Support to the possible increased use of the concept of Derived Minimal Effect Level (DMEL) for non-threshold substances in REACH

Draft final report under framework contract ENV.B.2/FRA/2020/0010

WSP E&IS GmbH – March 2023
Report for
European Commission
Directorate General – Environment
Directorate B – Circular Economy and Green Growth
Unit B.2 – Sustainable Chemicals
BU 9
B-1049 Brussels

Main contributors

Issued by

Approved by

WSP E&IS GmbH
Regus EU Commission
Rond Point Schuman 6
1040 Brussels
Belgium

Doc Ref. 807693-WSP-RP-OP-00004_A_P06.1
http://projects\807693 pp-ch sr3 dmels assessment\delivery\c
client\reports\final report v7\dmel study final
report_v7.0_final_version.docx

Copyright and non-disclosure notice
The contents and layout of this report are subject to copyright
owned by WSP save to the extent that copyright has been
legally assigned by us to another party or is used by WSP
under licence. To the extent that we own the copyright in this
report, it may not be copied or used without our prior written
agreement for any purpose other than the purpose indicated
in this report. The methodology (if any) contained in this report
is provided to you in confidence and must not be disclosed or
copied to third parties without the prior written agreement
of WSP. Disclosure of that information may constitute an
actionable breach of confidence or may otherwise prejudice
our commercial interests. Any third party who obtains access
to this report by any means will, in any event, be subject to the
Third Party Disclaimer set out below.

Third party disclaimer
Any disclosure of this report to a third party is subject to this
disclaimer. The report was prepared by WSP at the instruction
of, and for use by, our client named on the front of the report.
It does not in any way constitute advice to any third party who
is able to access it by any means. WSP excludes to the fullest
extent lawfully permitted all liability whatsoever for any loss or
damage howsoever arising from reliance on the contents of
this report. We do not however exclude our liability (if any) for
personal injury or death resulting from our negligence, for
fraud or any other matter in relation to which we cannot legally
exclude liability.

Management systems
This document has been produced by WSP E&IS GmbH in full
compliance with our management systems, which have been
certified to ISO 9001, ISO 14001 and ISO 45001 by Lloyd’s
Register.

Document revisions

<table>
<thead>
<tr>
<th>No.</th>
<th>Details</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Draft Final</td>
<td>20/05/2022</td>
</tr>
<tr>
<td>2</td>
<td>Final</td>
<td>12/07/2022</td>
</tr>
<tr>
<td>3</td>
<td>Version 2 (further edits)</td>
<td>15/08/2022</td>
</tr>
<tr>
<td>4</td>
<td>Version 3 (edits to App E and Section 8)</td>
<td>24/08/2022</td>
</tr>
<tr>
<td>5</td>
<td>Version 4 (edits to App E)</td>
<td>01/09/2022</td>
</tr>
<tr>
<td>6</td>
<td>Version 5 and 6 (editorials)</td>
<td>13/09/2022</td>
</tr>
<tr>
<td>7</td>
<td>Version 7 (final edits plus executive summary)</td>
<td>03/03/2023</td>
</tr>
</tbody>
</table>

March 2023
# Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glossary</strong></td>
<td>17</td>
</tr>
<tr>
<td>1. Introduction</td>
<td>19</td>
</tr>
<tr>
<td>1.1 This report</td>
<td>19</td>
</tr>
<tr>
<td>1.2 Objectives of the project</td>
<td>19</td>
</tr>
<tr>
<td>1.3 Structure of the report and coverage of tasks within the report</td>
<td>20</td>
</tr>
<tr>
<td>2. Methodology</td>
<td>21</td>
</tr>
<tr>
<td>2.1 Overview of approach</td>
<td>21</td>
</tr>
<tr>
<td>2.2 Literature review</td>
<td>22</td>
</tr>
<tr>
<td>2.3 Consultation</td>
<td>22</td>
</tr>
<tr>
<td>2.3.1 Targeted survey</td>
<td>22</td>
</tr>
<tr>
<td>2.3.2 Targeted interviews</td>
<td>23</td>
</tr>
<tr>
<td>2.3.3 Public consultation</td>
<td>23</td>
</tr>
<tr>
<td>3. Political and legal context</td>
<td>24</td>
</tr>
<tr>
<td>4. Problem definition</td>
<td>25</td>
</tr>
<tr>
<td>4.1 The problem</td>
<td>25</td>
</tr>
<tr>
<td>4.2 Who is affected by the problem?</td>
<td>27</td>
</tr>
<tr>
<td>4.3 How the problem might evolve</td>
<td>28</td>
</tr>
<tr>
<td>5. Why should the EU act?</td>
<td>29</td>
</tr>
<tr>
<td>6. Objectives of the intervention</td>
<td>31</td>
</tr>
<tr>
<td>7. What are the available options to achieve the objectives?</td>
<td>32</td>
</tr>
<tr>
<td>7.1 Introduction</td>
<td>32</td>
</tr>
<tr>
<td>7.2 High-level options</td>
<td>32</td>
</tr>
<tr>
<td>7.3 Sub-options</td>
<td>33</td>
</tr>
<tr>
<td>7.3.1 Selection of hazard end-points (option 1 and 2)</td>
<td>36</td>
</tr>
<tr>
<td>7.3.2 Who develops the DMEL? (option 1 and 2)</td>
<td>37</td>
</tr>
<tr>
<td>7.3.3 Is the quantitative DMEL approach mandatory? (Option 2)</td>
<td>37</td>
</tr>
<tr>
<td>7.3.4 Which populations are covered? (Option 1 and 2)</td>
<td>37</td>
</tr>
<tr>
<td>7.3.5 Which substance tonnage groups are covered? (Option 2)</td>
<td>37</td>
</tr>
<tr>
<td>7.3.6 How many quantitative risk thresholds are applied? (Option 1 and 2)</td>
<td>37</td>
</tr>
<tr>
<td>7.3.7 Is the quantitative risk threshold mandatory? (Option 2)</td>
<td>37</td>
</tr>
</tbody>
</table>
8. What are the impacts of the different policy options and who will be affected?  
8.1 Introduction  
8.2 Baseline  
8.3 Overview of impact types considered  
8.3.1 Overview  
8.3.2 Actors affected  
8.4 Environmental impacts  
8.5 Social (including human health) impacts  
8.5.1 Benefits – qualitative assessment  
8.5.2 Benefits – quantitative assessment  
8.5.3 Costs – qualitative assessment  
8.5.4 Costs – quantitative assessment  
8.5.5 Summary  
8.6 Economic impacts  
8.6.1 Benefits – qualitative assessment  
8.6.2 Benefits – quantitative assessment  
8.6.3 Costs – qualitative assessment  
8.6.4 Costs – quantitative assessment  
8.6.5 Summary  
8.7 Impacts on other legislation  
9. How do the options compare?  
10. Conclusions  
10.1 Summary of analysis  
10.1.1 Development of dose-response to support DMELs  
10.1.2 Cost-benefit analysis  
10.1.3 Political opinion  
10.1.4 Guidance documents  
10.1.5 Alignment to related policy  
10.2 Conclusion  
11. How would impacts be monitored and evaluated
Table 8.8 Overview of tolerable risk thresholds for CrVI 61
Table 8.9 Calculation of additional cancer cases for CrVI 62
Table 8.10 Summary of information for different risk levels 63
Table 8.11 High-level calculation of costs associated with developing DMELs – all substances 85
Table 8.12 High-level calculation of costs associated with developing DMELs - low and medium effort substances only. 86
Table 8.13 High-level calculation of costs associated with developing DMELs 1-10 tonnes 88
Table 8.14 qualitative indication of required effort for additional RMMs 88
Table 8.15 DMEL threshold scenarios compared to baseline 89
Table 8.16 Comparison of costs and benefits for DMELs with assumed mandatory use and minimum risk levels 93
Table 9.1 Comparison of options – Option 1 Enhanced use of DMELs using non-regulatory measures 99
Table 9.2 Comparison of options – Option 2 Enhanced use of DMELs using regulatory measures 100
Table 10.1 Overview of preferred option and sub-options 110
Table A.1 Overview of reference sources 10
Table A.2 Consolidated table for comparative analysis (risk thresholds relate to excess lifetime cancer risks). 30
Table C.1 Breakdown of workshop participants by stakeholder categories 2
Table E.1 Overview of assumptions. 5
Table E.2 Overview of assumed existing thresholds under qualitative risk assessment equivalent to DMELs for baseline. 6
Table E.3 Baseline assumed rates of cancer and associated costs 7
Table E.4. Assumed costs for additional RMMs. 11
Table E.5. DMEL threshold scenarios and associated costs of additional RMMs 12
Table E.6 Assumed rates of cancer and associated costs for hypothetical mandatory minimum thresholds. 16
Table E.7 Comparison of baseline and assumed DMEL thresholds to illustrate avoided costs 17
Table E.8 Comparison of costs and benefits depending on assumed DMEL threshold 18

Figure 2.1 Overview of the proposed workflow 21
Figure 8.1 Results of the PC for whether the existing approach is sufficient 46
Figure 8.2 Disaggregation of responses by stakeholder type for question 9f of the public consultation (is the existing situation sufficient?) 47
Figure 8.3 Results of the PC for whether there should be enhanced use of DMELs 48
Figure 8.4 Disaggregation of responses by stakeholder type for question 9g of the public consultation (Whether there should be enhanced use of DMELs) 49
Figure 8.5 Overview of selected tolerable risk thresholds. 54
Figure 8.6 Response of SME panel members – How would you expect the increased use of DMELs for non-threshold hazards to impact your business? 67
Figure 8.7 PC responses to preferred threshold for worker settings (life-time excess cancer risks over 40 years) 75
Figure 8.8 Breakdown of responses to question 9h (workers) – tolerable risk thresholds for excess lifetime cancer (40 years) 76
Figure 8.9 Breakdown of responses to question 9h (workers) (by company size) 77
Figure 8.10 PC responses to preferred threshold for consumer settings (life-time excess cancer risks over 70 years) 78
Figure 8.11 Breakdown of responses to question 9h (general public) – tolerable risk thresholds for excess lifetime cancer (70 years) 79
Figure 9.1 Colour code key for the ratings used in Table 9.1 and 9.2 98
Figure A.1 Overview of the risk-based concept used in Germany. 11
Figure B.1 Overall responses to question 9f 3
Figure B.2 Disaggregation of responses by stakeholder type 4
Figure B.3 Breakdown of responses to question 9f (company size) 5
Figure B.4 Overall responses to question 9g 8
Figure B.5 Breakdown of responses to question 9g 9
Figure B.6 Breakdown of responses to question 9g (company size) 10
Figure B.7 Overall responses to question 9h (workers) – tolerable risk thresholds for excess lifetime cancer (40 years) 12
Figure B.8 Breakdown of responses to question 9h (workers) – tolerable risk thresholds for excess lifetime cancer (40 years) 13
Figure B.9 Breakdown of responses to question 9h (workers) (by company size) 14
Figure B.10 Overall responses to question 9h (general public) – tolerable risk thresholds for excess lifetime cancer (70 years) 16
Figure B.11 Breakdown of responses to question 9h (general public) – tolerable risk thresholds for excess lifetime cancer (70 years) 17
Figure B.12 Breakdown of responses to question 9h (general public) (by company size) 18
Appendix A  Assessing the state of play
Appendix B  Review of Public Consultation responses
Appendix C  Feedback from study workshop and finalisation of sub-options (screening)
Appendix D  Further analysis of chemical safety reports [confidential]
Appendix E  Cost-benefit calculations (occupational settings)
Appendix F  References
## Glossary

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD</td>
<td>Benchmark Dose</td>
</tr>
<tr>
<td>C&amp;L Inventory</td>
<td>Classification and labelling inventory</td>
</tr>
<tr>
<td>CARACAL</td>
<td>Competent Authorities for REACH and CLP</td>
</tr>
<tr>
<td>CAS</td>
<td>Chemical Abstract Service</td>
</tr>
<tr>
<td>CAT 1A/1B</td>
<td>Category 1A – substances known to have potential carcinogenic or mutagenic effects (respectively) for humans, largely based on human evidence. Category 1B – substances presumed to have potential carcinogenic or mutagenic effects (respectively) for humans, largely based on animal evidence.</td>
</tr>
<tr>
<td>CAT 2</td>
<td>Category 2 – substances suspected to have potential carcinogenic or mutagenic effects (respectively) for humans, based on human and animal evidence but which is not sufficiently convincing to place the substance in CAT 1.</td>
</tr>
<tr>
<td>CLP</td>
<td>EU regulation on Classification, Labelling and Packaging EC 1272/2008</td>
</tr>
<tr>
<td>CMD</td>
<td>The Carcinogens and Mutagens Directive 2004/37/EC</td>
</tr>
<tr>
<td>CMR</td>
<td>carcinogenic, mutagenic, reprotoxic</td>
</tr>
<tr>
<td>CSA</td>
<td>Chemical Safety Assessment</td>
</tr>
<tr>
<td>CSR</td>
<td>Chemical Safety Report</td>
</tr>
<tr>
<td>DG ENV</td>
<td>European Commission, DG Environment</td>
</tr>
<tr>
<td>DMEL</td>
<td>Derived Minimal Effect Level</td>
</tr>
<tr>
<td>DNEL</td>
<td>Derived No Effect Level</td>
</tr>
<tr>
<td>ECHA</td>
<td>European Chemicals Agency</td>
</tr>
<tr>
<td>EFSA</td>
<td>European Food Safety Authority</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>GHS</td>
<td>Global Harmonised System of classification</td>
</tr>
<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
</tr>
<tr>
<td>MoA</td>
<td>Mode of Action</td>
</tr>
<tr>
<td>Non-Threshold for some hazard classes, especially germ cell mutagenicity and carcinogenicity, the available information may not enable a toxicological effect threshold to be determined.</td>
<td></td>
</tr>
<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>OELs</td>
<td>Occupational Exposure Limits</td>
</tr>
<tr>
<td>PC</td>
<td>Public Consultation</td>
</tr>
<tr>
<td>OSH</td>
<td>The Occupational Safety and Health Framework Directive 89/391/EEC</td>
</tr>
<tr>
<td>PNEC</td>
<td>Predicted No Effect Concentration</td>
</tr>
<tr>
<td>QSAR</td>
<td>quantitative structure-activity relationship</td>
</tr>
<tr>
<td>RAC</td>
<td>Risk Assessment Committee</td>
</tr>
<tr>
<td>REACH</td>
<td>EU regulation on registration, evaluation, authorisation, and restriction of chemicals EC 1907/2006</td>
</tr>
<tr>
<td>SEAC</td>
<td>Socio-Economic Assessment Committee</td>
</tr>
<tr>
<td>SEv process</td>
<td>High Severity Incident risk assessment processes</td>
</tr>
<tr>
<td>SIEF</td>
<td>Substance Information Exchange Forum</td>
</tr>
<tr>
<td>SWD</td>
<td>Staff Working Document</td>
</tr>
<tr>
<td>T25</td>
<td>Toxicological approach using a simplified potency index, where &quot;T25&quot; represents the dose giving a 25% incidence of cancer in an appropriately designed animal experiment</td>
</tr>
<tr>
<td>UN GHS</td>
<td>United Nations' Globally Harmonized System of Classification and Labelling of Chemicals</td>
</tr>
<tr>
<td>USEPA</td>
<td>United States Environmental Protection Agency</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
</tbody>
</table>
1. Introduction

1.1 This report

WSP E&IS GmbH (hereafter ‘WSP’) alongside Ramboll and the Environment Agency of Austria (EAA), has been contracted by the European Commission, DG Environment (‘DG ENV’) to provide:

- “Support to the possible increased use of the concept of Derived Minimal Effect Level (DMEL) for non-threshold substances in REACH”.

The study commenced with a kick-off meeting held between WSP, our project partners and the Commission and European Chemicals Agency (ECHA) on the 1 September 2021. Subsequently, the study has worked through five discrete tasks (including a study Workshop held in January 2022, and presentations at relevant CARACAL meetings) to reach its completion.

This report provides the final study results and supporting information to feed into the wider ongoing work for revision of the REACH Regulation.

1.2 Objectives of the project

As part of a wider tranche of impact assessments aimed at appraising different options for the further revision of REACH, the current study has focussed on the risk assessment processes for non-threshold hazards. The overall aim of the project is to assess the costs and benefits for the wider adoption of quantitative approaches (DMELs) for non-threshold hazards. This includes the following sub-objectives:

- An identification of types of toxicological human health hazards, including cancer, for which no toxicological threshold can be derived, but where it normally would be possible to establish dose-response relationships and an overview of available methodologies for developing such dose-response relationships.

