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OECD OEL online workshop report

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OECD OEL online workshop report

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OECD Environment Directorate,
Environment, Health and Safety Division
2 rue André-Pascal
75775 Paris Cedex 16
France

E-mail: ehscont@oecd.org

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Note from the Secretariat

The OECD Occupational Exposure Limit Workshop was held online in October 2022. The aim of the Workshop was to follow up on the Survey Report of methods used to establish OELs led by Canada completed in 2022 (ENV/CBC/MONO(2022)6). The Workshop presented several case studies demonstrating approaches for establishing OELs for different endpoints and by different regulatory authorities and included discussions on how such approaches could be standardised and to provide examples for countries that will be establishing OELs.

Foreword

Various organisations derive Occupational Exposure Limits (OELs), however the approach for calculating OELs is not globally harmonised. A project was proposed jointly to the Working Party on Hazard Assessment (WPHA) and the Working Party on Exposure Assessment (WPEA) in June 2020 to examine approaches and guidance for OEL development, explore opportunities to harmonise OEL derivation, and identify areas for collaboration related to worker OELs through case studies. The project was led by Health Canada, in collaboration with experts from Canada, Finland, Germany, Japan, the Netherlands and Switzerland.

Health Canada circulated a survey to members of the WPHA and WPEA in order to collect information from countries on policies and scientific approaches used to develop OELs. Survey responses were summarised in a report that outlined similarities in approaches, noted considerations for future OEL development, and identified potential areas for collaboration through case study development. This survey report was published on the OECD website in June 2022 (ENV/CBC/MONO(2022)6).

As a follow-up activity, a workshop was proposed by Japan and held on 21 and 24 October 2022. The objectives of the workshop were to present Case Studies to highlight different approaches to setting OELs included in the OECD survey report, and to discuss the possibility of harmonisation.

In addition, Japan launched a new legal framework for establishing new OELs. Using Japan as an example, the workshop also aimed to provide an example of a standard method of setting OELs for countries that will be establishing OELs in the future.

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Presenters and Panellists

Paul C. DeLeo	American Chemistry Council
Michelle Deveau	Health Canada
Claudia Drossard	Federal Institute for Occupational Safety and Health (BAuA)
Andrea Hartwig	Karlsruhe Institute of Technology (KIT)
Laurence Hoffstadt	European Chemicals Agency (ECHA)
Andy Maier	Workplace Environmental Exposure Level (WEEL) Committee
Bruce D. Naumann	American Conference of Governmental Industrial Hygienists (ACGIH)
Mariko Ono	Japan National Institute for Occupational Safety & Health (JNIOSH)
Robert Pasanen-Kase	State Secretariat for Economic Affairs (SECO)
Klaus Schneider	Forschungs- und Beratungsinstitut Gefahrstoffe GmbH (FoBiG)
Yvette Selby-Mohamadu	US Environmental Protection Agency (EPA)
Stefan Vink	Health Council of the Netherlands

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Abbreviations and acronyms

ACGIH	American Conference of Governmental Industrial Hygienists
ADE	Acceptable daily exposure
ALARA	As low as reasonably achievable
AGS	Committee on Hazardous Substances
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	Benchmark dose
BMDL	Benchmark dose level
BMC	Benchmark concentration
BMCL	Benchmark concentration level
CRV	Cancer risk value
DFG	Deutsche Forschungsgemeinschaft
ECHA	European Chemicals Agency
EC3	3-fold increase in lymphocyte proliferation
JNIOS	Japan National Institute for Occupational Safety & Health
JSOH	Japan Society for Occupational Health
LLNA	Local lymph node assay
LOAEL	Lowest observed adverse effect level
MAK	Germany Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area
MoA	Mode of action
NOAEL	No observed adverse effect level
OEL	Occupational exposure limit
OSHA	Occupational Safety and Health Administration
PBK	Physiologically based kinetic
PEL	Permissible exposure limit
PoD	Points of departure
QSAR	Quantitative structure-activity relationship
RAC	ECHA Risk Assessment Committee
SECO	Switzerland State Secretariat for Economic Affairs
STEL	short-term exposure limit
SUVA	Swiss Accident Insurance Fund
TLV–SL	Threshold Limit Value–Surface Limit
TWA	Time-weighted averages
UF	Uncertainty factor
US EPA	US Environmental Protection Agency
WEEL	Workplace Environmental Exposure Level
WPEA	Working Party on Exposure Assessment
WPHA	Working Party on Hazard Assessment

Executive summary

The OECD Occupational exposure limit (OEL) survey report (OECD, 2022a) was published in June 2022 to summarise the results of a survey of OECD stakeholders on OEL derivation activities, with the goal of highlighting similarities and differences. In a follow-up to the report, a workshop was held on 21 and 24 October 2022 in order to clarify the differences in regional approaches for setting OELs summarised in the survey report (OECD, 2022a) and discuss and develop possibilities for a harmonised approach for setting OELs. Another objective was to develop a general scheme for setting OELs, which could be used by countries that intend to set/update OELs.

The workshop proposed a general scheme to establish an OEL as a reference for countries setting new OELs. The scheme constitutes three main steps: (1) definitions and scope of OEL values, (2) data evaluation to support and develop OELs, and (3) methodology for deriving OELs. The first step defines the endpoints, types of OELs, and notations. The data evaluation step discusses which types of data are included, how data quality is assessed, and how critical studies are identified. Lastly, OELs are derived through defined methodologies, including Points of Departure (PoD) selection/modification and uncertainty factors (UFs). In addition, specific approaches are considered for genotoxic carcinogens.

The workshop also discussed considerations in applying OEL values set by other countries and organisations. The need to develop review schemes was highlighted, including a review process of existing literature, data and OEL values set by other countries/organisations which could be conducted by an independent committee. During the review process, the scientific rigour of the data used to derive the OELs should be discussed, including a review of key studies (toxicological data) to evaluate the data quality, transparency of the data used which should be publicly available, and the process and result of expert judgement and weight of evidence should be documented. In addition to the scientific review, social-economic impacts may be assessed in setting OELs. Specific considerations were raised for genotoxic carcinogens, such as discussing acceptable risks and Mode(s) of Action data. The workshop also emphasised the importance of including biomonitoring data, which can affect the characteristics, thresholds, and toxicological classification of substances.

In exploring possible harmonisation of setting OELs, information and data sharing by authorities were highlighted. This can be done, for example, through documentation of the complete process of OEL setting and sharing this information and underlying data used to establish OELs on public web databases. The OECD could play a key role by providing a forum for information sharing fostering approaches for standardising methodologies and developing guidance documents on modelling and QSAR applications for OEL setting.

