Johnson & Johnson

May 11, 2015

OSHA Docket Office
Docket No. OSHA-2012-0023
U.S. Department of Labor
Room N-2625
200 Constitution Avenue, NW
Washington, DC 20210

Dear Sir or Madam:

The health and safety staff at Johnson & Johnson is pleased that OSHA is reviewing its overall approach to managing chemical exposures in the workplace. In support of your efforts, we are happy to provide responses to several of the questions posed in your Request for Information. Our input reflects the collaborative effort of our toxicology and industrial hygiene experts, who are seasoned professionals with several decades of experience. We hope our insights are valuable to the agency and we are available to provide additional details as necessary.

Feel free to contact me at 732-524-2548 or via email at jvanhou1@its.jnj.com if you have any questions or would like additional information.

Sincerely yours,

Joseph Van Houten, Ph.D., CSP
Senior Director, Technical Support
Environment, Health, Safety & Sustainability

Question IV.A.2

If there is no OSHA PEL for a particular substance used in your facility, does your company/firm develop and/or use internal occupational exposure limits (OELs)? If so, what is the basis and process for establishing the OEL? Do you use an authoritative source, or do you conduct a risk assessment? If so, what sources and risk assessment approaches are applied? What criteria do facilities/firms consider when deciding which authoritative source to use? For example, is rigorous scientific peer review of the OEL an important factor? Is transparency of how the OEL was developed important?

We have an Occupational Toxicology and Health Committee that develops occupational exposure limits (OELs) for active pharmaceutical ingredients (API) that we manufacture and for critical non-pharmaceutical compounds. The basis for these OELs is compound-specific data. Our OELs are peer-reviewed, documented and communicated. We have a process whereby business criticality is evaluated with the business segment using the compound. The Committee members include toxicologists, industrial hygienists, and other subject matter experts who review the OEL monograph that summarizes available data, select the key endpoint as the basis for protection, and specify the safety factors used in calculating the OEL.

For non-pharmaceutical compounds, Johnson & Johnson uses the ACGIH TLVs as an authoritative source unless there is a stricter local regulatory requirement/value and considers NIOSH RELs on a case-by-case basis.

For industrial chemicals and isolated process intermediates (IPIs) used during API synthesis, we may generate data to categorize the compound into a hazard band, or we use QSAR to assign into a hazard band.

Our internal program for occupational exposure limits begins when our scientists discover new molecular entities (NMEs) for development into pharmaceutical products. By definition, NMEs are novel compounds that have little, if any, known toxicological data. The first step is to assign a compound of interest into one of six health hazard categories while it is still in the very early stages of research. A compound is assigned to one of six Health Hazard Categories (HHC). The six HHC groups range from the least hazardous Category 1A through to Category 4, which includes compounds that are potentially extremely hazardous. Examples of Category 4 are highly potent active pharmaceutical ingredients and compounds that may cause life-threatening adverse effects, or irreversible effects such as cancer.

When a NME is first synthesized and little toxicological data are available, the compound is assigned to a default HHC based on the table below.

Default Health Hazard Category	Basis
2	Large protein and high molecular weight APIs, AIs and IPIs. Monoclonal antibodies (MAbs)
3A	Nanoparticle, small protein and low molecular weight APIs, AIs and IPIs
4	Abortifacients, 5-alpha reductase inhibitors, antineoplastic cytotoxics (antibiotics, enzymes, mitotic inhibitors, antimetabolites, nucleoside antagonists, etc.) cardiac anti-arrhythmics, cytokines, cytostatics, GnRH antagonists, gonadotropins, nucleoside antivirals, potent opioid narcotics, proteolytic enzymes, purine and pyrimidine antagonists (immunosuppressants, antineoplastics), retinoids, sex steroid hormones (androgens, estrogens, oxytocics, progestins, etc.)