- An estimate of the number of substances registered under REACH which present human health hazards for which no toxicological threshold can be derived but for which it would be possible to establish dose-response relationships, divided into types of hazards and tonnage bands (including the 1-10 tonnes per year tonnage band). An estimate of the number of substances for which registrants have already derived and used DMELs in their registrations.

- An overview of regulatory uses (within and, where available, outside the EU) of dose-response relationships for non-threshold substances for derivation of risk levels (including a description of types of effect), including the levels that have been accepted politically and where they are used.

---

6 The Regulation on the Registration, Evaluation, Authorisation, and restriction of Chemicals. EC 1907/2006
• An assessment of costs to registrants and downstream users, as well as the impact on the level of protection of the general population and workers of applying selected politically acceptable risk levels for deriving DMELs.

1.3 Structure of the report and coverage of tasks within the report

This report has been structured in a complementary fashion to work alongside the other impact assessments being developed for the revision of REACH. In particular, the report has been structured to help mirror the layout of the Staff Working Document (SWD) format for the proposed changes to REACH.

Section 2 of this report will provide an overview of the methodology implemented, with the remaining sections following the SWD format:

• Section 3 Political and legal context
• Section 4 Problem definition
• Section 5 Why should the EU act?
• Section 6 Objectives of the intervention
• Section 7 What are the available options to achieve the objectives?
• Section 8 What are the impacts of the different policy options and who will be affected?
• Section 9 How do the options compare?; and
• Section 10 The preferred option

The current study included in depth analysis using a variety of approaches. To maintain the structure that is outlined above and for the sake of brevity, the report makes use of some key appendices to present data in a more detailed fashion. This includes:

• Appendix A – providing the “state of play” and key outputs of Task 1 and 2.
• Appendix B – Review of public consultation responses.
• Appendix C – Workshop report (under Task 5).
• Appendix D – [confidential] Appendix for CSR analysis.
• Appendix E – Cost calculations for costs and benefits in worker settings.
• Appendix F – References.
3. Political and legal context

In accordance with the REACH Regulation, manufacturers, and importers of substances in a quantity of more than or equal to 1 tonne per year per manufacturer or importer are required to submit a registration to European Chemicals Agency (ECHA). The registration must contain information on, e.g., the physicochemical, toxicological and ecotoxicological properties of the substances depending on the tonnage, the uses and exposure. For substances registered in a quantity of more than or equal to 10 tonnes, the registrant must also conduct a Chemical Safety Assessment (CSA) and include this in a Chemical Safety Report (CSR) as part of the dossier submission for REACH registration.

As part of the CSA, the registrant shall establish Derived No-Effect Levels (DNELs) for human health, i.e., a level of exposure above which humans should not be exposed. Similarly, the registrant shall establish Predicted No-Effect Concentrations (PNECs) for the environment, i.e., a concentration below which adverse effects to the environment are not expected to occur. These levels shall be used for documenting through a quantitative comparison of exposure levels and DNELs and PNECs that risks to humans and the environment, respectively, are adequately controlled.

It is stated in REACH that “for some hazard classes, especially germ cell mutagenicity and carcinogenicity, the available information may not enable a toxicological threshold, and therefore a DNEL, to be established” (Annex I, 1.4.1). Furthermore, “for those human effects […] for which it was not possible to determine a DNEL […] a qualitative assessment of the likelihood that effects are avoided when implementing the exposure scenario shall be carried out” (Annex I, 6.5).

This approach has implications for how registrants should conduct their CSA and document that their substances are manufactured and used safely, as only a qualitative assessment is required for non-threshold substances. Thus, while it is anticipated that for some carcinogens and mutagens there are no safe exposure levels, no specific quantification of possible effects is required.

Nevertheless, ECHA has provided guidance on how to set Derived Minimal Effect Levels (DMELs) for a non-threshold carcinogens. A DMEL is reference risk level which is considered to be of very low concern and therefore the level of effects can be considered tolerable. The guidance further comments that such risk levels have been used in different contexts (consumer protection or worker protection, different Member States, countries or institutions) and that cancer risk levels of 1 out of 1 million (10^{-6}) could be seen as an indicative tolerable risk level for the general population and 1 out of 100,000 (10^{-5}) could be seen as an indicative tolerable risk level for workers. An overview of decision points for cancer risk levels that have been used in various countries, organisations and committees is provided in Appendix R.8-14 to the guidance.

Additionally, ECHA’s Risk Assessment Committee (RAC) has and continues to develop reference dose-response relationships for non-threshold carcinogens for the evaluation of applications for authorisation, as a guidance for the applicants with substances under evaluation, and for restriction proposals.

---

7 cf. the ECHA guidance on information requirements and chemical safety assessment, chapter R.8: Characterisation of dose [concentration]-response for human health, chapter R.8.5
4. Problem definition

4.1 The problem

The REACH Regulation aims to ensure a high level of protection for human health and the environment (Article 1). In part it achieves this aim by drawing together manufacturers and importers (through SIEFs) to work collectively on developing data within the REACH registration dossier (promoting one substance: one registration), and undertaking a Chemical Safety Assessment (CSA), which is included in the REACH registration as a Chemical Safety Report (CSR). The exposure scenarios from the CSR are then further communicated down the supply chain as a means of clearly and effectively providing risk and safety information for those making use of chemicals, mixtures, or articles (that contain chemicals).

Article 117 of the REACH Regulation requires the Commission to carry out a review of the operation of REACH every five years. The first of these reviews was published in 2013, with the most recent review published in 2018. Both reviews comment that one of its biggest successes has been the development of key information which is publicly available through the ECHA database (covering 26,500 unique substances – “one of the most comprehensive databases on chemicals globally” (Commission, 2018)), and an increased awareness of hazards, risks, and risk control across the whole supply chain. This has inherent EU-added benefits for the EU economy, workers, and consumer safety, and harmonising the approaches to risk management.

Substances with non-threshold hazards pose a particular challenge, as in essence there is no safe level of exposure. This complicates how risk can tangibly be determined and managed to an appropriate level. The quantitative risk assessment approaches (DNELs and PNECs) for hazards with a threshold provide a clear approach to determining safe use and outcomes that both have regulatory certainty and ease of communication. For substances with non-threshold hazards REACH currently allows a qualitative approach with written explanation of how risks and risk controls have been determined and applied. This narrative is then communicated down the supply chain. This approach potentially has three key problematic issues:

- There is no harmonised approach to the qualitative risk assessment, meaning a lack of harmonisation and variation in quality of the assessment.
- The qualitative assessment is textual (rather than numeric), with the exposure scenarios and operational conditions then communicated down the supply chain. Where the exposure scenarios and operational conditions (including risk management measures) are also textual (and potentially subject to language translation) it can impair

---

8 Substance Information Exchange Forums


11 European Commission, 2018, REACH Review - factsheet
communication. Particularly, where downstream users are less well placed to judge if the exposure scenario is of good quality.

- Based on the interviews with regulators and the EU risk assessment committee (RAC), the qualitative assessment often focuses primarily on the risk management measures, with often far less details on the specific activity and potential exposure. Which undermines confidence in the assessment.

- The development of a quantitative approach for risk assessment of non-threshold hazards (DMELs) is intended to provide a more accurate assessment of the risk in quantifiable terms (i.e., current situation and any future situation with improving RMMs). To this effect ECHA has provided guidance on development and use of DMELs. Additionally, since 2012, the RAC has provided support to ECHA through the development of dose-response reference values for substances listed in Annex XIV (SVHCs) prior to Authorisation. This has included the development of DNELs for threshold substances, and DMELs for substances with non-threshold hazards, primarily carcinogens\(^\text{12}\). However, while this is the case, the use of DMELs to date has been relatively limited. REACH registrants have highlighted concerns over the complex and specialist nature of DMELs. This includes the need to first develop dose-response curves in order to derive a DMEL, and the potential significant data burden this presents. An issue further exacerbated by the complexity of the topic, and technical proficiency needed to develop and implement DMELs as barriers.

- Additionally, while there has been slow uptake for the use of DMELs at EU level, some national authorities have gone beyond the minimum requirements set by REACH and further evolved the approach to use of DMELs (including the development of two-tier systems\(^\text{13}\)). This may further complicate issues creating less regulatory harmony and exacerbating the concerns and issues highlighted further.

Therefore, the problem identified is three-fold:

- The accuracy of the qualitative risk assessment for non-threshold hazards may be weaker than quantitative approaches, falling below the aims of the REA CH Regulation. This has knock-on effects for selection of risk controls, and overall protection of human health and environment.

- Communication of hazards, risks, and risk controls down the supply chain may be weaker when using qualitative risk assessments. This is further undermined where downstream users may be less well placed to judge the quality of exposure scenarios and operating conditions, particularly if the information provided is not comprehensive and lacks transparency.

\(^{12}\) ECHA, 2018, ‘Working procedure for RAC on setting of risk estimates such as DNELs and dose-response functions in the REACH applications for Authorisation and/or on request of the European Commission’, 620dad5f-9ed3-a302-18a6-c2d7aede989d (europa.eu)

\(^{13}\) Some Member States have created two-tier systems with a tolerable threshold (i.e., the safe limit which must not be exceeded) and an acceptable threshold (i.e., an aspiration threshold below which the risks are assumed to be very low). It is explained that such two-tier systems provide a minimum setting and a target for continuous improvement.
- The operation of different approaches at national level may have consequences for level playing field, and further exacerbate the regulatory certainty and clarity of communication. This could potentially create coherence issues with REACH and related legislation such as OSH, while also further undermining the trust in the information provided at downstream user level.

4.2 Who is affected by the problem?

Based on the problems identified above it is also possible to identify who might be affected by the problems. These issues are outlined in the table below.

Table 4.1 Overview of who is affected by the problems identified

<table>
<thead>
<tr>
<th>Actors</th>
<th>Issue</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Businesses</td>
<td>Selection and costs of risk control selection.</td>
<td>Potential for the qualitative risk assessment to incorrectly gauge the level of risk. This has two possible consequences: Firstly, if the risk assessment is overly cautious then the selection of risk controls will equally be over cautious meaning unnecessary costs will be incurred. Secondly, if the risk assessment is under cautious it may mean that the safety of working environments and consumer safety are misjudged. This would have direct impacts in terms of lost time injuries/work force unable to work affecting both business continuity and productivity, additionally, for consumers it would equate to impacts on health and healthcare burden (covered further down this table).</td>
</tr>
<tr>
<td>Businesses</td>
<td>Level playing field effects</td>
<td>Evolution of policy at different rates and under different national schemes may have impacts for level playing field. This has direct economic impacts for requirements under different jurisdictions.</td>
</tr>
<tr>
<td>Workers</td>
<td>Health effects / safety</td>
<td>If the assessment of risks underestimates the risk and therefore necessary risk controls, there are direct potential health effects. This is likely to have impacts on quality of life, indirect impacts on wellbeing of family members/dependents, as well as potential to work.</td>
</tr>
<tr>
<td>Consumers</td>
<td>Health effects / safety</td>
<td>If the assessment of risks underestimates the risk and therefore necessary risk controls, there are potential direct health effects for consumers and the population in general. This is likely to have impacts on quality of life, indirect impacts on wellbeing of family members/dependents, as well as potential to work.</td>
</tr>
<tr>
<td>Society</td>
<td>Healthcare burden</td>
<td>The increased incidence of avoided illness would place burden upon health care services and deplete resources that could otherwise be used for other things. This has the potential impact of increased costs of healthcare for the general public or lack of availability for critical resources in cases where the available resource if finite.</td>
</tr>
<tr>
<td>Environment</td>
<td>Environmental impacts</td>
<td>If the assessment of risks underestimates the risk and therefore necessary risk controls, any releases to environment have the potential to cause negative impacts on the natural environment. This includes potential impacts for ecosystem stability and biodiversity.</td>
</tr>
</tbody>
</table>
4.3 How the problem might evolve

While the RAC have been supportive in helping develop dose-response relationships for a select number of non-threshold substances through the SVHC / Authorisation process, in practice the work required is labour intensive and the RAC also have a wide range of other activities which need to be covered. Work under related occupational legislation (OSH\textsuperscript{14} and CMD\textsuperscript{15}) has aimed to develop binding occupational exposure limits (BOELs) for non-threshold substances which could be useful, but again the number of substances is very limited, with 28 substances identified in the annexes of CMD, and work to add further substances progressing at a rate of 2-3 substances per annum.

As a comparison, 1,286 unique substances have a harmonised classification as CAT 1A,1B, or CAT2 carcinogens or mutagens under the CLP Regulation.

It should, however, be clarified that the work under OSH encompasses a bigger body of work beyond the development of BOELs. This has included further consideration of the issues for many carcinogenic substances (based on priority), and the kind of measures that need to be implemented within the work-place to limit exposure. In that respect a BOEL for each and every situation may not be needed.

The analysis presented here in totality does suggests that without further intervention the further development of quantitative approaches for risk assessment on non-threshold substances could evolve slowly. While the qualitative approach to risk assessment is a reasonable compromise and if suitably managed should provide valuable consideration and management of the risks, further input via quantitative approaches would improve clarity, transparency, and communication across the supply chain.

\textsuperscript{14} The Occupational Safety and Health Framework Directive 89/391/EEC

\textsuperscript{15} The Carcinogens and Mutagens Directive 2004/37/EC. Note that in March 2022 the Council approved the amendment of the Directive to include 12 reprotoxic substances currently managed under other EU legislation. Based on this move the CMD will therefore be renamed the carcinogens, mutagens, and reprotoxic substances directive or CMRD for short. EU strengthens protection of workers from dangerous chemicals - Consilium (europa.eu)
5. Why should the EU act?

The REACH Regulation has an overarching aim to ensure a high level of protection for human health and the environment, which includes the promotion of alternative methods for assessment of hazards of substances (Article 1). For substances with non-threshold hazards, the complexity of the topic matter, need for specific technical expertise, and data (which is difficult and costly to produce) highlights why a harmonised EU approach is needed. In particular to share the burden of that effort by making processes and data as comparable as possible across different geographies, and make sure the technical expertise on offer is drawn together to be greater than the sum of its parts.

This underscores why an EU level intervention is both relevant and appropriate, and the REACH Regulation already delivers on this aspect. This is evidenced by the existing approaches for hazards with thresholds, and the use of DNELs and PNECs through standardised approaches to help appropriately assess risks and communicate them down the supply chain in a clear and transparent fashion. The REACH Regulation puts in place the option to use qualitative approaches for risk assessment where a DNEL cannot be derived as a suitable compromise. Provided a risk-based approach and thorough consideration of the issues is completed, this should be sufficient to manage the risks in a satisfactory manner.

The problem definition highlights that the approach to using qualitative risk assessments for non-threshold hazards may not be harmonised, and that the quality of assessments themselves is variable. This is an issue that may be more challenging to address at national level. It is possible that part of the issue could be addressed by more tripartite discussions between regulators, trade associations and industry, which would focus on the quality of assessments. There may also be a need to promote quantitative approaches to be used more often where possible (including additional/improved guidance from ECHA, particularly on threshold/non-threshold carcinogens). The wider issues identified within the problem definition have broader geographic scope.

The problem definition highlights that the communication aspect of the qualitative risk assessment down the supply chain is of weaker clarity (particularly if the exposure scenarios and operating conditions are textual and translated multiple times into other languages) and this may have knock-on consequences for human health protections. The issue is driven in part by the fact that downstream users are less well placed to judge on whether the qualitative assessment was of good quality, and the resulting exposure scenarios and operating conditions can be fully trusted (e.g., DNELs provide a hard numerical threshold for comparison against). The issue is further exacerbated by the fact that regulatory certainty and scrutiny is challenging and uncertain within qualitative assessments, an issue commented on by both industry and regulators.

ECHA has developed guidance for the use of quantitative assessments (DMELs) which could both improve the clarity of the risk assessment outcomes (regulatory certainty and scrutiny) and communication down the supply chain (threshold values which can be clearly presented and understood), which would ultimately benefit human health protections. The use of DMELs to date is voluntary, and relies on the co-operation of REACH registrants, Member State Authorities, and expert groups such as the RAC. It could be expected that the enhanced use of DMELs would address the issues identified in the problem definition and maintain the objectives of REACH.
However, because of the specific issues highlighted at the top of the page (complexity of the topic, required data, guidance, and expert agreement) progress in the enhanced use of DMELs has struggled. This has seen some Member States begin to spearhead their own initiatives outside of REACH, such as two-tier systems for use in occupational settings to make the use of DMELs more widely applicable. The need for further harmonised approaches that maintain a level playing field and provide clarity over how the topic should be approached cannot be achieved at Member State level alone.