1 Introduction

1.1. Background

Occupational exposure limits (OELs) generally represent the maximum airborne concentration of a substance to which a worker can be exposed over a period without suffering any harmful consequences. OELs are set by many international government agencies (as enforceable limits and/or as guidelines) and professional organisations to protect workers' health from possible risks when using chemicals and determine the effectiveness of existing controls or risk management measures. OELs are mainly intended to prevent workers from inhaling chemicals as vapours, mists and dust. Notations are used in conjunction with an OEL to indicate when dermal protection is needed or when there are effects related to sensitisation or carcinogenicity.

No global harmonised approach exists for OEL derivation and values often differ between organisations and government agencies. To examine commonalities and differences in approaches and guidance for OEL development and explore opportunities to harmonise occupational exposure limit development, a project led by Canada, Establishing Workplace Exposure Limits (OELs project) was launched in 2020 under the OECD Working Party on Hazard Assessment (WPHA) and Working Party on Exposure Assessment (WPEA).

A survey to gather information on global approaches for determining OELs was launched in 2021 and responses were received from 27 regulatory agencies in 12 countries (some responses covered multiple agencies within a country), as well as the European Chemicals Agency (ECHA). The Survey Report on Establishing Occupational Exposure Limits (referred to as "OEL Survey Report" for hereon) was published in June 2022 [ENV/CBC/MONO(2022)6] (OECD, 2022a), which included sections on roles, responsibilities and scope for OEL development, methods for development and derivation of OELs, and successes and challenges of OEL programme implementation in member countries.

As a follow up activity, the OECD Expert Group supporting the OEL Survey Report proposed considering as a potential case study, Japan's revision of the Industrial Safety and Health Act aimed at shifting the responsibility of occupational risk assessment and management of chemicals from regulatory agencies to industries. In line with this concept, the Japanese government will set OEL values for 150-200 substances per year.

To further explore this, the OECD and the Japanese National Institute of Occupational Safety and Health (JNIOSH) jointly hosted an online workshop on 21 and 24 October 2022 (OECD workshop on approaches for establishing Occupational Exposure Limits (OELs) - OECD). The aim of the workshop was to examine opportunities for harmonisation in setting OELs by;

- summarising various approaches for establishing OEL values which could be used by Japan and other countries for establishing new OELs; and
- scoping possible future OECD activities related to OELs.

The virtual workshop was attended by more than 250 delegates representing government agencies and the EU, industry, academic institutions, and non-governmental organisations.

1.2. Overview of the online workshop

The workshop included two sessions:

- Session 1: Approaches to Set OEL Values
- Session 2: Future Perspective – Exploring International Harmonisation for Approaches to Set OELs

Session 1 focused on the general workflow/process to set OEL values illustrated in the OECD OEL Survey Report, as well as the new scheme of setting OELs in Japan. Speakers presented methodologies used to set OEL for specific endpoints (e.g. carcinogenicity, skin sensitisation, and biomonitoring) described in the 2022 Report. Presentations were followed by a discussion on:

- What are some considerations when applying OEL values set by other countries or organisations from scientific and legal points of view?
- How could occupational regulatory agencies practically consider OELs for specific endpoints in establishing their OELs?

Session 2 presented survey results on the potential for international harmonisation for setting OELs also described in the OECD report. The session focused on four existing harmonisation initiatives by the USEPA, non-governmental organisations (Workplace Environmental Exposure Levels (WEELs) Committee), BAuA, FoBiG and ECHA, for setting OELs, followed by a discussion on the following topics:

- Are there any specific endpoints or procedures for establishing OELs that may be more amenable to international harmonisation?
- What are some procedures that may help to make establishing OEL values more efficient? e.g., Sharing toxicological and mechanism information and OEL setting methods.
- Is there a role for the OECD to play in increasing OEL harmonisation and/or efficiently setting OEL limits within countries?

The workshop agenda can be found in Annex A, and the workshop results are summarised in Chapter 2 and Annex B. In addition, video recordings and presentation slides are available on the OECD website[1].

[1] OECD workshop on approaches for establishing Occupational Exposure Limits (OELs) - OECD

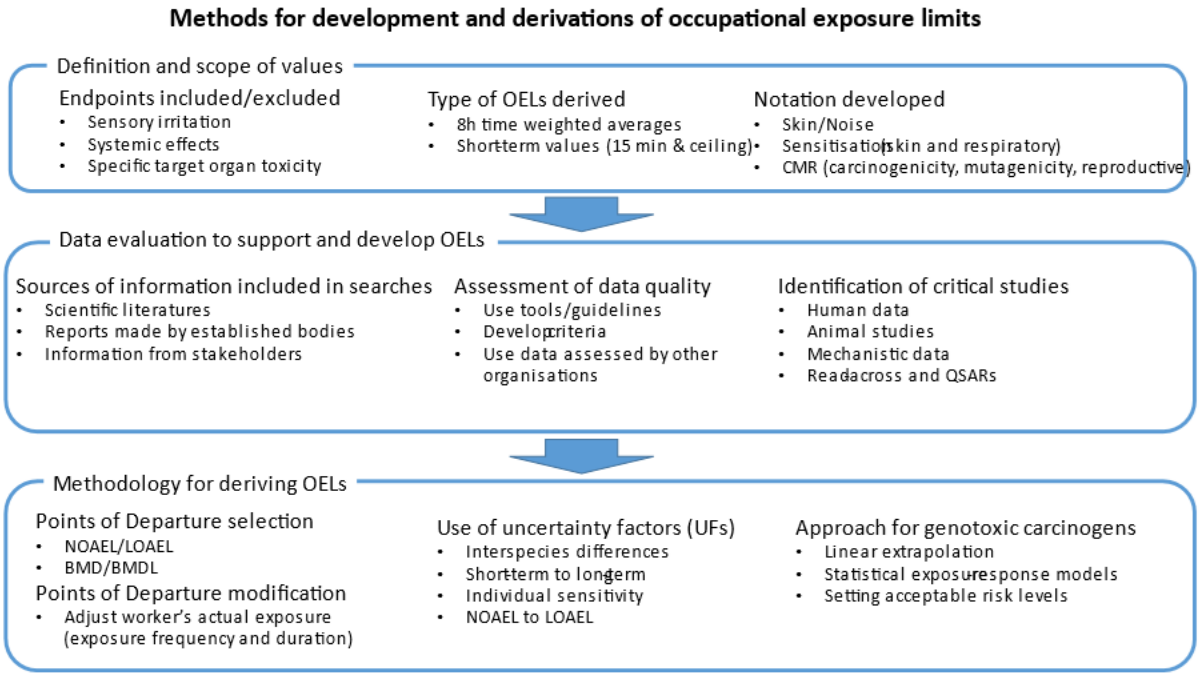
2 Approaches to setting OEL values

Session 1 of the workshop summarised the general process/workflow of setting OELs, which can inform countries establishing new OELs, such as Japan. It also included a discussion focused on carcinogenicity and skin sensitisation, as specific endpoints of concern and inclusion of biomonitoring data.