Through experience, we have determined that classifying unknown chemicals into these default HHCs provides sufficient protection throughout early research and development when minimum quantities are handled. As the NME becomes more promising as a drug candidate, toxicity testing begins and includes many of the following procedures: structural activity, acute toxicity (in vivo), eye irritation (in vitro/in vivo), skin irritation (in vitro/in vivo), dermal sensitization (in vivo), and genotoxicity, including mutagenicity and/or chromosomal damage. As sufficient toxicological data begin to emerge, the NME is classified into one of the HHCs by our occupational toxicology staff. Data are evaluated with respect to specific criteria regarding the inherent hazardous properties of the chemical material and characterized with respect to the severity of each. A HHC summary is written and used in advance of setting a numerical occupational exposure limit (OEL) to support sites in determining the controls needed to handle the chemical safely.

NMEs that show desired biological activity and pass their initial toxicity tests are chosen for further development. This requires that larger quantities of the chemical are synthesized so that clinical testing in humans can progress. At this point sufficient toxicity information is available to calculate a numerical value called an Occupational Exposure Limit (OEL) that is similar to the Permissible Exposure Limits (PELs) promulgated by OSHA and the Threshold Limit Values (TLVs) established by the American Conference of Governmental Industrial Hygienists (ACGIH). To establish an OEL, Johnson & Johnson's occupational toxicologists assess all of the available toxicity data and calculate a value using data-adjusted assessment factors to account for uncertainty. The OEL and accompanying scientific data are documented in a monograph that is used to communicate with research scientists and manufacturing personnel.

In addition to setting an OEL, we assign a notation if there are specific hazardous properties of the material in an occupational setting, such as DSEN or RSEN for dermal and respiratory sensitizers, CA for carcinogens, REPRO for reproductive hazards and SKIN for substances that can enter the body via the dermal route.

Question IV.A.3

OSHA is considering greater reliance on peer-reviewed toxicological evaluations by other Federal agencies, such as NIOSH, EPA, ATSDR, NIEHS and NTP for hazard identification and dose-response analysis in the observed range. What advantages and disadvantages would result from this approach and could it be used in support of the PEL update process?

In our experience, NIOSH and NTP conduct thorough, well-reasoned toxicological evaluations. Such peer-reviewed evaluations would be useful in the PEL update process, and we have used NIOSH RELs and NTP reports to inform our OEL process. The other agencies have different review processes that are neither transparent nor amenable to industry input, and in our experience are not on par with NIOSH or NTP.

The advantages of using a peer-reviewed approach is that it results in a science-based, high quality hazard assessment that can be used for risk assessment. The science of risk assessment has progressed tremendously over the last few years and allows for compound-specific calculations, which are more challenging and difficult to make. The use of default uncertainty factors in the OEL calculations make the process much simpler but much less scientifically based. A major disadvantage of the peer review process is that this methodology places higher demands on the time of scientific experts (e.g. toxicologists, pharmacokinetics experts, etc.) that conduct the peer review.

Question IV.A.4

OSHA is considering using the Point of Departure (POD) (e.g., BMD, LOAEL, NOAEL), commonly employed by other authoritative organizations for carrying out noncancer risk assessments as a suitable descriptor of the Low End Toxicity Exposure (LETE) level that represents a significant risk of harm. Is this an appropriate application of the POD by OSHA? Are there other exposure values that OSHA should consider for its LETE?

No. By definition the BMD and NOAEL are not indicative of toxicity; rather, they are levels where toxicity is *not* expected. Thus, the LETE terminology is not appropriate for POD. The European Chemicals Agency (ECHA) has a procedure for determining Derived No Effect Levels (DNEL) that would be useful to OSHA. The ECHA provides a thorough discussion on this topic (see ECHA Guidance on Derivation of DNEL/DMEL from Human Data, Draft Rev. 2.0, 2010).

The POD should be based on the most critical effect that may be observed in the employee. In some instances this may be an adverse effect, or in the case of APIs, may be pharmacological endpoint (considered to be beneficial to the patient, but adverse for the healthy worker).