Furthermore, where these processes already sit within an EU-wide policy instrument (REACH) there is a need for continuity both within REACH against related processes (e.g., DNELs/PNECs, restriction, authorisation, etc.) and externally to related legislation (e.g., OSH). Therefore, based on the problem definition and stakeholder engagement there are two clear drivers for the EU to act at this point:

- The complexity of the subject matter for non-threshold hazards requires close agreement across EU stakeholders to help manage the issue in an effective manner that maximises the resources available. Issues with regulatory certainty and scrutiny of the qualitative risk assessment, and lower clarity/quality in communication down the supply chain could hamper human health protections. The use of quantitative assessment may provide a solution to these issues, but there is a need for EU-level intervention to help make clear the role of DMELs and how the benefits can be materialised.

- The evolution of policy approaches at national level could have the potential to affect harmonisation of approach and level playing field. This could further exacerbate an already complex situation and would therefore warrant a further review of how DMELs are applied at EU level to help maintain best practice.

  ▶ Based on these two drivers there is an inherent need for the EU to act and further explore how the issues identified in the problem definition can be addressed.
6. Objectives of the intervention

The overarching objective of the intervention should be to uphold Article 1 of the REACH Regulation:

"Article 1 (aim and scope): The purpose of this Regulation is to ensure a high level of protection of human health and the environment, including the promotion of alternative methods for assessment of hazards of substances, as well as the free circulation of substances on the internal market while enhancing competitiveness and innovation."

The problem definition (see Section 4) identified that there may be concerns with the current approaches for the risk assessment covering non-threshold hazards, on the basis that the qualitative assessment may be more uncertain. This issue is exacerbated where there is no harmonised approach to the qualitative assessment and the quality of the assessment may be variable, including transparency of reporting.

The guidance from ECHA has provided a quantitative approach (DMELs) to the risk assessment for non-threshold hazards which could reduce the uncertainty of the assessment and potentially improve the communication down the supply chain. This is further strengthened on the basis that the outputs of the DMEL approach are likely to have better regulatory scrutiny and certainty, which benefits both REACH Registrants and government regulators.

The intervention should therefore aim to develop an approach which can reduce the uncertainty in the risk assessment for non-threshold hazards and ensure the high level of protection for human health and the environment.

The second half of Article 1 also addresses the need for free circulation of substances on the internal market while enhancing competitiveness and innovation. These aspects rely at least in part on a level playing field and good levels of harmonisation across industry operating in EU countries. The problem definition also identified that the policy landscape is evolving in an irregular fashion, with some Member States spearheading new initiatives.

There is an inherent need for EU policy to learn and evolve from new initiatives both within the Commission Services, but also activities at national level. Therefore, the objective of the intervention should also consider these developments and how the approach can be adopted to meet Article 1 in full.

---

7. What are the available options to achieve the objectives?

7.1 Introduction

The options to address the problems identified in Section 4 have followed the guidance set out in the Better Regulation Toolbox #16. This includes a baseline as the ‘no-policy-change’ scenario, including relevant EU-level and national policies in force.

Based on the analysis from the state of play (see Appendix A), the baseline can be concluded to include:

- The current situation, which includes all phase-in substances currently registered under the 2010, 2013 and 2018 deadlines as well as all new substances registered, and information on the extent to which (a) DMELs could have been used; (b) DMELs have been used in practice. (i.e., the existing number of REACH registrations have been used as the baseline)

- Assumed current regulatory position at EU level. i.e., qualitative risk assessment is assumed as the primary method for non-threshold substances. Quantitative method (DMELs) is voluntary (see bullet above about uptake of use).

- National approaches in place already would be included as part of the baseline (see Appendix A – Task 2). This identifies the use of two-tier systems for some Member States.

- Related legislation (OSH, CMD, Drinking Water Directive, Water Framework Directive) continues in the same fashion as it is currently presented for 2022. I.e., no further regulatory changes in related legislation are included in the baseline.

7.2 High-level options

Based on the approach detailed within the introduction the study has identified a baseline (see the bullet points in the previous sub-section above), and two high-level overall options to help reduce the uncertainty in risk assessments for non-threshold hazards. These two options can be described as follows:

**Option 1:** Enhanced DMEL use through non-legislative measures within REACH. This option would include modifying e.g., the REACH guidance to give clearer expectations that a

---

17 As per Tool #16 of the Better Regulation Toolbox, there are four suggested steps in order to identify a realistic set of options:

(1) Construct a baseline from which the impacts of the policy options will be assessed.

(2) Start by compiling a wide range of alternative policy options.

(3) Identify the most viable options; explain the discarded policy options.

(4) Describe in reasonable detail the key aspects of the retained policy options to allow an in-depth analysis of the associated impacts.
quantitative approach to CSA is expected where possible. It would not include changes to the REACH regulation itself.

**Option 2:** Amend REACH to further require use of the DMEL concept. This option would include a specific legislative change indicating that a quantitative approach to estimating a DMEL is expected for substances with certain hazard types, as well as a quantitative measure of acceptable risk.

As a basic premise, option 1 and 2 define that the enhanced use of DMELs can be implemented either legislatively through regulatory amendment, or through approaches that do not require a change to the legislation itself. These options provide the broad overarching structure for analysis under the impact assessment. However, given the issues identified under the problem definition, further nuance is needed in how these overarching options are applied and assessed.

The study has followed the guidance set out under Tool#16 of the Better Regulation Toolbox to develop a wide range of sub-options which are broadly grouped under different elements (e.g., which hazard endpoints should be included under Option 1 and 2). These sub-options were then subsequently screened following a two-step process:

- The grouped sub-options were assessed and screened in/out based on legal feasibility; technical feasibility; previous policy choices; coherence with other EU policy objectives; effectiveness and efficiency; proportionality; political feasibility; and relevance.

- The preliminary conclusions of the screening were presented at the study workshop for further feedback. The workshop included a background paper introducing the study (and its approach), the outputs of Task 1 and 2, the sub-options and preliminary screening. The delegates were then invited to discuss and provide feedback, which was incorporated into the final screened set of sub-options.

  ▶ Further description of the key elements (and their sub-options) provided in the next section.

### 7.3 Sub-options

This section provides some further detailed discussion around which sub-options have been retained, based on the outputs of Task 1, 2, the study workshop and analysis against the criteria set out in the Tool#16. Note that these sub-options are grouped under a set of key elements, and that some of these elements/sub-options may only be relevant under a regulatory change (i.e., they only appear under Option 2).

Table 7.1 sets out the finalised version of the sub-options (post feedback from the study workshop) with details of the different sub-options and alternative parameters that need to be considered in order to define how the options would be implemented in practice.

Based on the initial screening, options were screened into one of three categories: ‘included’, ‘excluded’, or ‘potentially excluded pending further discussion’. The preliminary outcomes of this screening were then presented at the study workshop with suitable supporting material for a full discussion. Based on that discussion, a second screening step was completed with the sub-options either included or excluded. Table 7.1 provided the final outputs of this process with some further narrative detailing the decisions made following the table.
| Table 7.1  Initial screening of sub-options and alternative parameters |
|---------------------------------|-----------------|-----------------------------------------------------|
| **Element**                     | **Possible sub-options** | **Comments from screening**                           |
| A. Which endpoints are covered? | (i). Carcinogens and germ cell mutagens – cat. 1A/18 | Relates to both harmonised and self/notified classification. DMEL concept applied for various substances already. **Include.** |
|                                 | (ii) Carcinogens and germ cell mutagens – cat. 2 | Typically, insufficient data for cat. 2 to definitively conclude that a substance is carc/muta. **Include.** |
|                                 | (iii) Respiratory sensitisers | Some DMELs have already been developed under REACH. However, in most cases it is not possible to develop a dose-response relationship for respiratory sensitisers. **Exclude on the basis of technical non-feasibility.** |
|                                 | (iv) Endocrine disrupters | Note technical challenges based on e.g., non-linear dose response relationships and challenges identifying dose response relationships. **Exclude on the basis of technical non-feasibility.** |
| B. Who develops the DMEL?      | (i) Registrants only | This mirrors the current process under REACH. **Include.** |
|                                 | (ii) Authorities only | Unlikely to be a relevant option given that REACH aims to place burden of proof on industry. Could retain to assess resource implications but likely to be dismissed. **Exclude on the basis of coherence with other EU policy objectives; effectiveness and efficiency; and political feasibility.** |
|                                 | (iii) Registrants for most substances but authorities can develop EU harmonised DMEL in certain cases | Allows for a consistent approach to be applied e.g. similar DMELs for related substances which could otherwise have very different DMELs. Cases where authorities develop DMEL could be prioritised based on e.g. the SEv process. **Exclude on the basis of proportionality and policy objectives.** |
|                                 | (iv) As (iii) with amendment to the Substance Evaluation process to all for authorities to over-ride DMEL used by registrants | Sub-option iii and iv considered together. Sub-option iii excluded on the basis of proportionality. However, sub-option iv may have greater possible application. **Include.** |
| C. Is the quantitative DMEL approach mandatory? | (i) Mandatory to develop a numerical DMEL value only if suitable dose-response relationship can be derived from the data available for the substance in question | Potentially merge with (ii). **Include.** |
|                                 | (ii) Mandatory if registrant can develop new dose-response relationship based on use of read-across or modelling | Potentially merge with (i). **Include.** |
| (iii) | Mandatory to develop new dose-response relationship even if this involves new animal testing | Information requirements in Annexes VII-X should be aligned with the need to classify and to do risk assessment (safe level), but the need to be able to derive safe levels should not in itself drive the animal testing. Exclude on the basis of political non-feasibility. |
| (iv) | Approach is voluntary | Not included as this is essentially the baseline situation. Exclude. |
| **D. Which populations are covered?** | (i) Workers (occupational exposure) | Note potential issues with political feasibility based on overlap with worker protection legislation. Include. |
| | (ii) Humans exposed via the environment | Include. |
| | (iii) Consumers | Note that all combinations of sub-options (i), (ii) and (iii) should be assessed. Include. |
| **E. Which substance tonnage groups are covered?** | (i) Only those that currently require CSA | Include. |
| | (ii) Those that currently require CSA but also those at 1-10t (if data allows dose-response curve to be developed) | This should be included as per the terms of reference (wider consideration of including CSA / increased information for 1-10t substances). However, information requested may not allow for establishment of D-R curves. Include. |
| **F. How many quantitative risk thresholds are applied?** | (i) Single value for tolerable risk level | As is currently the case with the values included in guidance. Consistent with the current CSA approach. Include. |
| | (ii) One value ('acceptable') below which risk is acceptable and second value below which risk is 'tolerable' if RMM reduce risk as far as practicable (and above which risk is unacceptable) | Potentially not consistent with the existing CSA approach. However, this is the approach applied in some Member States, albeit not directly for CSA under REACH. Include. |
| **G. Is the quantitative risk threshold mandatory?** | (i) Non-binding quantitative risk threshold, as included in current REACH guidance. | Note that this is not simply the baseline, as other sub-options would enhance the use of the DMEL concept. Would be less politically challenging. Include. |
| | (ii) Binding politically-agreed value for tolerable risk level. | Would need to take into account values currently applied by EU Member states and elsewhere (e.g. DE, NL, FR, PL). Would enhance consistency of approach. Include. |
| **H. When must the quantitative / DMEL approach be applied?** | (i) Only when routine update of registration dossiers is done (note link to wider REACH IA and dossier update provisions) | Include. |
(ii) By a specified deadline after entry into force  
Include.

| I. What is the agreed excess lifetime cancer risk for workers (over 40 years)? |
|-------------------------|------------------------|
| (i) 1 in 1 000         | These are the options included in the REACH public consultation. Note some Member States have different values e.g. $4 \times 10^{-3}$ prohibitive/tolerable and $4 \times 10^{-5}$ acceptable in NL and DE. Include all as alternative options/parameters. |
| (ii) 1 in 10 000       |                        |
| (iii) 1 in 100 000     |                        |
| (iv) 1 in 1 000 000    |                        |

| J. What is the agreed excess lifetime cancer risk for the public (over 70 years)? |
|-------------------------|------------------------|
| (i) 1 in 1 000         | These are the options included in the REACH public consultation. Include all as alternative options/parameters. |
| (ii) 1 in 10 000       |                        |
| (iii) 1 in 100 000     |                        |
| (iv) 1 in 1 000 000    |                        |

7.3.1 Selection of hazard end-points (option 1 and 2)

To date much of the focus on the use of DMEls has centred on non-threshold carcinogens\(^\text{18}\) and germ cell mutagens, but it is recognised that other non-threshold hazards exist. The study conducted an analysis of other possible end-points, particularly, respiratory sensitisation, immunotoxicants, neurotoxicants, and endocrine disruptors (Appendix A). The study also gathered data from the ECHA database to assess where DMEls have been used to date. The results indicated that for some hazard endpoints (e.g., neurotoxicants, and immunotoxicants) there are issues around how the dose-response curves work (e.g., non-linear) that make the use of DMEls challenging or unviable at the current time. For other endpoints there was greater potential, despite a number of issues, for example endocrine disruptors are highly substance specific, so specific approaches may be needed on a case-by-case basis.

The ECHA database results indicated that carcinogens and mutagens were the most common endpoints using DMEls (102 substances), with the next biggest hazard type being respiratory sensitisers (23 substances). Based on the analysis, respiratory sensitisers and endocrine disruptors were included as possible sub-options within the amber category (potentially exclude) for further discussion at the study workshop.

Feedback from the delegates at the workshop highlighted that there were still significant technical challenges to address carcinogens and mutagens, and respiratory sensitisers and endocrine disruptors would be even more challenging. Many delegates highlighted that the preference would be to further make use of DMEls within the carcinogen and mutagen endpoints first to help evolve and develop mature approaches, before attempting other endpoints.

Respiratory sensitisers and endocrine disruptors were therefore screened out as sub-options under the current study.

A second issue was around whether the DMEl approach should be applied only to Cat 1A/1B substances or also include Cat 2. The original analysis for the state of play cast some doubts over whether sufficient data on substances with Cat 2 classification would be available to support the

---

\(^{18}\) Bevan and Harrison (2017), comments that carcinogens can broadly be divided into two groups: genotoxic and non-genotoxic. The latter category have numerous modes of action (other than genotoxicity) where a no-effect level can very often be defined. In these cases, a DNEL should be applied.
derivation of a DMEL, but delegates at the workshop felt that Cat 1A/1B and 2 should be included in scope. Additional analysis on the state of play (see Appendix A) confirms that Cat 2 carcinogens and mutagens should be in scope, with further discussion on the impacts in Section 8.

7.3.2 Who develops the DMEL? (option 1 and 2)

The outputs of Task 2 (see Appendix A) highlighted that in the USA regulators have a more proactive role in developing and agreeing on thresholds used within slope-factors (US equivalent of DMELs). Therefore, this element explored the possibility of a more significant role in DMEL development by the RAC. Delegates at the workshop highlighted that based on the polluter pays principal which is enshrined in the REACH Regulation by placing responsibility on registrants, REACH registrants should develop the DMEL. Members of the RAC also highlighted the labour-intensive nature of DMELs and the finite resources of the RAC. It was noted however the RAC could act as a review body in specific cases where DMELs needed to be evaluated. The sub-options have been amended accordingly.

7.3.3 Is the quantitative DMEL approach mandatory? (Option 2)

This element set in place a set of sub-options to help determine rules for how the mandatory option might work. Note that the sub-options that result in a significant increase in animal testing were excluded on the basis that sufficient information from other approaches should take priority, and that animal testing is a last resort. In this case the argument could be made that increase in animal testing is not proportionate to the standard information requirements.

7.3.4 Which populations are covered? (Option 1 and 2)

The sub-options are disaggregated to cover workers, consumers, and exposure via the environment. All three categories are included.

7.3.5 Which substance tonnage groups are covered? (Option 2)

As part of the wider body of work on the revision of the REACH Regulation, an assessment is currently underway to look at the data requirements and obligations on REACH registrants for substances in the 1-10t per annum bracket. Therefore, this element also assesses the possible mandatory obligation of developing DMELs within the 1-10t bracket as a new CSA/CSR obligation.

7.3.6 How many quantitative risk thresholds are applied? (Option 1 and 2)

Following on from the outputs of Task 2 (see Appendix A) the sub-option for a two-tier system approach on an EU-wide basis is included alongside the existing approach.

7.3.7 Is the quantitative risk threshold mandatory? (Option 2)

Under the existing approach the use of quantitative risk assessments such as DMELs for non-threshold substances is voluntary. This includes allowing the REACH registrants discretion to select their own DMEL threshold. The ECHA guidance does provide some steer on what threshold values for tolerable risk should be used, but the registrants are able to deviate from the guidance. This
element therefore poses the question over whether the specific threshold value (e.g., $10^{-4}$) should form a binding minimum level, similar to binding OELs used under OSH.

Based on the results of Task 2, the use of minimum mandatory thresholds for DMELs (and their equivalents) has been identified both within related EU legislation (e.g., OSH) and in other OECD geographies, such as the USA and Canada (slope-factors). Therefore, these sub-options are included.

