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An approach for the delineation of a generic cut-off value for local respiratory tract irritation by irritating or corrosive substances as a pragmatic tool to fulfill REACH requirements

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ABSTRACT

Under the current European legislation for the Registration, Evaluation, Authorisation and restriction of Chemicals (REACHs) a Derived No Effect Level (DNEL) has to be delineated for acute and chronic inhalation effects. The majority of available experimental studies are performed by the oral route of exposure. Route to route extrapolation poses particular problems for irritating or corrosive substances but the necessity for additional animal studies with inhalation exposure needs to be balanced with the regulatory information requirements. Existing occupational exposure limits (OEL) as surrogate for cut-off limits representing safe exposure under working conditions were grouped under certain criteria for substances that are legally classified in Europe as irritating or corrosive. As a result, it was shown that the OEL for irritating substances in this dataset is not lower than 10 mg/m^3 and for corrosives not lower than 1 mg/m^3. Under certain conditions these generic limits could be applied as a pragmatic, but still sufficiently reliable and protective upper cut-off limit approach to avoid additional animal tests with irritating or corrosive chemicals. The respective systemic toxicity profiles and physical–chemical properties need to be considered. Specific exclusion criteria for the discussed concept apply.

1. Introduction

The European chemical policy requires a comprehensive safety and risk assessment for (most) substances that need to be registered in accordance with Regulation (EC) 1907/2006 (REACH). For that purpose, various reference values need to be delineated for all relevant routes of exposure, population groups and exposure durations. The so called 'Derived No Effect Level' (DNEL) describes the safe level of exposure for workers or consumers, subdivided into DNELs for local and systemic effects, long term and short term exposure as well as for the inhalation, oral and dermal routes of exposure (European Chemicals Agency (ECHA), 2010). The essential step for the delineation of a DNEL is the correct identification of a qualified point of departure upon which assessment factors are applied to cope with the existing uncertainties of intra- and interspecies differences, exposure durations and route-to-route considerations.

A particular problem occurs, when for animal welfare, technical or legal reasons the point of departure is difficult or impossible to determine. In these cases, this gap cannot be filled by simply applying additional assessment factors (the term "assessment factor" is used in this paper according to the REACH nomenclature, i.e. in the meaning of "uncertainty factor"). A majority of available experimental studies are done with the oral route of exposure and therefore a route to route extrapolation is needed to derive a DNEL for inhalation exposure. Such route to route extrapolations pose particular problems for irritating or corrosive substances for which local effects in the respiratory tract might determine the most sensitive threshold relevant for the DNEL derivation. However, for obvious animal welfare reasons the need for additional studies with inhalation exposure needs to be balanced with the information requirements in such circumstances. Although technically possible, the experimental determination of such irritation thresholds in animals involves necessarily the establishment of concentration–response relationships and thus testing also in the irritating (corrosive) concentration range which is critical under animal welfare considerations. This conflict is also reflected in the ECHA guidance for acute inhalation (European Chemicals Agency (ECHA), 2008).

With the aim to evaluate whether it would be possible to define a DNEL for local respiratory irritation of substances with reliable data to evaluate systemic toxicity, but with a lack of inhalation

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toxicity information despite existing indication of a local irritation potential, the Working Group Toxicology of the German Chemical Industry Association (VCI) assessed the relationship between established occupational exposure limit values and classification for local irritation and corrosion. Based on this assessment the hypothesis was derived that it would be possible to define pragmatic, but sufficiently reliable and safe upper cut-off limits to fulfill the requirements under REACH without the need for additional inhalation toxicity testing as a standard procedure. Different from current Threshold of Toxicological Concern (TTC) approaches, the present approach is not probabilistic but absolute and thus results in cut-off limits below which no example for an irritating substance is found in the database.

It needs to be highlighted that the proposed generic cut-off limits are not to be used in isolation, but in the context of all available substance related data. Exposure considerations and physical chemical properties of the respective substance can help to identify the real need for inhalation toxicity testing. Thus, the generic cut-off limits are not intended to supersede substance specific exposure limits, e.g., Occupational Exposure Limits, but are intended to provide a tool to fulfill REACH requirements and to balance the information requirements with animal welfare considerations.

2. Materials and methods

As irritation is a concentration dependent effect, it is plausible to assume that generic cut-off limits exist for unspecific direct local inhalation effects induced by corrosive and irritating substances. Therefore, to further develop and proof the hypothesis, a pragmatic approach was applied to analyze existing databases under various aspects. The database shall cover in particular industrial chemicals. This focus on industrial chemicals reflects the scope of REACH and guarantees that the required applicability domain of the concept is matched.