There are a number of other issues in low-dose extrapolation and threshold response. Dose-response curve modeling and its effect on low-dose extrapolation is one example. For example, if one uses linear,

Weibull, multi-stage, probit (or others) equations to fit a dose response curve and extrapolate responses, what effect does that have on estimated thresholds? It can be orders of magnitude.

Endogenous production, such as for ethylene or isoprene, and a natural background for their epoxides might be a strong argument for setting a practical threshold for such compounds. For endogenously produced materials, the dose-response modeling could be to that "practical threshold," rather than extrapolating to "zero dose, zero response" which would never be attainable for such materials.

Further, although one particular chemical may be below the detectable adverse effect threshold, we live in a complex world with a population subject to a broad range of genetic factors, varying health status, pre-existing medical conditions, medications, life-style factors, etc. Add to that the generally mixed chemical exposures, at the workplace and via the general environment. One must consider, in occupational settings too, the potential for multiple agents to impact the same target cells via the same or similar modes of action. Then, although each individual chemical exposure may be below the threshold of effect, the sum of the exposures is not.

Question V.A.6

OSHA is interested in the experiences of companies that have had to prepare chemical dossiers and submit registration information to the European Chemicals Agency (ECHA) ECHA. In particular, how might the approaches be used to support occupational exposure assessments and development of use-specific risk management in the United States?

Some of the hazard classifications that have been developed by ECHA could be useful in establishing OELs, and more importantly the notations that accompany a compound. These are instrumental in communicating the hazards of compounds to industrial hygiene staff and the workforce. The ECHA process also allows for consolidation of all hazard data available for a compound and allows for use of that data in the OEL setting process. The resulting exposure assessments are then based on this information. We base OELs on systemic effects, and not all hazard classification relate to systemic toxicity.

Question V.A.7

To what extent is information developed under REACH used by U.S. businesses to promote product stewardship and ensure safe use of substances and mixtures by product users?

REACH dossiers available from EChA contain legally binding harmonized classification of human health (and environmental) endpoints that can be used to predict hazards under typical use scenarios for products. The extent of use will vary by chemical/product type. As mentioned in IV.A.4, the DNELs can be useful in setting an OEL. Further, ecotoxicity data are useful in life-cycle assessment for end of product life (see: Oltmanns et al. 2014 for additional information).

The information developed under REACH is currently used by our company to conduct hazard assessments, which in turn are used to perform risk assessments for human and environmental health and safety. This helps us promote product stewardship and ensure safe use of substances. The REACH and CLP approach from the EU also allows for classification and safe handling of mixtures.

Question V.B.1

To what extent do you currently consider elimination and substitution for controlling exposures to chemical hazards?

Preference for elimination and substitution as a means of controlling exposure to chemical hazards is incorporated into the Johnson & Johnson EHS&S Standards, which apply universally to all operations across the globe. In the EHS&S Standard on Chemical Substances Management, we state the following:

> "The organization shall establish, implement, and maintain a process to ensure that non-carcinogenic, non-hazardous or less hazardous material alternatives are considered for use, whenever possible. Chemicals, such as polychlorinated biphenyls (PCBs), shall be eliminated from use and storage.
>
> The organization shall develop an action plan to control employee exposures below the applicable J&J or Local/State/Country legislation OEL with the goal of reducing reliance on administrative and PPE controls. Management of risk shall follow the hierarchy of controls (preference most to least) to eliminate the hazard, substitute with less hazard, engineering controls, administrative controls, and reliance on personal protective equipment."

Our chemical development process includes a stage gate review whereby the chemical synthesis steps are assessed by both product developers and EHS stakeholders. A key component of this assessment is the identification of hazardous chemicals for elimination or reduction in use.

In addition, we have programs that focus on the environmental impact of chemicals in our products that have an added benefit of improving safety and health for our employees as well. Two programs of note are Earthwards® and the Global Aquatic Ingredient Assessment™ (GAIA).