7.3.8 **When must the quantitative / DMEL approach be applied? (Option 2)**

This element provides some additional flexibility to the timing of when data would need to be provided under a mandatory approach.

7.3.9 **What is the agreed excess lifetime cancer risk (element I: Workers and element J: General public, including consumers) (option 1 and 2)**

The final two elements pose the question of what the appropriate threshold for DMELs under different settings might be. The work under Task 1 and 2 highlighted that the thresholds in use typically range from $10^{-3}$ to $10^{-6}$, depending on the substance and setting. Therefore, the sub-options under both of these elements include the full range of possible thresholds based on increasing orders of magnitude. $10^{-3}$, $10^{-4}$, $10^{-5}$, and $10^{-6}$.
Appendix A
Assessing the state of play
1. **Task 1 – Identification of types of hazard and estimation of numbers of substances**

1.1 **Introduction**

There are essentially three parts to Task 1, the first part was to identify health hazards and toxicological modes of action (MoA) for which it is not possible to establish a toxicological threshold for human health effects, but for which it is nevertheless possible to derive a dose-response relationship for the lead effect and to develop a DMEL.

The second part to Task 1 was to provide an overview of methodologies currently used or proposed for deriving DMELs (in addition to those for deriving dose-response relationships).

The third and final part to Task 1 was to use the ECHA database of registered substances to assess the extent to which DMELs have been used to date by registrants and the risk assessment approaches that have been taken. In addition to this, based on the ECHA database of substances registered under the REACH regulation, an estimate is included to illustrate how many substances could potentially benefit from the use of a DMEL approach versus how many have actually made use of a DMEL. This estimate will consider:

- the type of hazards and modes of action
- the available data (i.e., in vivo or in vitro); and
- the tonnage band.

These estimates will also consider the Commission’s intention to propose an increase in information requirements and to require a chemical safety assessment for substances in the 1-10 tonne tonnage band.

1.2 **Results of analysis**

1.2.1 **Review of non-threshold hazard classes**

A number of health hazard endpoints were identified during the literature search that were considered to be acting via a non-threshold mode of action\(^{30}\). These were germ cell mutagens, genotoxic (non-threshold) carcinogens, (respiratory) sensitisers, immunotoxins, neurotoxicants and

---

\(^{30}\) The characteristics of exposure and the spectrum of toxic effects come together in a correlative relationship commonly referred to as a dose-response relationship. Individual dose-response relationships are characterised by a dose-dependent increase in the severity of the response. The dose-dependence of the response often results from a change in a particular biochemical process. Therefore, the minimum effective dose of a chemical that produces a stated all-or-nothing
endocrine disrupting chemicals. Germ cell mutagens, non-threshold carcinogens and (respiratory) sensitisers are known to act via a non-threshold mode of action.

It is generally assumed that a threshold exists for most types of toxic reactions. In contrast, experiments with mutagens almost always show a linear dose-response curve, suggesting that there may be no threshold for mutagenesis. Similar results are also obtained in studies with radiation Linear No-Threshold (LNT) single-hit model. The biological plausibility of the single-hit model for mutagenicity is controversial and the current thinking on this is moving away from this concept. It is assumed that for most mutagens and non-threshold carcinogens, the available data are generally insufficient to establish an effective threshold with sufficient confidence. The default or baseline assumption for these compounds will therefore assume no threshold.

One aspect of this first task was to identify other hazards or modes of action, in addition to mutagenicity and non-threshold carcinogenicity, for which a dose-response relationship can be determined but practically no threshold can be derived.

Based on the requirements under REACH and the Commission’s inception impact assessments (IIAs) on its chemicals strategy actions, it is already foreseeable that a new hazard class may be needed for endocrine disrupting (ED) chemicals. This would mean the possible need to review and include ED effects, immuno- and neurotoxic compounds as possible candidates for use of the DMEL approach. However, there is some debate around whether immunotoxic, neurotoxic and endocrine disrupting chemicals exhibit non-threshold modes of action and this is briefly discussed below.

**Immunotoxicants** can influence two immune parameters and cause an effect at different dose-response ranges as well as exhibit different shaped dose-response curves. Therefore, what is considered a “safe” dose for one immune parameter may not be “safe” for the second. The way in which an immunotoxicant can act may also be influenced by the immune status of the organism. There is some controversy regarding the existence of a threshold for immunotoxicity. This is mainly fuelled by the concept of a latency effect, where sub-threshold exposures to substances appear to rewire the immune system for a later-life response which could be adverse (IPCS, 201231). Immunotoxicants may also exhibit a hermetic U-shaped dose-response curve which may indicate that a subthreshold effect may just be the bottom of the "U" on the U-shaped curve.

**Neurotoxicity** has been defined as an adverse change in the structure or function of the central nervous system (CNS) and/or peripheral nervous system (PNS) following exposure to a chemical (natural or synthetic) or physical agent that diminishes an organism’s ability to survive, reproduce or adapt to the environment (IPCS, 200132). As with other non-cancer endpoints, it is assumed that there is a nonlinear dose-response relationship for neurotoxicants. However, while theoretically there may be a threshold for neurotoxic effects, these are often difficult to determine empirically. Therefore, a linear relationship is assumed to exist for some neurotoxicants and thus, they have been included here.

**Endocrine disruption** is addressed in various legislative acts within the EU. The regulation of endocrine disrupting substances is typically undertaken using a hazard-based approach possibly as a result of the assumed absence of thresholds for the adverse effects of such substances. This lack

---

32 https://inchem.org/documents/ehc/ehc/ehc223.htm#_223220000
of a threshold is on the basis that the complex nature of the endocrine system means that it is not possible to identify and derive safe levels of exposure to such EDC chemicals. While in non-EU authorities, such as North America, Australia and Japan, a risk-based approach is undertaken for endocrine disruptors. Therefore, there is no agreed global consensus on whether endocrine disrupting substances act via a non-threshold mode of action and it may be necessary for a definition that encompasses this aspect so that registrants can form a decision on how to approach the health hazard assessment.

The second part to Task 1 was to provide an overview of methodologies currently used or proposed for deriving DMELs (in addition to those for deriving dose-response relationships). The results of this exercise are discussed as part of Task 2 - overview of regulatory uses of dose-response relationships – given the significant overlap between the two tasks.

1.3 Review of ECHA data for REACH registrations

As elaborated already above the third sub-task within task 1 concentrates on an analysis of the ECHA database of registered substances to get an overview on the extent to which DMELs have been used to date.

During the round-table discussion with ECHA and the Commission held on the 17 September 2021 it was agreed that the primary focus should be on substances classified as carcinogenic and mutagenic category 1A or 1B. The data request to ECHA therefore required all substances with these classifications to be identified (including substance name, chemical identifier (CAS and EINECs), and tonnage bracket), and specifically which substances have been notified as making use of a DMEL as part of the registration. Additionally, the search criteria were intended to include all substances irrespective of hazard class where notification is made that a DMEL has been used.

Therefore, the outputs of this data search can broadly be disaggregated into two main groupings.

- Firstly, the total number of Cat 1A or 1B carcinogenic and mutagenic substances registered under REACH at or above 10 tonnes per annum and what proportion of that number includes a DMEL within the REACH registration.

- Then secondly, a group defined by the use of DMELs but hazard classes other than carcinogenicity or germ cell mutagenicity.

A first overview prepared by ECHA was based on a list of 6397 substances from ECHA database corresponding to 6423 latest registration dossiers that was used for the further analysis. This list revealed a total number of 140 substances that used a DMEL for long-term exposure assessment. This included 102 substances classified as carcinogenic cat 1A or 1B or mutagenic cat 1A or 1B, and 38 substances with other classifications.

A total of 533 substances were identified as being classified (both harmonised classifications and self-certified classifications) as carcinogenic or mutagenic (category 1A or 1B), with 102 making use of a DMEL, which is broadly around 20%. This suggests that while DMELs are in use, their practical application is perhaps less widespread than other qualitative approaches to avoid health effects, and further that there could be potential here to make greater use of DMELs.

The remaining 38 substances which uses a DMEL have been further reviewed against the hazard classifications named within the C and L inventory, again including both harmonised and self-certified classifications. The majority of these substances (23) are classified as respiratory sensitisers,
with a further five classified as skin sensitisers. Additionally, there was one substance classified as having specific target organ toxicity (STOT) affecting the thyroid gland with chronic effects expected. This could be included within the EDC category. The remaining substances had a range of classifications and require further investigation to understand how and why a DMEL might have been used.

Following a first analysis of the publicly available information regarding the registration dossier it became obvious that there is very limited publicly available information on how a DMEL has been derived or why it has not been derived although potentially possible. Therefore a second data request has been sent to ECHA in order to share a number of CSRs.

A subset of 146 substances (thereof 78 substances that have used a DMEL and 68 that could potentially use a DMEL but did not) was chosen for further analysis. When selecting the substances, care was taken to identify some similar substances in both groups - DMEL used and not used - so that further comparisons are also possible. These substances can be further divided in the following categories:

1. Group 1 - General substances: DMEL used for CM substances
2. Group 2 - General substances: DMEL used without CM classification
3. Group 3 - General substances: Could use DMEL but did not
4. Group 4 - Chromates (CM) with DMEL
5. Group 5 - Chromates (CM) without DMEL
6. Group 6 - PETCO with DMEL
7. Group 7 - PETCO without DMEL
8. Group 8 - Enzymes with DMEL without CM classification

The CSRs of the substances were requested from ECHA and CSRs for most of the substances were received. The evaluation was done in a password protected Excel file (still to be treated confidential), with separate sheets for the categories mentioned above.

First, for all substances the classification according to CLP for the health hazards germ cell mutagenicity (Muta.) and carcinogenicity (Carc.) was extracted that was used in the CSRs. Those classifications might differ from the recent harmonized CLP classification and can affect hazard assessment.

For substances that have used a DMEL information on the derived DMEL(s) (route, type of effect, most sensitive endpoint) were extracted from part 5.11 “deviation of DNEL(s)/DMEL(s) and other hazard conclusions” of the CSR. For each DMEL a separate entry was created. If provided in the CSR, also details on the method for derivation of the DMEL(s) was extracted.

As a first assessment it could be mentioned:

Group 1:

1. A lot of substances do not have a classification for mutagenicity (mostly conclusive but not sufficient for classification)
2. In most of the cases the most sensitive endpoint for deviation of a DMEL was carcinogenicity (oral or by inhalation) and routes were usually systematic long-term inhalation, dermal (and oral for general population).
3. As methods used to derive the DMEL mostly the ECHA Guideline is mentioned. For chromates also some specific methods are mentioned (based on BMDL01 as presented by ECHA; based on OEL as proposed by RAC).

For substances that used a DMEL without a CM classification, the CSRs were examined for any justifications why they have used DMELs as threshold.

A brief evaluation revealed the following:

4. For the fast majority of substances, it is indicated that data for carc. and muta. classification is conclusive but insufficient for classification
5. Again, the ECHA Guideline is cited most often as method for derivation of the DMEL

For substances that have not used a DMEL the CSRs were screened for reasons why no DMEL was derived. Also, information on the threshold that has been used instead was extracted.

The first assessment led to the following first information:

6. In several CSRs it is indicated that derived value for long-term (inhalation) exposure for the general public is a DNEL and not a DMEL because the value was set based on thresholds for respiratory effects (toxicity and tumorigenicity) and no residual health effects (e.g., excess tumor risk) are expected at this level
7. In some other cases, it is mentioned that the quality of the information does not comply with the criteria for DNEL/DMEL derivation, as laid down in the ECHA guidance R8 (Appendix R8-15, p148 in conjunction with regulation (EC) 1907/2006, Annex XI).
8. For nearly all substances, DNELS were derived.
9. Especially for some PETCO substances, detailed justifications are provided focusing on the availability of new data.

1.4 Screening of registration dossiers of Carc Cat 2 substances with regard to the suitability of the available data to derive a DMEL:

1.4.1 Introduction

A selection of substances with either harmonized or self-classified Carc Cat 2 classification were screened with focus on the availability of reliable carcinogenicity studies and additional mechanistic studies (including information on genotoxic potential) in order to assess whether a DMEL or DNEL could be derived with sufficient confidence.

The information on how a DNEL/DMEL was derived by the registrant was extracted from the CSRs. The relevant information on toxicological studies was taken from the ECHA dissemination site.

The selected substances consisted of 5 substances for which the registrant had derived a DMEL, and 17 substances for which the registrant either did not cover the endpoint carcinogenicity, considered it covered by DNELs for other endpoints or a DNEL was derived for carcinogenicity, without a justification why not a DMEL was used instead.

The available carcinogenicity studies were screened with regard to dose selection, with focus on whether doses were available without carcinogenic response. Where applied a superficial assessment of the reliability of read-across was carried out and whether this information was considered suitable to support a reliable DNEL or DMEL derivation.
For the mechanistic studies it was looked at whether they could be sufficient to conclude that the carcinogenic response can be assumed to have a threshold or not.

### 1.4.2 Conclusions based on a general survey of the information

In several cases tumours occurred only at higher doses, indicating that a threshold for the effect exists. Mechanistic support for such thresholds was, however, of differing quality.

Good support for the existence of a threshold is available for certain substances which have been recently reviewed by scientific committees. For instance, for 1,4-dichlorobenzene, RAC concluded on a DNEL based on liver tumours in the top dose of one species only or for aniline, where the German MAK concluded based on detailed mode of action (MoA) analysis (Met-Haemoglobin formation) that a threshold for carcinogenicity exists (MAK evaluation, Hartwig, 2019).

Examples were identified in three cases where information on MoA were considered not sufficient but still the registrants used DNELs for these substances.

Arguments were for example that based on some negative genotoxicity studies it can be concluded that the carcinogenic effect is threshold dependent. This might not be sufficient, especially when tumours were also seen at the lowest dose tested. Despite indications for the existence of a threshold, in the absence of sufficient information on MoA, the precautionary approach should be taken, i.e. DMELs with appropriate assessment factors should be derived, not a DNEL (in line with Chapter R.8 of the REACH guidance).

In some cases it might be difficult to extrapolate to the low dose region, e.g. if tumours are only seen in the top dose. The linear approach might then be rather precautionary, but in the absence of sufficient knowledge on MoA this should be the way forward. In one example reviewed, the registrant derived a DMEL based on a calculated T25. No tumours were observed at the lower of two doses and an irritant local effect was considered the underlying cause of the observed lung tumours (though preneoplastic/irritant lesions of the respiratory tract were also seen at the low dose and in males and females). The registrant derived a DMEL indicating a risk of 1:2,000 and considered it acceptable, as it was likely that the dose-response was non-linear in the low doses region. However, without data that would allow deriving a threshold such a risk level appears not acceptable, despite the lack of politically agreed acceptable risk levels.

In other cases, there are some rare tumours with only single incidences and without clear dose dependence. It can be questioned whether these tumours would be covered by a DMEL based on other tumours for which a clear dose-response can be derived from the study. Such rare tumours are sometimes regarded as supportive evidence for a Carc Cat 2 classification, whereas a Carc Cat 1 classification is normally based on clear evidence for statistically significant increases in tumour incidences.

Compared to Cat 1A/1B substances, it appears that the assessment of Cat 2 substances more often involves threshold effects. The evidence to derive such thresholds does, however, not seem to be sufficient in most cases. For Cat 1A/1B substances even if there is no evidence for a genotoxic MoA, it might sometimes not be possible to derive doses without effect (more potent carcinogens),

---


---

© WSP E&IS GmbH

March 2023
Doc Ref. 807693-WSP-RP-OP-00004_A_P06.1
which seems to lead the registrants towards non-threshold and DMEL (rather than threshold and DNEL).

In a few cases read-across was applied, while for some substances the justification for the application of read-across was considered insufficient, for other substances read-across appears to be sufficiently justified and it might also be used for the derivation of DNELs/DMELs (i.e. where concentrations can be clearly calculated from source substance to target substance).

1.4.3 Overall Conclusions for analysis of Carc 2

It appears to be crucial that DNELs/DMELs for carcinogens should be more frequently reviewed by authorities (e.g., by reviewing dossiers for harmonized DNELs/DMELs).

An update of the DNEL/DMEL guidance (REACH guidance Chapter R.8) seems highly needed. A clear recommendation that for carcinogens the default assumption should be the non-threshold approach, leading to DMEL-derivation or a qualitative assessment should be included. For deviations from this approach, meaning that a DNEL is derived based on threshold considerations, adequate data have to be presented and a robust justification should be included.

Several of the studies available for Cat 2 studies consist of control plus two dose groups only (It is less clear based on this limited analysis whether this is less frequent for Cat 1A/1B substances – but this could be checked). Application of the BMD approach is not possible in such cases – such studies give only very little information on the dose response curve and leave a lot of uncertainty also when the conservative NOAEL/LOAEL or T25 approach is taken.