2.1. General workflow/process

Based on the results of the OECD survey (OECD, 2022a) and discussion at the workshop, the general workflow for derivations of OELs was developed (Figure 2.1). The workflow is composed of three main steps: (1) Definition and scope of values, (2) How data are evaluated to support and develop OELs, and (3) Methodology for deriving OELs. Some points to consider in each step, which are described in the survey report in detail, are summarised and listed in the sections of Annex B.

Figure 2.1. Methods for development and derivation of occupational exposure limits



2.2. Case study - Updating the chemical management system on occupational health in Japan

Japan shared their plan to set hundreds of new OELs in the near term. In their new system for the management of chemical substances, Japan will establish values for manufacturers and users of chemicals that are classified as dangerous or harmful chemicals according to the Globally Harmonised System (GHS) of Classification and Labelling. To limit potentially harmful effects of chemicals, inhalation concentrations for workers must not exceed a derived Concentration Standard. To ensure Concentration Standards are not exceeded, a protection factor can be added to measures of respiratory exposure inside personal protective equipment if other methods of limiting exposure are inadequate. Concentration Standards will not be set until an exposure measurement method has been established.

To facilitate Japan's goal to set Concentration Standards for 800 chemicals by 2026, chemicals for which OELs were derived by other occupational health organisations (e.g. American Conference of Governmental Industrial Hygienists (ACGIH), Deutsche Forschungsgemeinschaft (DFG) and Japan Society for Occupational Health (JSOH)) will be prioritised. Established limit values for the 8-hour time-weighted average and shorter time limit values will be considered. Chemicals with no threshold toxicity, such as genotoxicity and carcinogenicity, will be discussed by a group convened for an expert review.

A two-tiered approach for deriving Concentration Standards for hazardous chemicals was proposed. In some cases, the Concentration Standard can be determined from key literature sources referenced in the documentation of the OEL from other occupational health organisations and documents prepared in the risk assessment project[2], which is considered a first-tier assessment. For other chemicals, key citations may be old or unreliable and the proposed endpoint is not appropriate, in which case, a detailed evaluation will be conducted in a second-tier assessment, which will include a review of updated references to include recent literature and information on work-related accidents. The proposed Concentration Standard will be set by the Japanese Ministry of Health, Labour and Welfare after consulting the Governmental Committee[3].

2.3. Focus endpoints/approaches

The OECD Survey Report (OECD, 2022a) noted that some organisations set OEL values for certain specific health endpoints, such as carcinogenicity, genotoxicity, reproductive and developmental toxicity, and sensitisation. This chapter describes approaches for deriving OEL values for specific endpoints that were presented at the October 2022 workshop.

2.3.1. Carcinogenicity

According to the OECD OEL survey document (OECD, 2022a), methods for the establishment of OELs for carcinogenicity vary among organisations. For a certain group of carcinogenic compounds with a direct genotoxic mechanism, it is not possible to derive an exposure level below which adverse health effects are excluded (i.e. non-threshold substances).

[2] Ministry of Health, Labour and Welfare conducted the chemical risk assessment project from FY2005 to FY2020. The project held an annual Review Committee for Chemical Risk Assessment to review and assess two hundred chemicals if they show high risk. These candidate chemicals were selected from chemicals categorized by the Cancer Research Organization (IARC) as having carcinogenicity of Group 1, 2A and 2B; and recently selected chemicals having high reproductive toxicity and neurotoxicity. For these chemicals, monitoring methods were already proposed by the committee to conduct a field survey to determine exposure levels at the workplace for risk assessment.

[3] It consists of academic experts related to hazard assessment experts, exposure measurement experts, and general occupational health.

In the workshop, Stefan Vink from the Health Council of the Netherlands introduced the Dutch approach for deriving OELs for carcinogens. In the Netherlands, different approaches are used for indirect genotoxic carcinogens (e.g. those that promote various phases of the cancer process or can ultimately result in indirect DNA damage) and direct genotoxic carcinogens (those that cause DNA damage by direct interaction with DNA). A threshold-based OEL approach is used for an indirect genotoxic mechanism whereas for carcinogens with a direct genotoxic mechanism, cancer risk values (CRVs) are calculated using a non-threshold linear approach (Figure 3.1). CRVs are exposure levels that correspond to lifetime cancer risks (taking into account 40 years of occupational exposure).

2.3.2. Skin sensitisation

Many work-related diseases are associated with dermal exposure. The OECD survey document (OECD, 2022a) found that the most common notation developed among organisations is the skin notation indicating dermal exposure can cause adverse health effects, and another common notation used by many agencies is sensitisation. Bruce D. Naumann from ACGIH presented approaches for setting Threshold Limit Value–Surface Limit (TLV[4]–SL) during the workshop. The TLV–SL is the concentration on workplace equipment and facility surfaces that may not result in adverse effects by direct or indirect contact and is also intended to protect against systemic toxicity, sensitisation, and cancer from contact with contaminated work surfaces.

2.3.3. Application of Occupational Biomonitoring

In occupational medicine or occupational hygiene, biomonitoring (also referred to as 'biological monitoring') can be used to assess exposures by collecting biological materials from workers/persons and quantify the hazardous substances, their metabolites or their biochemical and/or biological effect parameters in the obtained biological materials (OECD, 2022b). Biomonitoring can address multiple exposures and does not need to consider the effects of intake. Some organisations use biomonitoring for occupational health and develop biomonitoring guidance and equivalent values.

Robert Pasanen-Kase from Switzerland, led of development of the OECD Guidance Document on Occupational Biomonitoring, introduced the ten lessons learned (Annex 2) (OECD, 2022b). This first international guidance document on biomonitoring will help organisations derive more practical OBL and will promote the use of biomonitoring in the process of risk assessment.

2.4. Considerations in applying OEL values set by other countries/organisations - Panel discussion results

During the panel discussion, the following panellists discussed considerations when applying OEL values set by other countries or organisations from a scientific and legal point of view.

