classification using three methods for reproductive toxicity.

| Example | Hazard identification category | Degree of hazard category | Overall classification |
|---|---|---|---|
| Repro 1 | Presumed | Medium | *Current:* **1B** *Integrated:* **1B** *Supplemental:* **$1B_{MED}$** |
| Repro 2 | Presumed | Medium | *Current:* **1B** *Integrated:* **1B** *Supplemental:* **$1B_{MED}$** |
| Repro 3 | Presumed | Low | *Current:* **1B** *Integrated:* **2** *Supplemental:* **$1B_{LOW}$** |
| Repro 4 | Suspected | Medium | *Current:* **2** *Integrated:* **2** *Supplemental:* **$2_{MED}$** |
| Repro 4b | Suspected | Low | *Current:* **2** *Integrated:* **N** *Supplemental:* **$2_{LOW}$** |
| Repro 4c | Suspected | High | *Current:* **2** *Integrated:* **1B** *Supplemental:* **$2_{HIGH}$** |

with low potency. The same supplementary phrases could be used with the other categories carcinogenicity and reproductive toxicity as shown in Table 8.

Adoption of the integrated scheme would mean that the hazard phrase May Cause Cancer would be reserved for those of high or medium potency. Those originally categorised as 1B through the strength of evidence but with low potency would receive the phrase Suspected of Causing Cancer. This could be achieved within the existing scheme.

The second consequence of C&L is the relation to other EU legislation which relies on certain classification aspects. The consequences of classification can be greater than a hazard label and may have a direct effect on risk management.

Under REACH, classification of a chemical as mutagenic, carcinogenic or toxic to reproduction (CMR) may lead to restrictions and the need to apply for authorisations (EC) No 1907/2006). The cosmetics Regulation (EC) 1223/2009 prohibits use of CMR, category 1A, 1B and 2 substances unless, a favorable opinion is available from the Scientific Committee on Consumer Safety for the given substance under the given exposure and use concentration, and, for 1A and 1B substances if compliant with food safety requirements. According to the European pesticide Regulation (EC) 1107/2009 or the EU Biocides Regulation 528/2012, CMR classifications in Cat. 1A and 1B preclude approval of the respective substance as an active substance, safener, or synergist in plant protection products or biocidal products.

These downstream risk management processes should be reviewed as a consequence of the change to classification for carcinogenicity and reproductive toxicity which are being suggested in this paper. If the supplementary approach were to be adopted then the risk management processes would have to be adjusted to take into account the different degrees of hazard. For instance, chemicals categorised as $1B_{LOW}$ would not be the subject to the same restrictions as is currently applied to all chemicals categorised as 1B. However, if the integrated system were to be adopted then the downstream risk management process could remain largely unchanged as chemicals with low potency would no longer be classified as category 1B but as category 2. While the risk management process could remain largely unchanged when adopting the integrated system, the consequences for chemical use in products are significant if the evaluation of the degree of hazard leads to a re-categorisation from 1B to 2 and from 2 to 1B and if these categories are regulated differently by downstream regulations.

## 7. Conclusion

Although risk assessment, assessing the safety of each particular exposure of a chemical, 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 on the suitability for a chemical in a range of use situations. Hazard classification is a process involving identification of the hazards of a chemical, followed by comparison of those hazards (including *degree of hazard*) with defined criteria in order to arrive at a *classification* of the chemical. Classification should therefore give guidance on degree of hazard as well as

**Table 8**
Examples of revised hazard phrases using the supplemental method of incorporating degree of hazard into classification.

| Hazard identification assessment categorisation | Degree of hazard categorisation | | |
|---|---|---|---|
| | High<br>Carc < 1 mg/kg<br>Repr < 4 mg/kg | Medium<br>Carc 1 < 100 mg/kg<br>Repr 4 < 400 mg/kg | Low<br>Carc > 100 mg/kg<br>Repr > 400 mg/kg |
| Known Carc | $1A_{High}$<br>Limited exposure may cause cancer | $1A_{Med}$<br>May cause cancer | $1A_{Low}$<br>Prolonged high exposure may cause cancer |
| Presumed Carc | $1B_{High}$<br>Limited exposure may cause cancer | $1B_{Med}$<br>May cause cancer | $1B_{Low}$<br>Prolonged high exposure may cause cancer |
| Suspected Carc | $2_{High}$<br>Limited exposure suspected of causing cancer | $2_{Med}$<br>Suspected of causing cancer | $2_{Low}$<br>Prolonged high exposure suspected of causing cancer |
| Known Repr | $1A_{High}$<br>Limited exposure may damage fertility or the unborn child | $1A_{Med}$<br>May damage fertility or the unborn child | $1A_{Low}$<br>Prolonged high exposure may damage fertility or the unborn child |
| Presumed Repr | $1B_{High}$<br>Limited exposure may damage fertility or the unborn child | $1B_{Med}$<br>May damage fertility or the unborn child | $1B_{Low}$<br>Prolonged high exposure may damage fertility or the unborn child |
| Suspected Repr | $2_{High}$<br>Limited exposure Suspected of damaging fertility or the unborn child | $2_{Med}$<br>Suspected of damaging fertility or the unborn child | $2_{Low}$<br>Prolonged high exposure suspected of damaging fertility or the unborn child |

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 for carcinogenicity and developmental/reproductive toxicity does not discriminate across the wide range of potencies seen (6 orders of magnitude). Therefore potency should be included in the classification process for carcinogenicity and developmental/reproductive toxicity. The methodology in the EU guidelines for classification for deriving specific concentration limits is a rigorous process for assigning chemicals which cause tumours or developmental toxicity in animals to high, medium or low potency categories. Methods are suggested on how the degree of hazard could be used in the classification process to improve hazard communication and downstream risk management.

## Declaration of interest

This paper was prepared by a Task Force of the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC). ECETOC is a scientific, non-profit making, non-commercial association with a mission to act as an independent, peer-reviewed technical resource to all concerned with the assessment of health effects and environmental impact of chemicals. It is financed by its membership, which comprises some 40 of the leading companies with interests in the manufacture and use of chemicals. For this Task Force, ECETOC paid an honorarium to Dr. Monika Batke and reimbursed her for travel expenses relating to the Task Force. Dr. John Doe's participation in the Task Force was supported financially by Syngenta Ltd, although Dr. Doe has sole responsibility for the writing and contents of the paper. All other authors participated in the Task Force in the normal course of their employment affiliation as shown on the first page. The employers that are commercial entities produce and market products that are subject to regulation by National and International authorities that may consider the guidance given in this paper. The authors have sole responsibility for the writing and contents of the paper.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.yrtph.2014.07.022.

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