In the absence of MoA information – a DMEL should not be derived for carcinogenic substances in general.

If there are MoA data – a DMEL or a DNEL might be derived, depending on type and quality of information.
2 Task 2 – Overview of regulatory uses of dose-response relationships

2.1 Introduction

Task 2 provides support to the overall study with research to analyse the various methods used to derive DMELs within EU member states or equivalents in other geographies (where terminology differs). Importantly, Task 2 also needs to assess and understand the political acceptability of risk thresholds developed as part of the DMELs, whether mandatory risk thresholds are prescribed within national legislation and who is responsible for the development and management of the DMEL.

As a further comment, it should also be recognised that risk can manifest differently depending on settings (i.e., occupational, consumer, man-via-the-environment), and also dependent on the type of risk effect and quantification (i.e., causes cancer as annual risk, life-time adjusted risk, etc.).

Where the use of DMELs and equivalent processes have been used primarily with carcinogenic and germ cell mutagenic hazards, the primarily focus has been on how these hazards specifically are managed within different national approaches. A high-level consideration of other non-threshold hazards has also been included albeit with broader focus.

A tailored search strategy was employed to retrieve relevant reports and discussion papers from European and non-European authoritative bodies as listed in Table A.1. Note a full list of the references reviewed is provided in Appendix C. The retrieved reports and papers have been screened for their relevance in discussing risk assessment methodologies, which can be applied to non-threshold toxicants. This initial search has been undertaken to gain an understanding on the risk assessment methodologies which can be employed.

The search, which was carried out in English, consisted of several parts and included all those documents up to September 2021 (inclusive). First, publicly available sources of information (e.g., Google, Google Scholar) were accessed. The risk assessment methods were not restricted to industrial chemical applications, but also included methods employed to other industries including food, occupational exposure, contaminated land, and pharmaceuticals. This allowed for a more comprehensive review of available methodologies and identification of the most appropriate and/or relevant method that has been employed.

To date, this search has been performed for carcinogens and germ cell mutagens (these two endpoints are considered to be well established) as well as endocrine disruptors (this endpoint is not as well established).
### Table A.1 Overview of reference sources

<table>
<thead>
<tr>
<th>Location of authority</th>
<th>Name of the authority</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EU authorities</strong></td>
<td>European Chemicals Agency (ECHA) (including relevant scientific committees such as the RAC-SCEOEL Joint Task Force)</td>
</tr>
<tr>
<td></td>
<td>European Food Standards Authority (EFSA)</td>
</tr>
<tr>
<td></td>
<td>European Medicines Agency (EMA)</td>
</tr>
<tr>
<td></td>
<td>European Parliament</td>
</tr>
<tr>
<td></td>
<td>Scientific Committee on Consumer Products (SCCP)</td>
</tr>
<tr>
<td></td>
<td>Scientific Committee on Consumer Safety (SCCS)</td>
</tr>
<tr>
<td></td>
<td>Scientific Committee on Occupational Exposure Limits (SCOEL)</td>
</tr>
<tr>
<td><strong>EU national authorities</strong></td>
<td>Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BauA) and Bundesinstitut für Risikobewertung (BfR)</td>
</tr>
<tr>
<td></td>
<td>European Trade Union Institute for Research (ETUI)</td>
</tr>
<tr>
<td></td>
<td>French Agency for Food, Environmental and Occupational Health (ANSES)</td>
</tr>
<tr>
<td></td>
<td>Miljøstyrelsen (Danish EPA)</td>
</tr>
<tr>
<td></td>
<td>National Institute for Public Health and the Environment (RIVM)</td>
</tr>
<tr>
<td></td>
<td>Nordic Council of Ministries</td>
</tr>
<tr>
<td></td>
<td>Swedish Chemical Agency (KEMI)</td>
</tr>
<tr>
<td><strong>Non-EU authorities</strong></td>
<td>Health Canada (HC)</td>
</tr>
<tr>
<td></td>
<td>Canadian Council of Ministers of the Environment (CCME)</td>
</tr>
<tr>
<td></td>
<td>Canadian Food Inspection Agency (CFIA)</td>
</tr>
<tr>
<td></td>
<td>National Industrial Chemicals Notification and Assessment Scheme (NINCAS)</td>
</tr>
<tr>
<td></td>
<td>Organisation for Economic Cooperation and Development (OECD)</td>
</tr>
<tr>
<td></td>
<td>UK Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC)</td>
</tr>
<tr>
<td></td>
<td>UK Department for Environment, Food and Rural Affairs (Defra)</td>
</tr>
<tr>
<td></td>
<td>UK Environment Agency (EA)</td>
</tr>
<tr>
<td></td>
<td>UK Food Standards Agency (FSA)</td>
</tr>
<tr>
<td></td>
<td>United States Environmental Protection Agency (US EPA)</td>
</tr>
<tr>
<td></td>
<td>United States Food and Drug Administration (US FDA)</td>
</tr>
<tr>
<td></td>
<td>US Occupational Health and Safety Administration (OSHA)</td>
</tr>
<tr>
<td></td>
<td>World Health Organization (WHO)</td>
</tr>
</tbody>
</table>

#### 2.2 Structure of results

As indicated, the research has primarily focussed on the national approaches to carcinogenic and germ cell mutagenic hazards, with a high-level review of other non-threshold hazards. The nature of the risk can also vary depending on setting: occupational, consumer, man-via-the-environment. Therefore, this section provides a brief overview on a country-by-country basis for DMEL (or equivalent) for carcinogenic and mutagenic hazards categorised by occupational, consumer, and environmental settings.

At the end of this section (see section 0), we have then provided a sub-section detailing the high-level review of other non-threshold hazard classes, primarily focussed on EDCs.

One further general comment from the wider analysis is the general difference in approach between the EU Member States and other OECD nations. Within the EU several Member States have taken a ‘traffic light’ approach (see Figure A.1) to defining risk. This uses two thresholds; an ‘acceptable risk’ level (between the green and yellow light) and a ‘tolerable risk’ level (between the yellow and red lights). This helps categorise the overall risks depending on whether they are in the acceptable, tolerable, or intolerable range. For the non-EU OECD countries only a single risk threshold is applied (tolerable risk) as more of a pass/fail approach.
It can therefore be commented that there is no overall international scientific consensus on an ‘acceptable’ cancer risk for substances that are non-threshold based genotoxic carcinogens.

Figure A.1 Overview of the risk-based concept used in Germany.

2.3 Overview of EU approaches

2.3.1 EU level approaches to quantify risks from non-threshold hazards

Occupational settings

Occupational exposure limits (OELs) are regulatory values which indicate health-based safe levels of exposure for a chemical substance in the air of a workplace. Within the EU context, OELs are set by regulatory authorities at EU and national levels. There is no uniform approach in the EU for the risk assessment of non-threshold carcinogens, nor is there EU legislation setting the ‘tolerable’ risk level for carcinogens in society. However, it is pertinent to note that in the EU, occupational limits proposed for non-threshold carcinogens are not solely based on scientific evidence. Following the adoption of the Committee for Risk Assessment (RAC) opinion that is based on scientific evidence, the setting of binding OELs (BOELs) involves a number of activities that include socioeconomic impact assessments and discussions with social partners. Risk assessment methodologies are
recommended by the European Chemicals Agency (ECHA) and EU Scientific Committee on Occupational Exposure Limits (SCOEL) and summarised below.

The RAC prepares the opinions of ECHA related to the human health and environmental hazards associated with substances as part of the REACH and CLP processes. For non-threshold carcinogens, dose-response relationships for carcinogenicity are normally derived by linear extrapolation so that it is assumed that any level of exposure, however small, might carry some finite risk. The RAC uses two methods the 'Linearised' approach and the 'Large Assessment Factor' approach\(^{34}\). The Large Assessment Factor approach is not risk-based, but rather qualitative, based on the margin of exposure (MoE) principle as applied by EFSA. Linear extrapolation procedure is risk based and can represent different lifetime cancer risks, e.g., an excess risk for cancer in 1 per 100,000 (10\(^{-5}\)) or 1 per 1,000,000 (10\(^{-6}\)) exposed individuals by using a LOAEC, T25 or when data is available BMDL10 approach with application of uncertainty factors to calculate the DMEL.

Generally, human data is preferred over animal data, but often reliable human data may not be available and under such circumstances animal data is used to calculate risk. The default method is linear extrapolation, and the high-to-low-dose factor is 25,000, with T25 used as the starting point, or 10,000 when using BMD10 (10% response) to calculate a DMEL representing a 10\(^{-5}\) excess risk of developing a specific type of cancer.

The risk assessment methodology has been described by the Scientific Committee on Occupational Exposure Limits (SCOEL\(^{35}\)) who developed a methodology to evaluate chemicals found in the occupational setting including non-threshold chemical carcinogens and mutagens. SCOEL recommends dividing chemical carcinogens into four groups based on its mode of action, i.e., non-threshold genotoxic carcinogens:

- **Group A**: Carcinogens with an MoA for which no threshold is assumed, due to direct DNA reactivity of the carcinogen or its metabolites.
  - **Group B**: Carcinogens that are likely to act by an MoA for which no threshold is assumed, either because direct DNA reactivity cannot be excluded or the evidence for genotoxicity due to non-DNA reactive mechanisms is insufficient.
  - **Group C**: Carcinogens for which a genotoxic threshold MoA is likely.
  - **Group D**: Carcinogens with a threshold MoA.

- For those substances with no threshold for effects, i.e., groups A and B, SCOEL proposes a risk-based linear non-threshold (LNT) model approach for the derivation of OELs. The REACH methodology for risk assessment (derivation of DMELs) of carcinogens and mutagens that do not act via a threshold mode of action typically involves the following steps:
  - **Step 1**: Gather typical dose descriptors (e.g. N(L)OAEL, BMD, LD50, LC50, T25, BMD(L)10) from all available and relevant studies on the different human health

\(^{34}\) [https://www.echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258](https://www.echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258)

\(^{35}\) [https://echa.europa.eu/documents/10162/17090/jtf_opinion_task_2_en.pdf/db8a9a3a-4aa7-601b-bb53-81a5eef93145?t=1512723248835](https://echa.europa.eu/documents/10162/17090/jtf_opinion_task_2_en.pdf/db8a9a3a-4aa7-601b-bb53-81a5eef93145?t=1512723248835)
endpoints and/or other information of the potency when no dose descriptor is available.

- Step 2: Decide on mode of action (threshold or non-threshold).

- Step 3: If possible, derive DMEL(s) for non-threshold endpoints by:
  - a) selection of relevant dose-descriptor(s) for the endpoint concerned;
  - b) modification, when necessary, of relevant dose descriptor(s) per endpoint to the correct starting point (i.e., correct the unit of exposure);
  - c) application, when necessary, of assessment factors/high to low dose risk extrapolation factor to the correct starting point to obtain endpoint-specific DMEL(s) for the relevant exposure pattern (duration, frequency, route and exposed human population).

- Step 4: Select the leading health effect(s) and the corresponding DNEL, DMEL or other qualitative/semi-quantitative description.

Within the context of REACH, DMELs can be set for occupational exposure for non-threshold substances. There does not appear to be a permitted risk level set by the European Commission given that in the past an acceptable risk level was considered to be a societal concern requiring policy guidance. However, ECHA in its REACH guidance\(^36\) states that possible excess lifetime risk levels for incidence of cancer are \(1 \times 10^{-5}\) and \(1 \times 10^{-6}\) and these could be seen as an indicative tolerable risk level when setting a DMEL for workers and general public, respectively.

**Consumers**

The risk assessment methodology for consumers is similar to that described above for occupational setting. The indicative tolerable risk level when setting a DMEL for consumers is the same as for the general public of possible excess lifetime risk levels for cancer incidence of \(1 \times 10^{-6}\).

**Food**

Food and food ingredients are managed at the Union level with national authorities adopting Union safe levels. For substances for which a threshold for adverse effects cannot be determined the general consensus in most countries including those in the EU jurisdiction is to reduce the exposure to such substances to as low as is reasonably achievable (ALARA principle). In order to provide risk managers a basis for setting priority for action the Scientific Committee of the European Food Standards Agency (EFSA) recommends using the margin of exposure (MOE) approach (EFSA, 2005\(^37\)). This approach is also known as the Large Assessment Factor approach and represents the ratio between a defined point (reference point or the point of departure) on the dose-response curve for the adverse effect and the human dietary intake, and therefore it makes no implicit assumptions about a “safe” intake. The reference point would ideally be based on human epidemiological data but such data are rarely available and therefore data from animal

---


studies may be used instead. The EFSA Scientific Committee recommends the use of the benchmark dose (BMD) and in particular the BMDL10 (benchmark dose lower confidence limit 10%) to obtain a MOE. The BMDL10 is an estimate of the lowest dose which is 95% certain to cause no more than a 10% cancer incidence in rodents. This approach can also be applied to human data when available. In the absence of reliable data for the BMD approach, the use of the T25 can be used. This is the dose corresponding to a 25% incidence of tumours. In general, an MOE of \( \geq 10,000 \), if it is based on the BMDL10 from an animal study, would be of low concern from a public health point of view and might be considered as a low priority for risk management actions. Inter-species differences and intra-species differences (human variability), the nature of the carcinogenic process as well as the type of reference point selected, e.g., BMDL10 or T25 should be considered when interpreting the MOE.

\textit{Cosmetic Products}

The safety of cosmetic products is undertaken by qualified and experienced safety assessors of the cosmetic industry as well as by the Scientific Committee on Consumer Safety (SCCS), the latter upon instruction by the European Commission. The SCCS sets the method for assessing the safety of substances in cosmetic products and the calculation of the Margin of Safety (MoS). The MoS represents the ratio between a systemic point of departure such as the BMD value from animal studies and an estimate of the exposure. Typically, a cosmetic product intended for the EU market will not contain substances that are carcinogenic or germ cell mutagens unless its presence is a technically unavoidable impurity that has been risk assessed by a safety assessor to show that it is safe.

Alternatively, a carcinogenic substance may be approved for specific uses under strict conditions following a rigorous safety assessment by the SCCS. The SCCS guidance states that for substances present at low concentrations with a structural alert for genotoxicity the default TTC value of 0.15 \( \mu \text{g/person/day}, \) corresponding to 0.0025 \( \mu \text{g/kg bw/day}, \) can be used for chemicals and therefore may be used for DNA reactive carcinogens. Alternatively, for the safety assessment of carcinogenic substances for which a threshold for effects cannot be established, follow the linear extrapolation approach. This approach has already been discussed in much detail in this document and summarised briefly here. A suitable point of departure (BMDL10 or T25) based on epidemiological or animal studies should be identified with the use of BMDL10 preferred over the T25. Both BMDL10 and T25 can be used as starting points to determine an additional lifetime cancer risk or to calculate a MoS, which represents the ratio between a dose descriptor and the estimated human exposure dose. The animal dose descriptor (T25) is converted to the human dose descriptor (HT25) taking into account comparative metabolic rates. The lifetime cancer risk is then calculated by dividing the systemic exposure dose by the sum of HT25/0.25. The SCCS notes that the excess lifetime cancer risk in the general population of less than \( 10^{-5} \) is considered tolerable by some countries and international organisations and that under REACH, the “indicative tolerable cancer risk level” for the general population is \( 10^{-6} \). However the SCCS considers setting acceptable risk level as a risk management issue and outside the scope of its remit.
Environmental receptors (man via the environment)

Drinking Water

The EU Drinking Water Directive lays down the minimal drinking water quality standard at the EU level, which is based on the World Health Organization's (WHO) guidelines for drinking water and the opinion of the Commission's Scientific Advisory Committee. The WHO uses mathematical modelling to determine guideline values for genotoxic carcinogens (WHO, 2017). These models provide an estimate of risk at a particular level of exposure, along with upper and lower bounds of confidence on the calculation. The default assumption for consumption for the calculation of guideline values is based on daily intake for an adult (60 kg adult drinking 2 litres of water per day). Guideline values are conservatively presented as the concentrations in drinking-water associated with an estimated upper-bound excess lifetime cancer risk of $10^{-5}$ (or one expected additional case of cancer per 100,000 of the population ingesting drinking-water containing the substance at the guideline value for 70 years). EU Member States when translating the standards into their own legislations must not set lower standards. However, Member States may set a different level of hypothetical risk and WHO states that values relating to excess cancer risks of $10^{-4}$ or $10^{-6}$ over a lifetime of exposure may be determined by multiplying or dividing the guideline value by 10, respectively.

Soil

There is no harmonised approach to deriving soil guideline values at the EU level. Individual countries have their own methods for deriving soil guideline values and is discussed briefly below.