Panellists

Paul C. DeLeo American Chemistry Council

[4] The TLVs are health-based values, and represent a scientific opinion based on a review of existing peer-reviewed scientific literature by committees of experts in public health and related sciences. The TLVs represent conditions under which ACGIH believes that nearly all workers may be repeatedly exposed without adverse health effects. The TLVs are developed as guidelines to assist in the control of health hazards. These guidelines are intended for use in the practice of industrial hygiene, to be interpreted and applied only by a person trained in this discipline.

For more information, please refer to the ACGIH website: https://www.acgih.org/science/tlv-bei-guidelines/policies-procedures-presentations/tlv-bei-policy-statement/.

Andrea Hartwig	Karlsruhe Institute of Technology (KIT)
Bruce D. Naumann	American Conference of Governmental Industrial Hygienists (ACGIH)
Mariko Ono	Japan National Institute for Occupational Safety & Health (JNIOS)
Robert Pasanen-Kase	State Secretariat for Economic Affairs (SECO)
Stefan Vink	Health Council of the Netherlands

2.4.1. General workflow/process for setting OELs

The considerations highlighted by the speakers are shown below, classified into four aspects: Review scheme, Scientific aspect, Transparency, and Considerations for the industry.

Review scheme

- develop a (systematic) review process of existing literature, data and OELs set by other countries (e.g., scientific committee), including a peer review process;
- develop an independent secretariat committee to prepare the discussion points;
- assess the effect of OELs based on not only scientific review but also a social economic impact.

Scientific aspects

- discuss OELs scientifically, e.g., uncertainty tolerance;
- review key studies (toxicological data) to evaluate the quality of OELs;
- distinguish between the assessment factor (extrapolation factor) and uncertainty.

Transparency

- ensure that all relevant data are publicly available with references used so that all parties involved can discuss OELs under the same information;
- document expert judgement and weight-of-evidence process and result.

Considerations for industry

- consider the burden on businesses and make the OELs similar to the GHS or existing regulation values.

2.4.2. Specific endpoints/approaches

- distinguish between scientific base discussion and risk base (acceptable) discussion. Regulators need to decide on acceptable risks, especially genotoxicity and carcinogenicity;
- MoA (mechanism data) needs to be considered when setting OELs on carcinogenicity;
- consider applying biomonitoring;
- biomonitoring can affect the characteristics, thresholds, and toxicological classification of substances.

3 Future prospects – Exploring international harmonisation for setting OELs

This second session of the workshop aimed to explore the potential international harmonisation of setting OELs among countries. While no global harmonised approach for deriving OEL values currently exists, some countries are working on national/regional harmonisation. The United States, non-governmental organisations, Germany, and the EU provided an overview of harmonisation efforts. Presenters and additional experts discussed international harmonisation, efficient approaches, and potential OECD contributions during the panel discussion.

3.1. Current status of harmonisation – OECD survey report

Michelle Deveau from Health Canada, who drafted the OECD OEL survey report, presented observations on global harmonisation described in the OECD report (OECD, 2022a). Some countries collaborate with other countries/regions, but because of challenges and barriers, there is currently no published OEL guidance at the global level.

3.2. Harmonisation practices around the world

3.2.1. Harmonisation initiatives – the US

The US has mainly three government agencies setting OELs:

- The US Occupational Safety and Health Administration (OSHA) is the primary regulatory agency setting workplace permissible exposure limits (PELs).
- US EPA sets new chemical exposure limits (NCELs) and existing chemicals exposure limits (ECELs).
- US NIOSH sets recommended exposure limits (RELs), which may also provide recommended values to a regulatory agency (OSHA and US EPA).

Yvette Selby-Mohamadu from US EPA presented the US national coordination and collaboration between US OSHA, US EPA, and US NIOSH. The three agencies regularly discuss policy and scientific implications as follows.

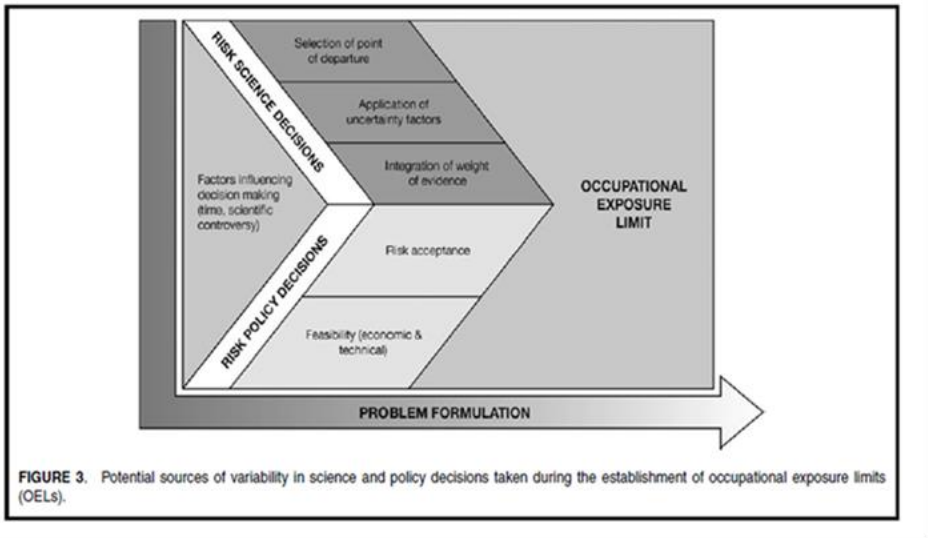
The purpose of the collaboration is to identify environmental and workplace health and safety problems and to effectively implement enforcement of the US national workplace and environmental statutes. Asbestos Rulemaking is an example of cross-referencing for consideration of adopting PELs. Creating a Memorandum of Understanding (MOU) is one means agencies can use to create more formal interagency interaction.

The three agencies have identified contact points to facilitate technical consultations. Experts from US OSHA, US EPA, and US NIOSH meet to discuss occupational monitoring data, representative sampling strategies, and US EPA test orders. NIOSH/OSHA experts have reviewed and provided input on documents related to the use of cascade impactors for exposure monitoring.

3.2.2. Harmonisation initiatives – non-governmental organisations

Andrew Maier from the WEEL Committee presented OEL methods harmonisation from the standpoint of NGOs. They focus on chemicals with limited available guidance. As shown in Figure 3.1, there are methodical and policy processes at the time of setting the OEL. The differences between countries were analysed in two parts.