Earthwards®

The Earthwards® approach is Johnson & Johnson's way of addressing the impacts of our products, throughout their lifecycles. Today more than ever, our customers and consumers expect us to incorporate sustainability in everything we do. This means being thoughtful and innovative in our approach to material selection, packaging, energy and water use, waste reduction, and even social impacts (Johnson & Johnson Earthwards® Overview, 2015).

When we launched Earthwards® in 2010, we used it to focus our product teams and challenged them to make significant improvements to 60 products. Today, we have surpassed our original goal, integrated and expanded the process across our company, and use the Earthwards® approach to drive continuous innovation by:

Requiring new products to:

1. *Meet product stewardship requirements*
   New products must achieve regulatory compliance and deliver on Johnson & Johnson's high standards.

2. *Be reviewed for lifecycle impacts*
   The lifecycle impacts of products are reviewed at the category level and opportunities to drive improvements are considered at the design, procurement, manufacturing and marketing stages of a product's development.

Inviting every product team to:

3. *Implement and validate improvements*
   Product teams collaborate with sustainability experts to implement recommended improvements, and environmental marketing claims are reviewed and approved in accordance with applicable guidelines.

Encouraging the most broadly sustainable product teams to:

4. *Achieve Earthwards® recognition, an honor celebrating our most innovative and broadly improved products.*

   If a product achieves at least three significant improvements across our seven impact areas (materials used, packaging, energy reduction, waste reduction, water reduction, positive social impact or benefit, and product innovation), a board of internal and external experts determines if the product warrants Earthwards® recognition and provides suggestions for additional improvements. Teams who receive Earthwards® recognition are publicly congratulated on earthwards.com and rewarded for their innovations by Johnson & Johnson leadership.

Global Aquatic Ingredient Assessment™ (GAIA)

Formulated personal care products (PCPs) are mixtures that comprise a chemically diverse class, including neutral organic compounds, polymers, cationic and anionic compounds, organic and inorganic metal salts, acids, bases, and botanical extracts largely of unknown chemical composition. Since PCPs are used globally wherever there is human activity, they can be emitted to the environment,

predominantly in wastewater, under normal use. As water quality concerns due to industrial point sources decrease, regulators and scientists have begun focusing on this class of compounds as a possible concern because of their widespread use. As a result, there is a desire to compile, interpret, and use available data on the potential environmental hazards due to PCP use as a guide for decision making regarding ingredients to select or avoid in PCPs, to minimize the potential for adverse environmental effects. We developed a novel algorithm to obtain environmental hazard data relevant to organic and inorganic, non-polymeric PCP ingredients, evaluate and interpret those data, and translate the information to a single numeric score that can be used by non-specialists to allow environmental protection goals to be included in decision making. The GAIA algorithm incorporates information on environmental persistence, bioaccumulation potential, aquatic toxicity of the parent compound and degradants, excess toxicity from ecological endocrine disruption effects, the potential for producing photochemical smog. It can be rapidly adapted to consider any new hazard endpoint that has been demonstrated to be a particular concern. The algorithm translates data to numeric scores capable of discerning modest differences in environmental hazard potential by aggregating empirical and modeled data for disparate endpoints using a system of weighting and penalties. The GAIA score is used to communicate environmental safety information for PCP ingredients and products to formulators in a form that is scientifically sound and sufficiently clear and unambiguous, so that no special expertise in environmental science is necessary to understand and use the result. The Johnson & Johnson Consumer Group of Companies has set environmental targets for GAIA scores for all new and reformulated products (Johnson & Johnson Consumer Group of Companies internal SOP, 2015 revision).