2.3.2 Netherlands

Occupational settings

The Netherlands has its own a methodology in place to set risk-based OELs using a three step procedure. Exposure levels corresponding to an extra risk of cancer are referred to as health-based occupational cancer risk values (HBC-OCRVs). The additional cancer risk is defined by the government of the Netherlands. There are two risk levels for an individual working a lifetime of 40 years calculated at the level of cumulative, inhalation exposure (expressed as mg/m$^3$):

1. Target risk level of $4 \times 10^{-5}$ (4 expected additional cases per 100,000 over 40 years).
2. Prohibitive risk level of $4 \times 10^{-3}$ (4 expected additional cases per 1,000 over 40 years).

Exposures below target risk level implies that no additional protective measures need to be taken while prohibitive risk levels may not be exceeded over an exposure period of 40 years.

When calculating risk both experimental human and animal studies can be used, with a preference for human data when of good quality and providing dose-response information. The methodology for deriving OELs includes calculating the relation between the substance concentration (inhalation) and the statistical probability of developing cancer – risk characterisation and identification of a

---

38 [https://www.who.int/publications/i/item/9789241549950](https://www.who.int/publications/i/item/9789241549950)
point of departure such as BMD10 if there is sufficient data otherwise a representative point estimate can be used. If required, the point of departure is converted to continuous exposure and corrected for differences in exposure time and duration of the experiment versus the standard life expectancy for the animal species used to generate the data. Standard assumptions for occupational exposure are 40 years exposure, 8 hours/day, 5 days/week, 48 weeks/year at an inhalation rate of 10 m$^3$/8 hours, as opposed to lifetime exposure for 75 years, 24 hours/day, 7 days/week, 52 weeks/year at an inhalation rate of 18 m$^3$/24 hours. Using the linear extrapolation method lower risk levels are extrapolated to calculate acceptable and tolerable risk levels.

Consumers
Food and cosmetic ingredients/products regulation is maintained at the EU level. There is no separate approach set by this country. Environmental receptors (man via the environment)

Drinking Water
The implementation of the European Water Framework Directive is set at the European level. The European Water Directors provide an informal structure in which guidelines are drafted for the further implementation of the directive. The European Water Framework Directive has been translated into Dutch legislation and is managed by the government.

Soil
Health-based soil guideline values are based on the application of exposure modelling and risk characterisation. The methods that are used for risk characterisation and development of guideline values are those published by the European Commission or developed by EU Member State authoritative bodies, such as RIVM. The methodology is essentially linear extrapolation to calculate excess lifetime cancer risk. There are values published for certain substances and in the absence of published values being available the advice is to employ those values that have been published by other country authoritative bodies, such as US EPA or UK Defra. The acceptable incremental cancer risk level is $10^{-4}$ for Intervention Values.

2.3.3 Germany

Occupational settings
Germany has its own a methodology in place to set risk-based OELs laid down in Technical Rule 910. These workplace limit values are derived by the German Hazardous Substances Ordinance, the Committee on Hazardous Substances (AGS) who advise the Federal Ministry of Labour and Social Affairs. There are three risk areas defined based on two, socio-politically established risk levels for an individual working a lifetime of 40 years.

1. Acceptable risk – an excess cancer risk level over 40 years that is generally accepted is 4:100,000.

2. Tolerable risk - 4:1,000 excess cancer risk over 40 years.

Exposures below the acceptable risk level are termed green/low risk, while yellow/medium risk area is the area between acceptable and tolerable risk. The red/high risk area is above the tolerable risk
and this is not considered acceptable (intolerable) and action has to be undertaken to return to at least to the medium risk area.

When calculating risk both experimental human and animal studies can be used, with a preference for human data when of good quality and providing dose-response information. The methodology for deriving OELs includes calculating the relationship between the substance concentration (inhalation) and the statistical probability of developing cancer – risk characterisation and identification of a point of departure such as BMDL10 if there is sufficient data or T25. The point of departure is corrected for potential differences between experimental animals and the target population and converted into a human equivalent lifetime daily dose (e.g., hT25). Standard assumptions for occupational exposure are 40 years exposure, 8 hours/day, 5 days/week, 48 weeks/year at an inhalation rate of 10 m³/8 hours for a 70 kg person, as opposed to lifetime exposure for 75 years, 24 hours/day, 7 days/week, 52 weeks/year at an inhalation rate of 20 m³/24 hours for a 70 kg person. The linear extrapolation method is used to extrapolate to lower risk levels to calculate acceptable and tolerable risk levels.

Consumers

Food and cosmetic ingredients/products regulation is maintained at the EU level. There is no separate approach set by this country.

Environmental receptors (man via the environment)

The implementation of the European Water Framework Directive is set at the European level. The European Water Directors provide an informal structure in which guidelines are drafted for the further implementation of the directive. The European Water Framework Directive has been translated into German legislation.

Soil

Health-based soil guideline values are based on the application of exposure modelling and risk characterisation. The methods that are used for risk characterisation and development of guideline values are those published by the European Commission or developed by EU Member State authoritative bodies, such as RIVM. There are essentially three levels for action:

1. “action levels” indicating as a rule a hazard which has to be warded off; further investigations to ascertain the hazard are usually not necessary;
2. “trigger levels” triggering further investigations to ascertain (verify/falsify) whether the pollution of the soil implies a hazard;
3. “precaution levels” indicating a certain chance of future soil problems which need to be addressed in order to avert upcoming damages.

The action and trigger levels are risk based. The risk assessment methodology is essentially linear extrapolation to calculate excess lifetime cancer risk from a dose that causes a level of cancer risk with application of a risk connecting factor of 5 for carcinogens. For carcinogenic substances an additional lifetime (70 years) cancer risk of $10^{-5}$ is regarded as tolerable (in accordance with WHO).
2.3.4 France

Occupational settings

France has its own a methodology in place to set risk-based OELs. When calculating risk both experimental human and animal studies can be used, with a preference for human data when of good quality and providing dose-response information. The methodology for deriving OELs includes calculating the relationship between the substance concentration (inhalation) and the statistical probability of developing cancer – risk characterisation and identification of a point of departure such as BMDL10 if there is sufficient data or T25, but the latter is discouraged. A slope factor is derived by extrapolating the BMDL10 to the origin and accounting for differences in the experimental and human exposure situation (often 40 years, 8 hours/day, 5 days/week, 48 weeks/year) to calculate the excess lifetime cancer risk per unit of exposure (µg/m$^3$ or mg/m$^3$). Using the linear extrapolation method lower risk levels are extrapolated to calculate three different risk levels, i.e., $10^{-4}$, $10^{-5}$ and $10^{-6}$ presumably for 40 working years.

Consumers

Food and cosmetic ingredients/products regulation is maintained at the EU level. There is no separate approach set by this country.

Environmental receptors (man via the environment)

Drinking Water

The European Water Framework Directive has been translated into French legislation. For substances considered to have no effect threshold, the French approach is based on the WHO method for derivation of guideline values:

- determination of a dose equivalent for humans;
- modelling of experimental data;
- extrapolation to low doses of the effects observed experimentally in animals at high doses.

French guideline values are set at as the concentration in the drinking water associated with a $10^{-5}$ lifetime excess cancer risk (one additional cancer case for every population of 100,000 people who would consume drinking water containing the substance in question at a concentration equal to the guide value). This is different to the EU directive which is set at excess risk of cancer of $10^{-6}$.

Soil

Health-based soil guideline values are based on the application of exposure modelling and risk characterisation. The dose-response relationship is typically selected from different toxicological sources and databases, including IRIS of the US EPA, HSDB, RIVM, ATSDR, UBA, WHO. It is unclear as to the methodology that is used to calculate excess lifetime cancer risk. However, the excess risk of cancer due to the site generally accepted is $10^{-5}$, but lower levels should be looked for, and higher levels, up to $10^{-4}$, may be allowed when there is no technically feasible alternative at a bearable cost.
2.3.5 Poland

Occupational settings

Poland has its own a methodology in place to set risk-based OELs which are termed Maximum Admissible Concentrations (MACs). The Interdepartmental Commission for Maximum Allowable Concentrations and Intensities for Harmful to Health Agents in the Working Environment has set the socially acceptable excess cancer risk at the level of $10^{-3}$ to $10^{-4}$. When calculating risk both experimental human and animal studies can be used, with a preference for human data when of good quality and providing dose-response information. In Poland, exposure to a non-threshold carcinogen in the workplace is considered to be high risk to health, even if that exposure is below the safe level. Poland has its own methodology for deriving OELs. The first step is to determine the probability of developing a disease or death from cancer as a result of occupational exposure to the carcinogenic substance. Relative risk per unit of exposure (slope factor or unit risk) is calculated by using quantitative dose-response information either from good quality animal data or cancer slope factors published by the US EPA. Standard assumptions for occupational exposure are 40 years exposure, 8 hours/day, 240 days/year at an inhalation rate of 20 m$^3$ for a 70 kg person undertaking heavy labour. The linear extrapolation method is used to extrapolate to socially accepted risk levels of $10^{-3}$ (one additional cancer case per 1,000) to $10^{-4}$ (one additional cancer case per 10,000) for a period of 40 working years.

Consumers

Food and cosmetic ingredients/products regulation is maintained at the EU level. There is no separate approach set by this country.

Environmental receptors (man via the environment)

Drinking Water

The implementation of the European Water Framework Directive is set at the European level. The European Water Directive provides an informal structure in which guidelines are drafted for the further implementation of the directive. The European Water Framework Directive has been translated entirely into Polish legislation.

Soil

No information found.

2.3.6 Headline Summary messages

Occupational exposure limits are generally set employing the linear extrapolation methodology using points of departure such as BMDL10 or T25 to calculate a set acceptable level of excess risk for cancer. The EU does not have an acceptable level of excess cancer risk from exposure to substances of concern, but ECHA guidance notes that $10^{-4}$ and $10^{-5}$ are acceptable for workplace exposure when calculating DMELs for workers.

Germany, the Netherlands, France, and Poland set risk-based OELs using the linear extrapolation methodology. Most other countries (among which Austria, Belgium, , Finland, Norway, Slovakia,
and Spain) do not set OELs for non-threshold carcinogens in their own right but adopt OELs for these substances as derived by other agencies/committees such as SCOEL. Austria uses the methodology used in Germany.

The risk assessment methodologies for food and cosmetics in the EU countries do not differ between Member States and the UK currently follows the same approaches, but this may change going forward.

The EU sets the drinking water standards which must be translated into Member State legislations; however, the acceptable risk levels may differ between Member States, but typically range between 10^{-5} and 10^{-6}. The risk assessment methodology is based on the WHO drinking water guidelines.

2.4 Overview of OECD approaches

2.4.1 United Kingdom

Occupational settings

The current methodology for the risk assessment of workplace chemicals is the same as for the EU. This may change going forward following the UK’s exit from the EU.

Consumers

The current methodology for the risk assessment of food and consumer products is the same as for the EU. This may change going forward following the UK’s exit from the EU.

Environmental receptors (man via the environment)

Drinking Water

The European Water Framework Directive has been translated into UK legislation. For substances considered to have no effect threshold, the UK approach is based on the WHO method for derivation of guideline values:

- determination of a dose equivalent for humans;
- modelling of experimental data;
- extrapolation to low doses of the effects observed experimentally in animals at high doses.

Soil

For non-threshold carcinogens, Index Doses (health criteria value) are derived and they convey minimal risk levels, with the additional requirement to keep any intake as low as reasonably practicable (ALARP). The UK uses two approaches to derive health criteria values for non-threshold contaminants, quantitative dose-response modelling, and non-quantitative extrapolation. Quantitative dose-response modelling is used to derive numerical estimates of risk (e.g., 1 in
100,000; 10^-5) for exposure to non-threshold carcinogens. Linear extrapolation is achieved by using the benchmark dose response approach and calculating the BMD10 or BMDL10 and then dividing this by orders of magnitude to calculate the Index Dose to achieve the desired risk level, e.g., dividing by 10,000 to give a 1 in 100,000 risk.

Health criteria values derived using the non-quantitative extrapolation approach is the predominant alternative approach when an assessment of all available data identifies a dose without a discernible carcinogenic effect, or the lowest dose tested if effects are apparent at all doses. BMDL and T25 are the most common indices of tumour formation and application of an appropriate uncertainty factor to derive the Index Dose.

The UK government does not set an acceptable risk level for soil contaminants.

### 2.4.2 United States of America

**Occupational settings**

Occupational workers, i.e., employees working in environments with chemicals (e.g., manufacturing, laboratories, etc.) are covered by Permissible Exposure Levels (PELs) promulgated by the US Occupational Safety and Health Administration (OSHA). The vast majority of PELs were taken from the 1968 Threshold Limit Values (TLVs) calculated by the American Conference of Governmental Hygienists (ACGIH), an independent scientific organization. Attempts at updates have not survived legal challenges. These OSHA PELS are primarily based on acute health effects and do not consider chronic exposures.

OSHA has recently promulgated new PELs and when carcinogenic effects are considered, it is based on 1 in 1000 risk over a 45-year working period. OSHA now uses the same methods as USEPA for determining genotoxic carcinogenic risk.

Note that while OSHA sets a minimum federal level risk threshold of 1 in 1000 for a tolerable risk threshold, at the state level and within practical application, more strict levels of risk control are set more in line with 10^-4 to 10^-6, although this will vary on a state-by-state basis and within different occupational settings specifically.

**Consumers**

The Food and Drug Administration (FDA) regulates consumer products including food, drugs, and cosmetics. The FDA determines risk by linear extrapolation from the dose giving 50% tumour incidence to 1 in one million using the TD50 data for the most sensitive species and most sensitive site of tumour induction. Linear extrapolation to a probability of 1 in 100,000 is achieved by dividing TD50 by 50,000. Lifetime exposures to mutagenic impurities in pharmaceuticals is calculated in which the acceptable cumulative lifetime dose (1.5 μg/day x 25,550 days = 38.3 mg) is uniformly distributed over the total number of exposure days during lifetime exposure.

**Environmental receptors (man via the environment)**

The United States Environmental Protection Agency (USEPA) establishes oral and inhalation carcinogenic slope factors (CSF) (equivalent terminology to DMELs), based on a lifetime (70 years) exposure to chemical substances from contaminated environmental media. The CSFs apply the
receptors with potential exposure to contaminated media (soil, groundwater, air) such as residents, trespassers, indoor and outdoor workers, and construction workers.

Cancer slope factors are calculated using a two-step dose-response assessment for each tumour type:

1. An assessment of observed data to derive a point of departure (POD), defined as an estimated dose (in human-equivalent terms) near the lower end of the observed range without significant extrapolation to lower doses, i.e., the upper and lower 95% confidence limit of effective dose (ED10).

2. Extrapolation to the lower exposure point, as warranted. The extrapolation is based on an extension of a biologically-based model, if supported by extensive data otherwise, default approaches can be applied consistent with the current understanding of the substance’s MoA, including approaches that assume linearity or non-linearity of the dose-response relationship.

A default approach for linearity extends a straight line from the POD to zero dose/zero response and is used when there is an absence of data for the MoA(s) or when MoA data indicate the dose-response curve is expected to be linear at a low dose. A non-linear approach is used by the USEPA to develop toxicity values for non-carcinogenic effects (USEPA (2005))

2.4.3 Canada

Occupational settings

The Canadian Centre for Occupational Health and Cancer refers to US OSHA and the National Institute Occupational Safety and Health (NIOSH.)

Consumers

Maximum residue limits (MRLs), maximum levels (MLs), guidelines, standards and tolerances are established by Health Canada to minimize potential health risk from excessive exposure to chemical residues and contaminants in foods. If test levels exceed established limits in food, the results are referred to Health Canada (HC) for a risk assessment. The Canadian Food Inspection Agency (CFIA) makes a final decision after receiving the risk assessment results from HC.

Environmental receptors (man via the environment)

Health Canada uses low-dose extrapolation that is achieved through application of the linearized multistage model (Crump, 1996). This statistical model can describe both linear and non-linear dose–response patterns, and produces an upper confidence bound on the linear low-dose slope of the dose–response curve. HC applied this methodology for the derivation of the tumourigenic concentration 05 (TC05) (the concentration in air or water found to induce a 5% increase in the incidence of, or deaths due to, tumours considered to be associated with exposure [HC, 1996]) or the tumourigenic dose 05 (TD05) (the dose found to induce a 5% increase in the incidence of, or deaths due to, tumours considered to be associated with exposure). HC may also apply a model-

39 USEPA, 2005. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F
free low-dose extrapolation method (Krewski et al., 1991), making no prior judgments regarding the shape of the dose–response curve in the low-dose range. The model-free approach can also provide an upper bound estimate on the slope of the dose–response curve in the low-dose range.

These upper bounds on the dose–response curve become the cancer slope factors or unit risks employed for the estimation of hypothetical cancer rates. As such, the slope factor or unit risk for non-threshold carcinogenic effects is believed to overestimate the true cancer incidence associated with low-dose exposure to environmental pollutants, such as those at contaminated sites (Kelly, 1991).