Figure 3.1. Potential sources of variability in science and policy decisions taken during the establishment of occupational exposure limits (OELs) (Deveau, M et al, 2015)



Examples of policy differences

- Consideration of feasibility: economic and technical, Analytical detection
- residual risk: endpoint, definitions can be quantitative or qualitative
- Periodicity of reviews and updates

Examples of methodological differences

- Benchmark dose (BMD) Modeling: default status or case-by-case
- Inhalation dosimetry adjustments: most organisations do not have a default methodology
- Toxicokinetic data: Most organisations try to maximise the use of available toxicokinetic data for route extrapolation, but default approaches exist
- Linear dose extrapolation: Most organisations consider MoA as an initial step, but some use it as default for direct genotoxicants; others use it to inform weight of evidence in 10^{-3} and 10^{-4} range.

These identified differences highlighted that harmonisation is not standardisation, but rather a 'shared understanding', and that transparency of methods is important though methods can differ. A key consideration is to balance scientific judgement and prescriptive guidelines. It was also highlighted that

methods will continue to evolve, and it is critical to maintain communication among agencies and develop practical guidance to increase consistency and transparency.

3.2.3. Harmonisation initiatives – Germany

A variety of exposure limit values exist at the EU level[5] and sometimes different exposure limit values for the same substances are observed among Member States. The BAuA Research Project F2437[6], presented by Claudia Drossard (BAuA) and Klaus Schneider (FoBiG), explored factors causing the deviations. Comparing default values and determining distributions of extrapolation factors based on comprehensive data analyses can pave the way to harmonisation.

Methodological differences that may lead to quantitative differences in OELs at all steps of the evaluation process were identified as follows:

- Size of assessment factors (especially intraspecies extrapolation)
- Use of the benchmark dose approach for deriving a PoD
- Non-/Application of allometric scaling
- Approach for local effects in the respiratory tract (incl. sensory irritation)
- Non-/consideration of certain endpoints (e.g., developmental toxicity or respiratory sensitisation for OEL quantification)

Large differences were observed in protection levels achieved by the existing frameworks (e.g., from 13.3 to 95% - subacute study, 95% of the target population, local effects), which indicated the need to clearly define the protection goals of frameworks with regard to the coverage of the target population and the remaining uncertainty.

The project demonstrated the use of probabilistic assessment distributions to investigate protection levels and uncertainties of OELs. The probabilistic approach can be used for comparing existing methodologies. It also showed that the selection and modification of PoD could be important sources of deviation of OEL values, and the benchmark approach can be used to describe the uncertainty of the PoD, which is a further advantage of the BMD as a PoD.

Careful consideration should be given identifying aspects of probabilistic OEL derivation that could be harmonised, taking into account the different premises of each framework. The harmonisation of methods should come first rather than of values. The following proposed approaches could help further harmonisation:

- Define values with regard to coverage and probability
- Agree on empirical databases informing extrapolation steps
- Agree on key methodological steps required for deriving OELs / OEL-analogue values
- Provide detailed guidance

[5] Derived No Effect Level (DNEL, EU-REACH regulation), Acceptable Operator Exposure Level (AOEL, EU-Plant Protection Products regulation), Acceptable Exposure Level (AEL, EU-Biocides regulation), Occupational Exposure Limits(OEL, EU-Committee), Arbeitsplatzgrenzwert (AGW DE-Committee), and Maximum workplace concentration (MAK, DE-MAK Commission)

[6] The international workshop summary and materials are available on the BAuA websites (https://www.baua.de/EN/Service/Events/Proceedings/Hazardous-substances/F2437-Workshop.html) and (https://www.baua.de/EN/Tasks/Research/Research-projects/f2437.html)

3.2.4. Harmonisation initiatives – EU

Laurence Hoffstadt from ECHA introduced legal frameworks of the OEL settings within the EU. OELs are adopted under two legal frameworks (Chemical Agents Directive (CAD) and Carcinogens, Mutagens or Reprotoxic substances Directive (CMRD)), which set out minimum standards for worker protection. EU Member States must transpose the requirements into a national legislative framework within the timeline set in the respective Directive. Regarding the OELs, these Directives provide legally-binding OELs as a minimum level of protection for all workers in the EU, and Member States must set corresponding limits that do not exceed the EU values.

Following the request from the EU, ECHA prepares a scientific report for its Committee for Risk Assessment (RAC) based on the available scientific data and any relevant information collected. The scientific report is then subject to an open consultation, and RAC develops its opinion based on a review of ECHA's scientific report. The scientific report becomes an integral part of RAC's opinion and forms an Annex to the opinion. The report includes the identification of MoA, related PoD, relevant assessment factors (AF), particularly for PoD, and the explanation of uncertainty. ECHA publishes it on its website (https://echa.europa.eu/oels-activity-list).

3.3. Exploring a more harmonised and efficient approach in establishing OELs - Result of the panel discussion

During the panel discussion, the following panellists discussed a more harmonised and efficient approach.

Panellists

Claudia Drossard	Federal Institute for Occupational Safety and Health (BAuA)
Andrea Hartwig	Karlsruhe Institute of Technology (KIT)
Laurence Hoffstadt	European Chemicals Agency (ECHA)
Andy Maier	Workplace Environmental Exposure Level (WEEL) Committee
Robert Pasanen-Kase	State Secretariat for Economic Affairs (SECO)
Klaus Schneider	Forschungs- und Beratungsinstitut Gefahrstoffe GmbH (FoBiG)
Yvette Selby-Mohamadu	US Environmental Protection Agency (EPA)

The discussion focused on three topics: information sharing, OECD roles, and others, which are summarised below.

3.3.1. Authority role - Information sharing

Panellists highlighted recommendations for authorities to facilitate information sharing and contribute to harmonisation of approaches for OEL derivations:

- Transparently explain and document all processes for other authorities, so that they can understand which points are different and where the differences come from. This information sharing would be the first step to harmonise the OEL process;
- Use guidance documents and make them accessible on their website in English to share their approach and data, including steps for systematic review and justification of their approach;
- Provide justification documents for OEL derivations, describe key studies in detail. Information on mechanism of action should also be shared for OELs on carcinogenicity;

- Updates and changes in methodologies are necessary due to new knowledge and should be explained and provided;
- ECHA's database is a good example of sharing toxicological key studies. OECD eChemPortal and the US EPA CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard/) are also helpful. The mechanistic information is available in the CompTox dashboard.