Chemical ranking and scoring systems have been developed for other purposes (e.g., Hansen et al., 1999; Klein et al., 1988; Russom et al., 2003; Swanson et al., 1997; Welch and Ross, 1982). The GAIA system differs from previous ranking and scoring schemes in that: (1) it was developed specifically for evaluating ingredients in PCPs, so human safety could be excluded, as those attributes are rigorously evaluated separately on a routine basis because of the nature of the products; (2) it is hazard-based, because many PCPs are widely used in other applications (e.g., industrial detergents, dyes, lubricants) and hence the incremental environmental risk due to a single company's products cannot be accurately quantified since overall exposure from all sources is not readily available; (3) scores are based on a consistent data set for each substance; (4) scores range between zero and one hundred, allowing relatively fine distinctions among substances; (5) the algorithm includes penalties for uncertainty when models are used to fill data gaps; and (6) scores are all tagged with a confidence level qualifier of "high," "medium," or "low," to identify cases where the generation of a new study could dramatically influence the score for ingredients where few data exist. Further, when data are available, but are of uncertain quality, "provisional" scores can be generated as a tool for formulators seeking some qualitative guidance on the use of an ingredient.

Question V.B.10 Please describe your experience in using health hazard and/or control banding to address exposures to chemicals in the workplace.

If we have chemical specific data we will calculate an OEL and do not utilize the banding approach. Companies can also calculate OELs for substances with limited data (ECETOC 101)

The purpose of hazard banding (classifying a compound based on its inherent toxicological properties) is to be able to safely handle compounds that have minimal data (and for companies that don't have the resources to establish OELs). These hazard bands need to be a part of a mature chemical handling program because the hazard bands then need to be linked to 'controls', but these controls are selected based on a risk assessment by EHS professionals. Our program includes hazard categorization (hazard banding), followed by exposure assessment and ultimately risk assessment (determining the appropriate handling of the compound). The risk assessment is dependent on numerous factors, including volume of compound handled, frequency handled, physical form of compound, task being performed, etc. To be effective this process has to be linked to a mature chemical handling/management program (AIHA 1996).

Other questions

Question V.A.2.

How might the information on the properties and toxicity of chemicals generated by CompTox, ToxCast, and/or Tox21 be utilized by employers to identify chemical hazards and protect workers from these hazards? OSHA is also interested to hear from commenters who may currently make use of these data in their worker protection programs.

Any such info would only be useful for setting hazard bands.

Question V.A.3:

Are QSAR, readacross, and trend analysis useful and acceptable methods for developing hazard information utilizing multiple data sets for a specific group of chemicals?

In a word, yes. A group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity should have similar values for an OEL. There are of course exceptions, such as n-hexane among the alkanes. The OECD provides the following guidance on this topic (see: OECD ENV/JM/EXCH (2005).

Structural similarities may create a predictable pattern in any or all of the following parameters: physicochemical properties, environmental fate and environmental effects, and human health effects.

The similarities may be based on the following:

- a common functional group (e.g. aldehyde, epoxide, ester, metal ion, etc.); or as an example from the pharmaceutical industry, β-lactam antibiotics.
- the likelihood of common precursors and/or breakdown products, via physical or biological processes, which result in structurally similar chemicals (e.g., the "metabolic pathway approach" of examining related chemicals such as acid/ester/salt); and,
- an incremental and constant change across the category (e.g. a chain-length category).

The applicability domain of a chemical category identifies the physicochemical property space within which the chemical category is considered to be reliable. The applicability domain is a concept borrowed from the QSAR field. In the context of a chemical category, it can be considered to identify the ranges of physicochemical, environmental, toxicological and/or ecotoxicological properties within which reliable estimations can be made of missing data points, by the use of trend analysis (interpolations and/or extrapolations), read-across, structure-activity relationships (SAR), quantitative structure-activity relationships (QSAR), activity-activity relationships (AAR). It can also be considered as a set of inclusion and/or exclusion rules that identify the ranges of values within which reliable estimations can be made for category members. To illustrate the concept of applicability domain, it might be observed that the category of ethylene glycols shows trends in certain properties in proportion to the chain length of the glycols, but that these trends are only applicable within a defined range of chain lengths.

Question V.A.4:

Are there other acceptable methods that can be used to develop hazard information for multiple chemicals within a group?