Given the conservative (safety) margin associated with the derivation of cancer slope factors and unit risks, and the negligible impact of a 1 in 100,000 incremental risk level for lifetime contaminated site exposures, a cancer risk level of 1 in 100,000 is recommended for the purposes of assessing and managing federal sites contaminated with substances eliciting non-threshold carcinogenic effects.

### 2.4.4 South and Central America

Many South and Central American nations have established guidance and legislative instruments to regulate exposure to genotoxic carcinogens using non-threshold approaches. There is a general tendency to heavily reference or base approaches on international standards including the WHO and USEPA.

**Occupational settings**

In Brazil, the Brazilian Regulatory Standards (NR) set occupational standards for chemical hazards. These standards are cited in Chapter V, Title II of the Consolidation of Labour Laws (CLT) approved in 1978 are obligatory for all Brazilian companies governed by the Labour Law. Exposure limits are provided in Tabela de Limites de Tolerância in Annex No.11 of Regulatory Standard NR N-15; however the basis is not provided, neither is the associated tolerable risk level for carcinogenic substances.

**Consumers**

Brazil’s Health Ministry sets drinking water quality standards for 89 parameters in Annex XX of Ordinance Number 5/2017, including inorganics, organics, pesticides, and disinfection by-products. Each parameter has a health-based target (HBT) to classify water potability. Review of the HBTs suggests these are based on the USEPA approach for setting Maximum Contaminant Levels (MCL); however the source was not referenced and could not be verified.

**Environmental receptors (man via the environment)**

In Brazil, the Companhia de Tecnologia de Saneamento Ambiental (CETESB) regulates contaminated land and uses standard international approaches including USEPA and WHO as primary references and as a basis for evaluating toxicity. The guidance recommends a single tolerable/acceptable excess lifetime cancer risk of 1 in 100,000. This applies to genotoxic carcinogens and is based on linear extrapolation. This risk level is also applied in Panama.
2.4.5 Australia and New Zealand

Australia and New Zealand have established guidance and legislative instruments to regulate exposure to genotoxic carcinogens using non-threshold approaches. Genotoxic carcinogens in both countries are regulated by evaluation of excess cancer risk, which is expressed as the number of permissible or acceptable excess cancers allowable in a population exposed to the contaminant of concern. A major point of recognition is the uncertainty in the adopted approaches for non-threshold chemicals and the difficulty of identifying if carcinogenic chemicals are operating by a genotoxic mode of action.

There is no scientific consensus on an ‘acceptable’ cancer risk for substances that are non-threshold based genotoxic carcinogens. However, most regulatory agencies in Australia and New Zealand have set the acceptable or regulatory limits 1 cancer per 100,000 individuals. Further details are provided in the following sections.

Occupational settings

Although both countries have legally enforceable occupational standards for inhalation of indoor air exposure over a working lifetime, neither country sets a specific ‘acceptable’ excess non-threshold cancer risk for these values. In 2018, Work Safe Australia published an accessory review of the approach to evaluating non-threshold based genotoxic carcinogens and made recommendations to update the health-based workplace exposure standards to a limit of 1 in 100,000 in order to reduce potential cancer risks to the working population at the current standards. These values are currently under review but have not been updated yet. Worksafe New Zealand’s November 2020 standards are based on threshold endpoints, however when the chemical is identified as a non-threshold carcinogen the chemical derivation also includes the associated excess lifetime cancer risk of $10^{-4}$.

Consumers

Both countries have legally enforceable drinking water standards based on standard health risk assessment approaches and linear extrapolation of slope factors for non-threshold chemicals. Australia’s National Health and Medical Research Council are more stringent, limiting excess lifetime cancer risks to 1 in one million to account for potential intake from sources other than drinking water. The New Zealand Ministry of Health limits drinking water standards to excess lifetime cancer risks of 1 in 100,000 and considers analytical and technical feasibility when assigning exposure limits for non-threshold based genotoxic carcinogens. Food Standards Australia New Zealand regulates foods in both countries and adopts a slightly different approach than the drinking water guidelines. When a threshold of toxicity is not evident, risk characterisation may involve an MOE approach to provide an estimate of relative risk. The MOE approach compares the BMD [or the lowest-observed-adverse-effect level (LOAEL), if the BMD is not available] with estimated dietary exposure to the chemical. While a large MOE (e.g. >10,000) generally indicates a low risk, the MOE is not a quantification of risk, and needs to be accompanied by some narrative to describe the way in which it has been derived and the limitations of this approach.

Environmental receptors (man via the environment)

Both countries have similar legislation and guidance for addressing non-threshold, genotoxic carcinogens in contaminated land. The Australian National Environment Protection Council and the
New Zealand Ministry of the Environment both recommend a single tolerable/acceptable excess lifetime cancer risk of 1 in 10,000. They both consider genotoxic carcinogens and allow for a threshold approach if appropriate following current WHO guidelines. Both agencies use WHO and USEPA as primary sources of toxicity values for non-threshold genotoxic carcinogens, which are based on linear extrapolation.

2.4.6 East-Asia

Many East-Asian nations (Japan, Thailand, Hong Kong etc) have established guidance and legislative instruments to regulate exposure to genotoxic carcinogens using non-threshold approaches. There is a general tendency to heavily reference or base approaches on international standards including the WHO and USEPA.

Occupational settings

The Japan Society for Occupational Health (JHOS) is a non-governmental society of occupational health professionals (academics and practitioners) that recommends occupational exposure limits or reference values. The reference values are considered by the Ministry of Health, Labour and Welfare. Occupational limits are provided for a limit of 1 in 1000 and 1 in 10,000 for genotoxic carcinogens. JHOS does not recommend these values as a safety exposure level or that these cancer risks are acceptable.

Consumers

In 2006, Japan’s the Ministry of Health, Labour and Welfare (MHLW) introduced the Positive List System for pesticides, veterinary drugs, and feed additives (“agricultural chemicals”). Prior to its enforcement, Japan provisionally established maximum residue limits (“provisional MRLs”) for chemical-commodity combinations without specific MRLs for 758 agricultural chemicals. These MRLs were generally based on Codex standards, which are set by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) following the MOE approach (calculating the ratio [BMDL] / [estimated intake in humans]). When an ADI could not be established due to carcinogenicity or other reasons, guidance suggested the established MRLs be set to “Not Detected” and no safe threshold assumed. Since the enforcement of the system, Japan has been reviewing the provisional MRLs based on assessment by the Food Safety Commission (“FSC”) to examine whether they are appropriate.

Environmental receptors (man via the environment)

The Ministry of the Environment in Japan regulates contaminated land and uses the WHO drinking water guidelines as a basis for evaluating toxicity. The guidance recommends a single tolerable/acceptable excess lifetime cancer risk of 1 x 10⁻⁵. This applies to genotoxic carcinogens and is based on linear extrapolation.

2.4.7 Headline Summary messages

Occupational exposure limits are generally set employing the linear extrapolation methodology to calculate a set acceptable level of risk for cancer. Guidance generally indicates that the acceptable level of risk is 10⁻⁴ for workers; however some occupational values are set at higher levels (10⁻³) and
may be out-dated, but still within the legislation. Some countries are developing recommendations to lower occupational limits to reduce cancer rates (Australia recommends $10^{-5}$). Many countries do not set OELs for non-threshold carcinogens but adopt OELs for these substances as derived by other agencies/committees such as OSHA and ACGIH.

Apart from the USA, the risk assessment methodologies for food typically follow the MOE approach based on established WHO/JECFA guidance for food additives. The FDA in the US uses linear extrapolation and a single acceptable level of risk of $10^{-5}$. Drinking water typically follows the linear extrapolation methodology based on WHO drinking water guidelines and use a single acceptable level of risk of $10^{-5}$, although $10^{-6}$ may also be used (Australia).

Acceptable risk ranges for non-threshold values for contaminated land typically range between $10^{-4}$ and $10^{6}$. The USEPA uses the range with $10^{-6}$ as the acceptable threshold and $10^{-4}$ as the tolerable threshold. Other countries (Canada, Australia, New Zealand, Japan, Brazil) set a single acceptable risk threshold, which is typically $10^{-5}$. Due to resource and technical restraints, many countries do not create contaminated land guidance themselves but adopt guidance for these substances as derived by other agencies/committees such as USEPA.

### 2.5 Overview of other non-threshold endpoints (beyond C and M)

#### 2.5.1 Introduction

As indicated within the introduction to section 4, Task 2 has provided a primary focus to the approaches adopted for carcinogens and germ cell mutagens. The study has also provided a high-level body of research to assess whether DMELs or equivalent approaches have been mandated for other non-threshold human health hazard classes. This has primarily focussed on EDC health effects, with a summary for the EU nations and other OECD territories provided in the sub-sections below.

#### 2.5.2 Endocrine disruptors

**European approaches**

The available published methodologies for the risk assessment for endocrine disruptors are less well developed than the methodologies for carcinogens and mutagens. Endocrine disruption is addressed in various legislative acts within the EU such as the plant protection product regulation (Reg. (EC) No 1107/2009), the biocide product regulation (Reg. (EC) No 528/2012) and REACH (Reg. (EC) 1907/2006). The regulation of endocrine disrupting substances is typically undertaken using a hazard-based approach possibly as a result of the assumed absence of thresholds for the adverse effects of such substances. This lack of a threshold is on the basis that the complex nature of the endocrine system means that it is not possible to identify and derive safe levels of exposure to such EDC chemicals. Common methodologies for the risk assessment of endocrine disruptions suggested by EU, non-EU authorities and the OECD are namely the Adverse Outcome Pathway (AOP), Weight of Evidence (WoE), Mode of Action (MoA), Margin of Exposure (MoE) and using *in-silico* approaches.

The potential endocrine disrupting hazard of chemicals are identified using a set battery of tests, which may include testing for carcinogenicity, reproduction and ecotoxicity as well as mechanistic
data that may include *in silico* modelling and *in vitro* testing for receptor binding for instance. Using the data generated from tests carried out during the hazard identification process together with a mode of action (MoA) analysis, and application of a weight of evidence (WoE), in order to establish whether the ED criteria, as defined by the WHO, have been met. There is currently no formal risk assessment process posed by endocrine disruptors – the EU uses a hazard-based approach.

**Approaches by other OECD nations**

**USEPA**

The USEPA Endocrine Disruptor Screening Program (EDSP) uses a two-tiered approach to screen pesticides, chemicals, and environmental contaminants for their potential effect on estrogen, androgen and thyroid hormone systems.

- **Tier 1 data** identifies substances with the potential to interact with the endocrine system.
- **Tier 2 data** identifies adverse endocrine-related effects and establishes a quantitative relationship between the dose and the adverse effects. The results are combined with other hazard information and exposure assessment in the risk assessment.

The series of tiered Test Guidelines ("Series 890") that determine if a chemical substance may pose a risk to human health or the environment through endocrine disruption are as follows:

1. **Tier 1 (Group A):** amphibian metamorphosis (frog); androgen receptor binding (rat prostate), aromatase (human recombinant); estrogen receptor binding; estrogen receptor transcriptional activation (human cell line HeLa-9903); fish short-term reproduction; Hershberger (rat); female pubertal (rat); male pubertal (rat); steroidogenesis (human cell line - H295R); uterotrophic (rat)
2. **Tier 2 (Group B):** avian two-generation toxicity test (Japanese quail); medaka extended one generation reproduction test; larval amphibian growth and development assay (LAGDA).

**Canada**

Endocrine-related effects data used in risk assessment can come from

1. standard (*in vivo*) lab tox studies with animals
2. lab studies documenting effects at the gene and cellular level in a controlled environment (*in vitro*)
3. predictive computer models
4. field or epidemiological studies that consider exposures and effects to wildlife and humans, respectively.

Risk assessment includes consideration of the adverse effects of a substance (including those caused by endocrine-disrupting substances) as well as the potential exposure. The ratio of exposure to the no adverse effect level is estimated in order to determine if substances may be harmful. In human health risk assessments, uncertainty factors are considered in the risk calculation.
which consider the particular sensitivity of the endocrine system and the potential for irreversible adverse effects. The acceptability of the resulting ratio, referred to as the margin of exposure (MOE), is determined by taking into consideration the magnitude of the margin in the context of uncertainties in the health effects and exposure information.

In ecological risk assessment, information on endocrine-related effects is one line of evidence that is considered in the overall weight of evidence and can be used in the determination of the predicted no effect concentration in the environment. Weight of evidence and precaution are applied in both human health and ecological risk assessments.

**Australia, Asia, and South/Central America**

Generally, the MOE and linear extrapolation approaches are limited to evaluation of non-threshold genotoxic carcinogens. All other potential non-threshold endpoints are evaluated using standard threshold approaches.

### 2.6 Comparative analysis

The preceding steps under Task 2 aimed to assess the different regulatory approaches employing the use of a DMEL or equivalent, noting that outside of Europe the term ‘DMEL’ is not recognised, and instead terminology such as dose-response or slope factor is more commonly used. To help provide a comparative assessment, key common metrics were selected and populated for the different legislation. Appendix B of this report provides the full comparative tables with all details presented for ready examination.

However, as indicated in the earlier parts of this chapter, a range of different legislation has been used even within the same nation for different settings and objectives. Therefore, the tables within Appendix B provide a fully disaggregated set of data for countries under review. This sub-section therefore provides a consolidated table for high-level comparative analysis purposes (see Table A.2). This comparative table is intended to only help provide some high-level headline overviews for how the different national approaches have implemented work for DMELs (or equivalent) under occupational, consumer and environmental settings. The full table under Appendix B provides complete details of all information.

Based on the analysis of Table A.2 it is possible to see that the typical excess lifetime cancer risks for occupational and consumer settings follow some broad agreement between EU nations and internationally with occupational values in the $10^{-3}$ to $10^{-6}$ range for occupational and $10^{-4}$ to $10^{-6}$ for consumer settings. It can also be identified that environmental risk thresholds are largely at the $10^{-5} / 10^{-6}$ range, with a caveat that this setting in particular has broad scope and specific aspects of the environmental legislation need to be considered, i.e., this setting in particular may be the least comparable in real terms.

The other key point of reference is how the approaches have been implemented, note that in the majority of cases the use of DMELs or equivalents is not mandatory, i.e., it is necessary to qualify risks but not necessarily using a DMEL/slope factor and a minimum mandatory risk level is not set. Exceptions to this position are the USA, Canada, and New Zealand. Note in these cases (particularly where Canadian approaches tend to follow precedents set within the USA), that the minimum thresholds for risk as excess lifetime cancer risk primarily relate to occupational settings and may be of a less conservative nature. The minimum thresholds set within the USA by OSHA have been in
use since 1969 at the $10^{-2}$ or $10^{-3}$ level, with strong political opposition from industry lobbying preventing revision to more strict thresholds since 1969.

Further comparative analysis will be undertaken following the further refinements to Task 2 and feedback from the study steering group.
Table A.2  Consolidated table for comparative analysis (risk thresholds relate to excess lifetime cancer risks).