3.3.2. OECD and international (regional) organisation role - guidance and portal

The panel also provided recommendations for regional and international organisations to promote harmonisation of OELs:

- Develop guidance documents on new approaches, such as modelling and QSAR in OEL settings for regulatory authorities;
- Provide a meeting platform to collaborate with other regulatory authorities in discussing the OEL approaches such as assessment factor and developing recommendation documents;
- Standardise and document OEL methodologies.

3.3.3. Other comments

International harmonisation of the OEL process is also beneficial for industries based on the experience of the EU harmonised approaches driven by the CAD and CMRD.

4 Conclusions

In follow up to the OECD report (OECD, 2022a), presentations and discussions were focused on the scheme of OELs setting and the possibility of harmonisation. Panellists and presenters raised considerations when setting OELs and suggested what needs to be considered in harmonising approaches on OEL setting, particularly the role of authorities and the OECD, which will greatly assist future OECD activities.

This OEL workshop was significant in that experts from Europe, the U.S., Canada and Japan discussed together general schemes and possibilities for harmonisation in the OEL setting. This discussion was a good starting point and could be developed further.

The OECD has provided test guidelines, guidance documents, and relevant databases, such as the AOP knowledge base[7] and eChemPortal[8], which have enhanced the global harmonisation of sound chemical management. These approaches would also work to harmonise the OEL setting, indicating the potential OECD contribution.

[7] https://aopkb.oecd.org/index.html

[8] https://www.echemportal.org/echemportal/

References

D A Dankovic, B D Naumann, A Maier, M L Dourson, L S Levy. The Scientific Basis of Uncertainty Factors Used in Setting Occupational Exposure Limits. J Occup Environ Hyg. 2015;12 Suppl 1(sup1):S55-68. doi: 10.1080/15459624.2015.1060325.

ECHA (2019) Guidance on information requirements and chemical safety assessment Appendix to Chapter R.8: Guidance for preparing a scientific report for health-based exposure limits at the workplace. f1d45aca-193b-a7f5-55ce-032b3a13f9d8 (europa.eu)

Basketter DA, Clapp C, Jefferies D, et al. (2005). Predictive identification of human skin sensitization thresholds. Contact Dermatitis 53(5): 260-267.

Deveau, M., C-P. Chen, G. Johanson, D. Krewski, A. Maier, K. Niven, S. Ripple, P. Schulte, J. Silk, J.H. Urbanus, D.M. Zalk, R. Niemeier. 2015. The Global Landscape of Occupational Exposure Limits - Implementation of Harmonization Principles to Guide Limit Selection. J Occup Environ Hygiene.12(Suppl 1): S127-S144.

DFG (Deutsche Forschungsgemeinschaft), editor (2022) List of MAK and BAT Values 2022. Maximum Concentrations and Biological Tolerance Values at the Workplace. Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, report 58. Düsseldorf: German Medical Science. https://doi.org/10.34865/mbwl_2022_eng

Gerberick GF, Robinson MK, Ryan CA, et al. (2001). Contact allergenic potency: correlation of human and local lymph node assay data. American Journal of Contact Dermatitis 12(3): 156-161.

Kimber I, Basketter DA, Butler M, et al. (2003). Classification of contact allergens according to potency: proposals. Food and Chemical Toxicology 41(12): 1799-1809.

Naumann BD, Sargent EV, Starkman BS, et al. (1996). Performance-based exposure control limits for pharmaceutical active ingredients. American Industrial Hygiene Association Journal 57(1): 33-42.

Naumann BD, Arnold SF (2019). Setting surface wipe limits for skin sensitizers. Toxicol. Indust. Hlth. 35(9):614-625. https://doi.org/10.1177/0748233719875365. Epub 2019 Sep 23.

Kimmel TA, Sussman RG, Ku RH, et al. (2011). Developing Acceptable Surface Limits for Occupational Exposure to Pharmaceutical Substances. Journal of ASTM International 8(8): 1-6.

Organisation for Economic Co-operation and Development (2011). Guidance Notes on Dermal Absorption. Series on Testing and Assessment. No. 156. [online]. Available at: https://www.oecd.org/chemicalsafety/testing/48532204.pdf

Health Council of the Netherlands (2012) Guideline for the calculation of occupational cancer risk values,

OECD (2022a) OECD, Establishing Occupational Exposure Limits, Series on Testing and Assessment, No. 351, ENV/CBC/MONO(2022)6. Paris, Available at https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/cbc/mono(2022)6&docl

anguage=en

OECD (2022b) Guidance Document on Occupational Biomonitoring, Series on Testing and Assessment, No. 370. Paris, Available at https://www.oecd.org/chemicalsafety/risk-assessment/occupational-biomonitoring-guidance-document.pdf

Annex A. Workshop agenda

DAY 1: Friday, 21 October

12:00

Item1. Opening

Speaker: Mariko Ono (JNIOSH)

Opening remarks will be provided by the Japanese National Institute of Occupational Safety and Health.

12:05

Item2. Introduction

Speaker: Koki Takaki (OECD)

The OECD Secretariat will provide an overview of the Exposure and Hazard Assessment programmes, recent activities on setting OELs, and the objective of this workshop.

1. Session 1 Approaches to set OEL values

This session is to summarise the general process/workflow to establish OEL values, which have been used by countries and may be used to inform to newly established OELs like Japan. It also includes a discussion about the OEL settings for specific endpoints to be concerned.

12:15

Item3. General workflow/process – from the OECD survey report

Speaker: Michelle Deveau (Health Canada)

Health Canada will present a general workflow/process in setting OEL values, which is illustrated in the OECD survey report.

12:30

Item4. General workflow/process – OEL settings in Japan

Speaker: Mariko Ono (JNIOSH)

JNIOSH will present an overview of their new legislation and upcoming processes for establishing OEL values.

12:45

Item5. Specific endpoints: Carcinogenicity

Speaker: Stefan Vink (Health Council of the Netherlands)

13:05

Item6. Setting Surface-Limits

Speaker: Bruce D. Naumann (ACGIH)

ACGIH will present the possibility of introducing a new category of OEL, such as OEL-SL(Surface-Limit).

13:25

Item7. Application of Occupational Biomonitoring

Speaker: Robert Pasanen-Kase (SECO)

SECO will present the application of Occupational Biomonitoring to the OEL setting, and recent activities of the OECD Occupational Biomonitoring project.

Coffee Break 13:45 – 14:00

14:00

Item8. Panel discussion

The panellists will discuss the following topics.

1. What some considerations when applying OEL values set by other countries or organisations from scientific and legal point of view.
2. How could occupational regulatory agencies practically consider OELs for specific endpoints (e.g., carcinogenicity, skin sensitisation, biomonitoring) in establish their OELs?