As a starting point, the list of substances as published in Annex VI of Regulation (EC) 1272/2008 and Annex I of Regulation 67/548/EC was used as an independent database for harmonized classification information, peer reviewed by national chemical authorities or the European Chemical Authority (ECHA). All substances that are legally labeled with R34, 35, 36/37/38, or 41 (corresponds to the Globally Harmonized System of Classification, Labelling and Packaging of Chemicals (GHS) classifications H314, H315, H318, H319, H335) were selected and analysed against the existing threshold limit value (TLV) in Germany as set by the Technische Regeln Gefahrstoffe (Technical Rules for Dangerous Substances, TRGS 900), which are derived by the Commission for Dangerous Substances (Ausschuss fuer Gefahrstoffe, AGS), an advisory committee to the Ministry of Labor and Social Affairs in Germany. The underlying toxicological data and the TLV derivation are well documented and often based on existing evaluations by the MAK Commission (Occupational Limit Value Commission) of the Deutsche Forschungsgemeinschaft, which is also a government-appointed panel. These comprehensive evaluations are publicly available. The basis for the AGS assessment in many cases is observational experience in humans, supplemented by animal data which are assessed for their human relevance. For the delineation of human respiratory effects, in particular if they are local, animal data usually can be used without applying further assessment factors (see REACH Guidance on information requirements and chemical safety assessment, Chapter R.8: Characterisation of dose [concentration]–response for human health, Table R. 8–4).

In individual cases, TLV group classifications (i.e. soluble barium salts, hexane isomers, heptane isomers, octane isomers, inorganic mercury compounds, inorganic selenium compounds, inorganic silver compounds, inorganic tin II and IV compounds, chromium II and III compounds, vinyltoluene isomers) were assigned to individual chemical species and/or classes in order to have a clear concordance in the database. Hydrocarbon mixtures and polymers were not assigned on an individual chemical species basis. The reason is that polymers are not in the scope of REACH and hydrocarbon mixtures are too complex to be matched properly.

The resulting list was reduced by all chemicals that are officially classified as carcinogenic, mutagenic or toxic to reproduction (CMR) in Category 1 according to the Regulation on Classification, Labelling and Packaging of Substances and Mixtures (CLP). In these cases the TLV is assumed to be primarily driven by CMR properties and not per se by the irritation thresholds at the respiratory tract. The CMR information used in the analysis was supplied by the CMR list of the German Institut für Arbeitssicherheit (Institute for Occupational Safety, IFA) (IFA, 2010) which is an official compilation of the European Annex I classifications. The resulting database was additionally cross-checked for those parameters that could influence the TLV level apart from the irritation threshold itself. If the TLV level was driven by other effects than irritation, the respective substance was removed from the list. Reasons for elimination from the list were recorded and considered exclusion criteria for the concept.

It must be noted that substances which are not legally classified as irritating or corrosive still can be irritants or corrosives by self-classification. Nevertheless, self-classification was not taken into consideration to expand the database since these data were not assessed by a peer review process. For the same reason, the current European Classification and Labelling Inventory that has been compiled in accordance with Article 42 of the CLP Regulation has not been taken into consideration.

3. Results

By 2012 there are 450 substances or substance categories for which TLVs are set in Germany (amendment: GMBl 2012 S. 11 [Nr. 1]). Breaking down the substance group categories (soluble barium salts, hexane isomers etc.) into the respective individual chemical species with a valid legal classification, the number of relevant substances increases to 477 from which 76 are excluded for their carcinogenic, mutagenic or reproductive toxic properties. Out of the remaining 401 entries, 129 are legally classified as corrosives (R34, R35) or irritants to the skin, the eye or the respiratory tract (R36/37/38, R41) with 89 falling in the "irritant category" and 40 in the "corrosive category".

At first sight, these two categories generally had TLV limits above 10 mg/m^3 (for irritants) and 1 mg/m^3 (for crrosives). Only a small number of substances still was below these generic limits but all of these substances had a pronounced systemic toxicity profile. Therefore, these substances were further evaluated.

Out of the 89 irritating substances, 7 have a TLV below the start-off hypothesis cut-off 1 mg/m^3 (for corrosives) and 22 have a TLV below 10 mg/m^3 (for irritants). 2-chloro-1-ethanol is classified as being very toxic and therefore was removed. In addition, it was apparent that the majority of substances with a very low TLV were skin or respiratory sensitizers. When removing skin and respiratory sensitizers, the number of substances with a TLV below 10 mg/m^3 drops to 15 (Table 1).

Whether the TLV of these remaining 15 substances is driven by respiratory tract irritation or other mechanisms of systemic toxicity was evaluated on a case-by-case basis (further details are given in the discussion section below).

Out of the 40 substances that are classified as being corrosive (R34) or very corrosive (R35), 15 have a TLV below 1 mg/m^3. Different from irritating chemicals, corrosives very often display