Yes.

<u>Hydrocarbon Solvent Group Guidance Values</u>

Much work has been done to establish Hydrocarbon Solvent Group Guidance Values. The reciprocal calculation procedure (RCP) method for deriving OELs for mixtures was applied to hydrocarbon solvents, which are widely used in commerce. These substances are volatile, and exposure to vapor is associated with a number of end uses. Exposures may be relatively high in some situations. Moreover, hydrocarbon solvents are often complex and variable in composition. Additionally, some of the constituents are well characterized and have their own TLV or OEL (e.g., benzene, toluene, n-hexane, polycyclic aromatics etc.), whereas for others, the information may be more limited. The development of occupational exposure limits has been difficult, and this in turn has led to inconsistencies in the health advice provided (ECETOC 1997). For these reasons, an approach that permits the calculation of a unique OEL for each hydrocarbon solvent based on relatively simple compositional information was developed by the hydrocarbon solvent manufacturers in the US (Hydrocarbon Solvents Panel) and Europe

(Hydrocarbon Solvents Producers Association) and published (McKee et al. 2005). Use of this approach is summarized below.

Refined hydrocarbon solvents often are marketed as mixtures created by distillation of petroleum oil over a particular boiling range. The mixtures may consist of aliphatic (alkane), cycloaliphatic (cycloalkane) and aromatic hydrocarbons ranging from 5 to 15 carbons. The application of the mixture formula is difficult in such cases because these petroleum mixtures contain a large number of unique compounds, many of which do not have a TLV recommendation or PEL.

The use of group guidance values allows hydrocarbon solvents with similar toxicological concerns (e.g., those that act additively) to be evaluated by the reciprocal calculation procedure (RCP), a special application of the mixtures formula. A mixture- specific time-weighted-average Group Guidance Value (GGV-TWA mixture) can be calculated based on the mass percent makeup of the designated groups utilizing the reciprocal mixture formula.

Sensory Irritation Related to Physicochemical Properties

The extent of mucous membranes irritation (local effect) can often be directly related to simple physicochemical properties. Alarie et al. (1995) showed that an increased vapor pressure of homologous substances correlated with an increased RD50 (the concentration in air which decreases the breathing rate of mice by 50%). Furthermore, an increase of the log (octanol-air partition coefficient) was related to a decrease of the RD50. Thus, an increase of the vapor pressure lowered the sensory irritation and an increase of the octanol-air partition (Koa) increased the irritation. This finding is not only related to the RD50. Hau et al (2000) showed a correlation between the Koa and odor thresholds, nasal pungency thresholds and median lethal concentrations for alkanes, alcohols, ketones and acetates. The finding of Hau et al (2000) on the relation between nasal pungency threshold as the dependent variable and the air-water coefficient (or dimensionless Henry's Law constant) (Kaw) and the octanol-water coefficient (Kow) as independent variables support the earlier observations of Alarie et al. (1995).

An ECETOC Task Force studied the relationship between the logarithm of the Kaw and the Kow on one side and the logarithm of the RD50 on the other, using the RD50 of all 75 substances in Table 1 of Alarie et al (1995). The log Kaw and the log Kow were derived from EpiSuite (US-EPA, 2000). The following relationship was obtained (Appendix F):

$$\log RD50 = 6.346 - 0.8333 \times \log Kow + 0.7139 \times \log Kaw$$

This equation explains 74.9% of the variance of the log RD50 with the log Kaw and the log Kow as independent variables. Thus, an increase of the log Kow is related to an increase of the irritation. If it is to be based only on sensory irritation, a provisional OEL can be derived by means of the equation above, using the lower 90% confidence limit of the RD50 as a starting point, divided by an arbitrary assessment factor of 10. This relationship might also be useful for estimating the RD50 of a substance that is a member of a series of homologous substances, for some of which the RD50 has been experimentally

measured. The ratio between the OELs is assumed to be identical to the ratio between the RD50s, if the OELs are based only on sensory irritation.