Panellists: presenters and additional experts.

End of Day 1 15:00

DAY 2: Monday, 24 October

12:00

Item9. Opening

Speaker: Koki Takaki (OECD)

The OECD Secretariat will make opening remarks for Day 2 and provide a short recap of the Day 1 discussion.

2. Session 2 Future perspective – Exploring International Harmonisation on the OEL settings

This session is to explore the potential to harmonise some, or all approaches used to establish OELs internationally and discuss if/what role OECD could play to add value.

12:05

Item10. Potential for harmonisation – summary of results from the OECD survey report

Speaker: Michelle Deveau (Health Canada)

Health Canada will present the survey results on the potential for international harmonisation in the OEL settings described in the OECD report.

12:20

Item11. Harmonisation initiatives –US coordination activities

Speaker: Yvette Selby-Mohamadu (USEPA)

The US EPA will share their experience of coordination and collaboration in OEL settings among OSHA, US EPA, and NIOSH as well as their further harmonisation attempts.

12:35

Item12. Harmonisation initiatives –non-governmental organisations

Speaker: Andy Maier (WEEL Committee)

The WEEL committee will share their experience of coordination and collaboration in OEL settings among other organisations.

12:55

Item13. Harmonisation initiatives –Germany

Speaker: Claudia Drossard (BAuA),

Klaus Schneider (FoBiG, Germany)

Germany will share the result of their project on OEL derivations for airborne chemicals focused on the comparison of methods and protection levels.

13:15

Item14. Harmonisation initiatives – EU

Speaker: Laurence Hoffstadt (ECHA)

ECHA will share their experience of coordination and collaboration in OEL settings among EU countries.

Coffee Break 13:30 – 13:50

13:50

Item15. Panel discussion

The panellists will discuss the following topics.

1. Are there any specific endpoints or procedures for establishing OEL that may be more amendable to international harmonisation?
2. What are some procedures that may help to make establishing OEL values more efficient? e.g., Sharing toxicological and mechanism information, and OEL setting methods.
3. Is there a role for OECD to play in increasing OEL harmonisation and/or efficiently in setting OEL limits within countries?

Panellists: presenters and additional experts.

14:50

Item16. Next steps

Speaker: Koki Takaki (OECD)

The OECD Secretariat will present the draft outline of the Workshop report and the possible next steps.

14:55

Item17. Closing

Speaker: Koki Takaki (OECD), Mariko Ono (JNIOSH)

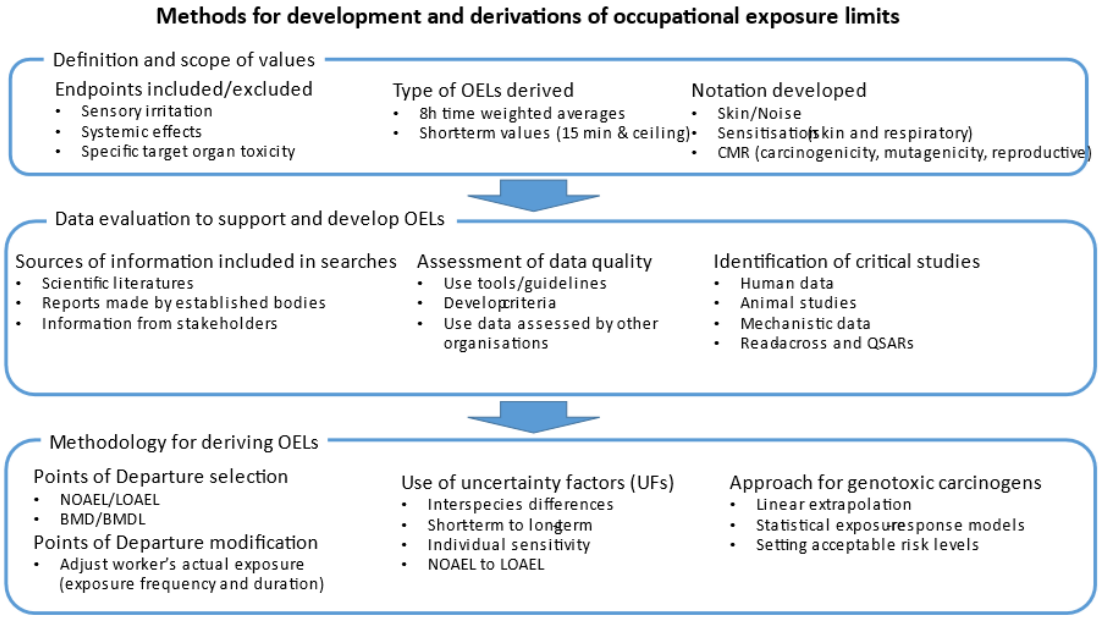
JNIOSH and the OECD Secretariat will make a closing remark.

End of Day 2 15:00

Annex B. General workflow/process

As introduced in Section 2.1, Figure 1 of the document, a general workflow was developed as part of the Workshop. A more detailed description of considerations for each step is included in the survey report [ENV/CBC/MONO(2022)6], and summarised below.

Figure A B.1. Methods for development and derivations of occupational exposure limits



Definition and Scope of Values

Endpoints included/excluded

In developing OELs, endpoints and effects to be included or excluded must be considered as the basis for deriving OELs. Endpoints typically included were sensory irritation (ocular, dermal, respiratory), systemic effects and specific target organ toxicity, however, the survey responses included considerable variation among organisations in endpoints used for setting OELs. When determining endpoints to include, one can consider whether/how to:

- Cover all exposure-related adverse health effects (in the workplace) and all diseases which are clinically diagnosable to assess a causal relationship between exposure and disease.
- Include systemic effects and specific target organ toxicity.
- Include carcinogenicity, genotoxicity, and/or reproductive toxicity as endpoints.
- Include skin and respiratory sensitisation, allergens, and/or sensitisers as endpoints.
- Obtain the endpoints to be considered from other trusted international organisations.

Types of OELs derived

A commonly used OEL is 8-hour time-weighted average (8h-TWA), which is the limit of the time-weighted average concentration of a chemical agent in the worker's breathing zone over the course of an 8-hour shift. Generally, 8h-TWAs are designed to protect workers exposed regularly and for the duration of a working life from the chemical in question. In addition, short-term exposure limits (STELs), also called short-term values, are typically set as 15-minute averages that shall not be exceeded during the working day. There is a case to set the 8h-TWA action levels, which are typically half of the 8h-TWA values, with certain requirements such as exposure monitoring, medical surveillance, or biological monitoring when 8h-TWA action levels are exceed.

Some organisations also establish 'ceiling' values or limits (names can differ across organisations), which are established for substances that would need a STEL over short exposure durations (i.e., less than 15 minutes). Ceiling values are typically the maximum concentration of a substance that must not be exceeded at any time as it is considered a threat to workers' health or life. Ceiling values should also be considered in the workflow as they are often derived by OEL organisations.

In addition to air 8h-TWA, STELs and ceiling limit values, biological limit values may be considered for substances for which internal levels may be more decisive.

The following points could be discussed in determining the endpoint setting.

- How the various limit values were derived and are defined (e.g. 8h-TWA, STEL, 'ceiling values' and biological limit values.
- Whether/how to set the action levels

Notations developed

Occupational exposure limits are often associated with advisory or hazard notations to indicate that a particular substance may cause an adverse health effect. The most common notation developed among organisations is the skin notation (although the notation label used can differ among agencies), which alerts that dermal exposure can cause irritation or cutaneous absorption. Another common notation used by e.g., in Germany, Japan, Australia, and Switzerland is (skin and respiratory) sensitisation. The following notations could be considered for development:

- Skin
- Sensitisation (skin and respiratory)
- Noise
- CMR (carcinogenicity, mutagenicity, reproductive)

Data evaluation to support and develop OELs

Sources of information included in searches

Searches for data to support the OEL can include scientific literature, reviews, and/or reports. Reviews and reports used by agencies are typically from internationally recognised organisations or scientific

committees (e.g. AGS[9], DFG[10], MAK[11], DECOS[12], NEG[13], ANSES[14], ATSDR[15], ACGIH[16], US NIOSH[17]). Unpublished studies from trustworthy sources can also be considered, as well as information from stakeholders, industries, or unions (if relevant and the source of information is indicated). The following points could be considered when deciding types of data to include in a search:

- Data sources to be included
- Inclusion of data from unpublished sources

Assessment of data quality

In general, when data quality assessed by evaluating relevance, reliability, and adequacy of the information. The methodologies and criteria for data quality assessment should be defined and described in the documents describing how OELs were derived. The following points could be discussed in the quality assessment:

- methodologies and criteria for assessing data quality (e.g. from scientific literature, other organisations, guideline toxicological studies, epidemiological studies)
- Whether/how to open the methodologies and criteria

Identification of critical studies

Primarily animal and/or human data are used for developing OELs. Higher weight is given to quality human/epidemiological data and data obtained from exposure conditions relevant to workers. Mechanistic data concerning the mode/mechanism of action can be considered. Non-test data, including read-across approaches and quantitative structure-activity relationships (QSARs), may be used for filling data gaps, e.g., when a data-rich substance has an OEL and is applied to a data-poor isomer. The following points could be discussed in identifying critical studies:

- Development and documentation of a weight of evidence approach
- Inclusion of non-test data

Methodology for deriving OELs

Points of Departure (PoD) selection and modification

OEL derivation is generally initiated by choosing PoD(s) with consideration for critical endpoints reported in epidemiological or animal studies, for which a dose-response information is available. As previously mentioned, typical PoDs are Benchmark dose (BMD), Benchmark dose level (BMDL), Benchmark

[9] Committee on Hazardous Substances

[10] Deutsche Forschungsgemeinschaft

[11] Germany Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area

[12] Dutch Expert Committee on Occupational Safety

[13] Nordic Expert Group

[14] French Agency for Food, Environmental and Occupational Health & Safety

[15] the Agency for Toxic Substances and Disease Registry

[16] American Conference of Governmental Industrial Hygienists

[17] US National Institute for Occupational Safety and Health

concentration (BMC), Benchmark concentration level (BMCL), No observed adverse effect level (NOAEL), or Lowest observed adverse effect level (LOAEL). The selection of the PoD is ultimately based on the data available. The following points could be discussed in selecting and modifying PoDs:

- PoDs to be adopted (BMD values, NOAEL, LOAEL…)?
- Preference among the PODs
- If PoDs should be modified to consider differences in:
  - exposure conditions
  - consideration of differences in absorption/distribution/metabolism/excretion (ADME) between experimental animal and humans.

Use of uncertainty and extrapolation factors

Uncertainty factors (UFs) (also referred to as 'assessment factors', 'adjustment factors', and 'variability factors') are commonly used when deriving OELs for threshold compounds. Generally, the relevant data available for a specific substance needs to be reviewed thoroughly for the establishment of appropriate values for the various uncertainty factors. The term "uncertainty factor" accounts for uncertainties, and the value is set without data-based, substance-specific justification. During the workshop, panellists concluded that it is important to differentiate between extrapolation factors (data-based assessment factors) and uncertainty factors. This holds true, for example, for time extrapolation or interspecies extrapolation (allometric scaling), for which data exist as a basis for the default values. Data from a large number of substances are used to derive a default extrapolation factor value for use when substance-specific data are unavailable. The BAuA/FoBiG (Federal Institute for Occupational Safety and Health / Forschungs- und Beratungsinstitut Gefahrstoffe GmbH) project [18] built a new database for calculating extrapolation factors.

Typical extrapolation factors account for inter/ intraspecies variation, LOAEL to NOAEL extrapolation, and time extrapolation. The following points could be discussed in setting uncertainty and extrapolation factors:

- Types of extrapolation factors (for animal-to-human, NOAEL to LOAEL, shorter-term to longer-term…)
- Consideration scientific opinions and assessments from other organisations and committees in setting the values.

Approach for genotoxic carcinogens

In general, the approach taken for genotoxic carcinogens depends on the MOA of the substance and the method used to derive a margin of safety or risk for cancer effects due to non-threshold-based genotoxic carcinogens. Exposure standards for non-threshold-based genotoxic carcinogens are generally at a concentration associated with specific cancer risk, but there are various methods for determining cancer risk and also different risk levels or safety margins. The following points could be discussed in defining an approach for genotoxic carcinogens to adopt:

- As low as reasonably achievable (ALARA) principle
- Threshold-based mechanism of action (MOA) to be adopted, particularly for data-rich carcinogens
- Linear vs. non-linear extrapolation
- Exposure-response modelling

[18] Derivation of occupational exposure limits for airborne chemicals - Comparison of methods and protection levels https://www.baua.de/EN/Tasks/Research/Research-projects/f2437.html

- Acceptable risk levels (e.g., 1 in 10,000, and 1 in 100,000)