European Centre for Ecotoxicity and Toxicity of Chemicals (ECETOC) Guidance for Setting Occupational Exposure Limits: Emphasis on Data-Poor Substances

In spite of the difficulty in setting reliable OELs based on limited data, ECETOC explored several approaches, which may be helpful for generating OELs (ECETOC Technical Report No. 101, 2006). These include:

The control (hazard) banding concept uses risk phrases as defined under GHS to assign substances to hazard categories for human health. Official OELs and GHS risk phrases of data-rich substances in every hazard category were gathered and the distribution of the OELs in each category was analysed by the ECETOC Task Force. The distribution of the OELs in each category was found to be log-normal and the geometric standard deviation appeared to be very wide. Evaluation of OELs in relation to a single risk phrase (e.g. R20 or R37, without more severe risk phrases) revealed that they differed by 3 orders of magnitude. In light of this wide spread, the 10-percentile of OELs of data-rich substances, assigned to a specific hazard category is proposed as a provisional OEL for all substances in any given category, including those with a limited set of data.

The LD50 can potentially be used as a predictor of chronic toxicity (as of 2007, the RTECS lists 15,827 rat oral LD50 and 33,806 mouse oral LD50 values). To validate this hypothesis, the rat oral LD50s were compared with the MTDs observed in carcinogenicity studies of the US National Toxicology Program. The rat oral LD50 (as modified by the Kow) appeared to be highly predictive of the MTD. The 5-percentile of the distribution of the estimated MTD might be used as critical effect level for deriving an OEL. This method should not be applied to carcinogenic, mutagenic or reprotoxic substances.

Since inhalation is the most relevant route of workplace exposure, the relationship between the official OEL and the 4-hour rat LC50 was evaluated. For the dataset used, the ratio between the LC50 and the OEL was log-normally distributed and the LC50 appeared to be a direct predictor of the OEL. The lower 90% confidence limit of the estimated OEL distribution can be adopted as a provisional OEL. This method should not be applied to carcinogenic, mutagenic or reprotoxic substances.

Comparing the chemical structure of a substance without toxicological data with substances of a similar structure but with known toxicity is a potentially useful way to get a better understanding of the type and severity of the effects. It may be used in combination with the hazard banding method or the relationship of LD50 and MTD. This read-across approach seems promising considering the increasing availability of internet-based tools that, upon entry of a molecular structure, generate a list of similar molecules sorted by structural similarity with links to their toxicological profiles. The experiences with these new internet sources have not yet been published.

Using data on the RD50 (airborne concentration in ppm, which decreases the breathing frequency of mice by 50%), a provisional OEL can be derived for those substances expected to exhibit sensory irritation. A few authors have shown that the Koa is closely related to the RD50, and as such this can be

used to predict the severity of the sensory irritation for homologous substances with the same mode of action, for which no RD50 has been established. The Koa can be estimated from the Kaw and Kow.

The threshold of toxicological concern (TTC) concept, widely applied in the risk assessment of the general population for protection from food and feed contaminants, might also be used to set OELs for substances with a systemic mode of action. The tolerable dose level for (healthy) workers is assumed to be 100 to 1,000 times higher than for the general population, as shown in this report for some substances belonging to Cramer class I. This means that an OEL could be based on a value of about 100 times any TTC established for the general population. The TTC-concept has been based on the Cramer scheme, designed to prevent underestimation of toxicity. Overestimation of toxicity has not received much attention in the Cramer classification. This may result in certain OELs being overly conservative, as observed for some substances assigned to Cramer class III.

Question V.A.5:

What are the advantages and disadvantages of each method?

Included in above discussion.

Question V.A.8:

Should OSHA pursue efforts to obtain data from ECHA that companies are required to provide under REACH?

Yes, these data will typically be from OECD guideline studies or other validated methods conducted under GLP requirements of the US Food and Drug Administration.

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