<table>
<thead>
<tr>
<th>Methodology (occupational)</th>
<th>EU Agencies</th>
<th>France</th>
<th>Germany</th>
<th>Netherlands</th>
<th>Poland</th>
<th>United Kingdom</th>
<th>Canada</th>
<th>United States of America</th>
<th>Brazil</th>
<th>Australia and New Zealand</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Linear extrapolation</td>
<td>Linear extrapolation</td>
<td>Linear extrapolation</td>
<td>Linear extrapolation</td>
<td>Slope factor / unit risk</td>
<td>Linear extrapolation</td>
<td>Linear extrapolation</td>
<td>Linear extrapolation</td>
<td>Unknown</td>
<td>Linear extrapolation</td>
<td>Unknown</td>
</tr>
<tr>
<td>POD (occupational)</td>
<td>BMDL(<em>{10}) (T</em>{25})</td>
<td>BMDL(<em>{10}) (T</em>{25})</td>
<td>BMDL(<em>{10}) (T</em>{25})</td>
<td>BMDL(<em>{10}) (T</em>{25})</td>
<td>Unknown</td>
<td>Unknown</td>
<td>TC(_{05})</td>
<td>ED(_{10})</td>
<td>Unknown</td>
<td>Evaluation and Modelling</td>
<td>Unknown</td>
</tr>
<tr>
<td>Tolerable risk level (occupational)</td>
<td>(1 \times 10^{-05})</td>
<td>(1 \times 10^{-4}; 1 \times 10^{-5}; 1 \times 10^{-6})</td>
<td>(4 \times 10^{-5})</td>
<td>(4 \times 10^{-3})</td>
<td>(4 \times 10^{-3})</td>
<td>(1 \times 10^{-3})</td>
<td>(1 \times 10^{-3})</td>
<td>(1 \times 10^{-3})</td>
<td>(1 \times 10^{-3})</td>
<td>(N = 1 in 10^{-4})</td>
<td>(AUS = Unknown but 1 in 10^{-5}) recommended</td>
</tr>
<tr>
<td>Methodology (consumer)</td>
<td>Linear extrapolation and/or Large Assessment Factor (Food) MoS (cosmetics)</td>
<td>Not applicable(^a)</td>
<td>Not applicable(^a)</td>
<td>Not applicable(^a)</td>
<td>Not applicable(^a)</td>
<td>Not applicable(^a)</td>
<td>Linear Extrapolation</td>
<td>Linear Extrapolation</td>
<td>Unknown</td>
<td>Large Assessment Factor for food, Linear Extrapolation for drinking water</td>
<td>Large Assessment Factor</td>
</tr>
<tr>
<td>POD (consumer)</td>
<td>BMDL(<em>{10}) (T</em>{25})</td>
<td>Not applicable(^a)</td>
<td>Not applicable(^a)</td>
<td>Not applicable(^a)</td>
<td>Not applicable(^a)</td>
<td>Not applicable(^a)</td>
<td>TC(_{05})</td>
<td>TD(_{20})</td>
<td>Unknown</td>
<td>BMD or LOAEL for food, Evaluation and Modelling for drinking water</td>
<td>BMD(_{10})</td>
</tr>
<tr>
<td>EU Agencies</td>
<td>France</td>
<td>Germany</td>
<td>Netherlands</td>
<td>Poland</td>
<td>United Kingdom</td>
<td>Canada</td>
<td>United States of America</td>
<td>Brazil</td>
<td>Australia and New Zealand</td>
<td>Japan</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>---------</td>
<td>---------</td>
<td>-------------</td>
<td>--------</td>
<td>----------------</td>
<td>--------</td>
<td>---------------------------</td>
<td>--------</td>
<td>--------------------------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>Tolerable risk level (consumer)</td>
<td>$1 \times 10^{-6}$</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>$10^{-3} - 10^{-6}$</td>
<td>$1 \times 10^{-5}$</td>
<td>Unknown</td>
<td>NZ Drinking water $= 1$ in $10^{-5}$ AUS Drinking water $= 1$ in $10^{-6}$</td>
<td>MOE approach, $&gt; 10,000$ (1 in $10^{-4}$)</td>
<td></td>
</tr>
<tr>
<td>Methodology (man exposed via the environment)</td>
<td>Not set</td>
<td>Unknown</td>
<td>Linear extrapolation</td>
<td>Linear extrapolation</td>
<td>Unknown</td>
<td>Linear extrapolation</td>
<td>Linear extrapolation</td>
<td>Linear extrapolation</td>
<td>Linear extrapolation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POD (environmental)</td>
<td>Not set</td>
<td>Unknown</td>
<td>Unknown (possibly BMD)</td>
<td>BMD</td>
<td>Unknown</td>
<td>BMD, BMD_{10}</td>
<td>T_{25}</td>
<td>TC_{50}</td>
<td>ED_{10}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolerable risk level (environmental)</td>
<td>$1 \times 10^{-5}$ (Drinking water)</td>
<td>$1 \times 10^{-5}$</td>
<td>$1 \times 10^{-5}$</td>
<td>$1 \times 10^{-5}$</td>
<td>Unknown</td>
<td>$1 \times 10^{-4}$</td>
<td>$1 \times 10^{-5}$</td>
<td>$10^{-4} - 10^{-6}$</td>
<td>$10^{-4} - 10^{-6}$</td>
<td>$1 \times 10^{-5}$</td>
<td></td>
</tr>
<tr>
<td>Risk threshold defined by law</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

*These countries do now have their methodology for assessing risks from consumer products such as cosmetics and food. Risk assessment methodologies used for evaluating safety is that set at the Union level. Food safety dossiers are submitted to EFSA and so typically follow the approach suggested by EFSA. For cosmetics the safety assessors typically use the approach set by SCCS and the MS do not mandate different approaches.*
3 Summary

3.1 Overall conclusions

Task 1 of the current study has undertaken an analysis of possible non-threshold hazard classes (beyond carcinogenicity and germ cell mutagenicity) that might benefit from a DMEL approach and reviewed the possible modes of action for those hazards. This has been supplemented by a review of the data held by ECHA as part of REACH registrations.

The ECHA data illustrated that the majority of REACH registrations that make use of a DMEL focus on carcinogenicity and germ cell mutagenicity, with the other major hazard class covered being respiratory sensitisation. The review of modes of action for non-threshold hazard classes provides some further explanation for why this may be the case. The research suggests that hazard classes with a linear dose-response relationship may be the most straightforward for applying existing DMEL approaches. The modes of action for neurotoxicants and immunotoxicants can vary for a range of parameters meaning direct comparison from one neurotoxicant to the next is very challenging. Similarly, endocrine disrupting chemicals (EDCs) in reality cover a broad range of effects and substances, with different philosophies and approaches taken within the scientific community. There may be possible application here for DMELs to EDC effects, but the effect needs to be clearly defined and quantifiable against the dose-response in order for the DMEL to be robust. This may mean greater care and consideration on a case-by-case basis for application, which would be a limiting factor.

Task 2 of the current study provided support by reviewing how and where DMELs or equivalents have been applied with national regulatory approaches, both across EU Member States, but also externally to the EU within OECD member countries. For all countries, (irrespective) application of tolerable risk (sometimes called acceptable risk) has been implemented in a range of legislation which can be broadly categorised by setting (occupational, consumer, man-via-the-environment). For EU Member States, a graded approach looks prevalent using more than one threshold (e.g., the traffic light approach adopted by Germany), while OECD countries have a single tolerable risk threshold operating as more of a ‘pass/fail’ type of approach. Furthermore, within occupational settings the adoption of tolerable risk (under DMEL type approaches) within OELs for non-threshold hazard classes are frequently adopted.

For occupational settings, the carcinogenic hazard class as excess lifetime risk, sets thresholds across most countries of tolerable risk levels between $10^{-3}$ and $10^{-6}$. The research has also identified examples where the national regulator has determined the minimum risk threshold that should be applied at least in occupational settings, for example OSHA in the USA sets minimum risk thresholds of $10^{-2}$ or $10^{-3}$. In Europe, Germany and the Netherlands have both adopted two-tier target levels for excess lifetime risk of cancer by inhalation as acceptable/target risk of $10^{-5}$ and tolerable risk as $10^{-3}$, while France has adopted an approach using linear extrapolation to calculate three different risk levels spanning $10^{-4}$ and $10^{-6}$. This notes that the risk thresholds are politically acceptable and that for a non-threshold hazard the risk is never zero. Also note the influence of international approaches with many countries following standards set by the WHO.

For consumer settings, particularly for food, excess lifetime cancer risk thresholds are more strict than occupational levels, operating primarily at the $10^{-5}$ or $10^{-6}$ level (noting one example at $10^{-4}$).
For example, in the EU risk thresholds for excess lifetime cancer risk include food ($10^{-5}$), drinking water ($10^{-5}$) and cosmetics ($10^{-6}$). For use of Directives, these translate into national regulations with non-threshold DMELs for excess lifetime risk of cancer between $10^{-4}$ and $10^{-6}$. Similar limits are seen in the OECD countries (USA sets a limit of $10^{-5}$ for food under the FDA, Australia sets a limit of $10^{-6}$ for drinking water, and New Zealand sets a limit of $10^{-5}$ also for drinking water).

For man-via-the-environment settings, similar limits are seen in the OECD countries. USA sets a two-tier limit of $10^{-4}$ to $10^{-6}$, whereas other countries (Canada, Australia, New Zealand, Japan, Brazil) set a single acceptable risk threshold, which is typically $10^{-5}$.

The research under Task 2 suggests that the concept of deriving quantitative approaches for non-threshold hazard classes (particularly carcinogens and mutagens) using either linear extrapolation methodologies or large assessment factor approaches is well established with some agreement on the typical orders of magnitude for excess lifetime cancer risks under different settings. The regulatory mechanism for application of these approaches varies significantly however, and in the case of the European Union, is perhaps complicated where approaches are applied within OELs under the carcinogens and mutagens directive (2004/37/EC) as well as a range of consumer legislation. This suggests an approach is needed to maintain continuity across legislation.
Appendix B
Review of Public Consultation responses
1.2 Introduction

This section provides the analysis of the results from the Public Consultation (PC). The PC was designed to support the wider evolution of the REACH Regulation, which spans multiple impact assessments. The section provided here covers the discussion for the disaggregated results of the PC covering only those questions related to the enhanced use of DMELs. The PC drew responses from a wide range of stakeholders, including representatives of business associations, company/business organisations, public authorities, non-governmental organisations, EU citizens, non-EU citizens, and other stakeholders. For the DMEL study specifically the PC included four key questions on the existing approach for the assessment of non-threshold risks, and the potential for a more extensive use of a quantitative approach (DMELs). Analysing these responses allows us to compare and contrast the responses given by the different types of stakeholders including SMEs as a sub-category of business. The remainder of this section is structured around the four questions from the OPC with a summary of the analysis and further examples of how different stakeholder groups had opposing views.

Question 1 To what extent do you agree that the existing approach for the assessment of non-threshold risks (i.e., use of DMELs) in certain situations is appropriate and effective? (Question 9f in the PC)

Overall response

A total of 771 respondents completed the overall public consultation. For question 9f a total of 537 respondents answered the question (with the other 234 leaving it blank). Additionally, for those that responded, 184 selected the option for neither agree/disagree, with the remaining 353 selecting the options ranging from strongly agree to strongly disagree. Excluding blanks and those that selected neither agree/disagree gives a response rate overall of 46%.

As indicated the respondents cover a broad range of stakeholder types. The table below provides the breakdown of the stakeholder types for question 9f (including those that selected neither agree / disagree).

<table>
<thead>
<tr>
<th>Stakeholder type</th>
<th>Number of respondents</th>
<th>Stakeholder type</th>
<th>Number of respondents</th>
<th>Stakeholder type</th>
<th>Number of respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academic/research institute</td>
<td>14</td>
<td>Environmental organisation</td>
<td>3</td>
<td>Public authorities</td>
<td>28</td>
</tr>
<tr>
<td>Business association</td>
<td>164</td>
<td>EU citizens</td>
<td>56</td>
<td>Trade unions</td>
<td>11</td>
</tr>
<tr>
<td>Company/Business</td>
<td>205</td>
<td>Non-EU-citizens</td>
<td>7</td>
<td>Other</td>
<td>16</td>
</tr>
<tr>
<td>Consumer organisation</td>
<td>2</td>
<td>NGOs</td>
<td>31</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figures B.1 and B.2 provide the overall responses to the question and a further breakdown by stakeholder type to add context. Based on the data presented 70% of the responses comment that existing approaches are appropriate and effective, by either agreeing or strongly agreeing with the question as presented. A smaller proportion (21%) either disagree or strongly disagree that the existing situation is appropriate and effective. The remainder selected neither agree or disagree option.
The response to the first question suggested that overall, the stakeholders believe the existing situation already works and does not need further intervention. Figure 2 provides some additional nuance to this overall position. Those respondents that selected ‘agree’ or ‘strongly agree’ primarily came from either industry (trade unions, companies/businesses, or business associations) or from public authorities, as indicated by the blue coloured segments in Figure 2. The main stakeholders that disagree that the existing situation is sufficient primarily come from NGOs, environmental organisations, consumer organisations, and academic research institutes, as indicated by the yellow and orange segments in Figure 2.

In this particular case the stakeholders from business associations and companies/businesses make up the biggest fraction of all respondents to the survey question, meaning that they will have the greatest impact on the overall results to the question.

Interestingly both industry representatives and public authorities largely agree that the existing approaches work well and that further intervention is not needed. This suggests that those developing the risk assessments and those reviewing the assessments and compliance are happy that the existing situation works relatively well. The responses from NGOs, environmental organisations, and consumer organisations could highlight a concern that the level of risks used under the existing situation are either not sufficiently well understood, or sufficiently well managed, hence why they disagree or strongly disagree that the existing approach is appropriate and effective.
Figure B.2 Disaggregation of responses by stakeholder type

The diagram shows the percentage of responses (stacked per stakeholder category) for different types of stakeholders. The categories include:

- Trade union
- Public authority
- Other
- Non-governmental organisation (NGO)
- Non-EU citizen
- EU citizen
- Environmental organisation
- Consumer organisation
- Company/business organisation
- Business association
- Academic/research institution

The responses are categorized into:

- Strongly agree
- Agree
- Neither agree nor disagree
- Disagree
- Strongly disagree

The figures indicate the percentage distribution of responses across these categories, allowing for a detailed analysis of stakeholder perspectives.
Industry response by company size

As a further analysis the stakeholders from the company/business category have been disaggregated by company size to assess whether there were any differences in the responses. For the stakeholder category “company/business” a total of 258 respondents completed the survey and provided details of company size. For question 9f specifically, 205 respondents provided a response (strongly agree, agree, neither agree or disagree, disagree, or strongly disagree), with the remainder leaving the question blank. Based on a further analysis, 71% of these companies are ‘large’ (based on the REACH definition\(^{40}\)). The remainder are SMEs, including 12% medium, 8% small, and 9% micro-sized companies, respectively.

Figures B.3 provides a breakdown of the response by company size. While overall Figure 3 agrees with the main results, illustrating that the majority of respondents (all company sizes) agree or strongly that the existing approaches are appropriate and effective, there is some additional nuance. The micro and small sized companies had a bigger proportion of respondents that disagree or strongly disagree. Some care is needed given that the number of respondents for micro and small-sized category are made up of less responses, however, it does potentially hint at underlying issues. The targeted consultation and workshop highlighted concerns over regulatory certainty and clarity of communication for exposure scenarios down the supply chain. The public consultation did not include open questions to provide further feedback on this topic specifically, but the fact that the micro and small-sized companies have a bigger proportion of disagree/strongly disagree compared to medium and large suggests there may be an issue with the very technical nature of assessments for non-threshold substances, and greater clarity in the outcome and managing RMMs using a DMEL.

Figure B.3 Breakdown of responses to question 9f (company size)

\(^{40}\) How to determine the company size category - ECHA (europa.eu)
Question 2 To what extent do you agree that more extensive use of a quantitative approach to chemical safety assessments for non-threshold substances should be introduced, including more extensive use of quantitative dose-response relationships coupled with politically agreeable thresholds (DMELs). Question 9g in the PC

Overall response

Following the same approach as presented to question 1 (question 9f in the PC), the different stakeholder types have been collated. This has been completed on the basis of 771 respondents in total, a number of whom left question 9g blank. A total of 541 respondents completed question 9g (including the neither agree or disagree option), with the table below showing a breakdown by stakeholder type. Very broadly the number of respondents per stakeholder category matches with question 9f.

<table>
<thead>
<tr>
<th>Stakeholder type</th>
<th>Number of respondents</th>
<th>Stakeholder type</th>
<th>Number of respondents</th>
<th>Stakeholder type</th>
<th>Number of respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academic/research institute</td>
<td>14</td>
<td>Environmental organisation</td>
<td>3</td>
<td>Public authorities</td>
<td>29</td>
</tr>
<tr>
<td>Business association</td>
<td>165</td>
<td>EU citizens</td>
<td>56</td>
<td>Trade unions</td>
<td>11</td>
</tr>
<tr>
<td>Company/Business</td>
<td>206</td>
<td>Non-EU-citizens</td>
<td>7</td>
<td>Other</td>
<td>16</td>
</tr>
<tr>
<td>Consumer organisation</td>
<td>3</td>
<td>NGOs</td>
<td>31</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figures B.4 and B.5 provide the overall response to question 9g and a further breakdown by stakeholder category, respectively. While the response to question 9f on whether the existing situation was appropriate and effective provided a strong and clear message that it is. The response to question 9g which poses whether there is a need for greater use of DMELs is more mixed. Almost equal numbers of respondents selected the agree (28% of all responses) and disagree (29% of all responses) options to the question. Overall including the “strongly agree” and “strongly disagree” options, 33% of all respondents agree or strongly agree that there is a need for wider use of DMELs. This compares to 49% who disagree or strongly disagree that there is a need for wider use of DMELs.

Figure B.5 helps provide some additional nuance to the responses received with a breakdown by stakeholder category. This illustrates that trade unions, public authorities, and EU citizens were the categories that most firmly believed that wider use of DMELs is needed with more than half of respondents (per category) selecting agree or strongly agree from the options. It was also noted that environmental organisations had 50% in favour and 50% against wider use of DMELs. The stakeholder categories that firmly believe the wider use of DMELs is not necessary (disagree/strongly disagree) were NGOs, non-EU citizens, consumer organisations, companies/businesses, and academic research. In the case of NGOs and consumer organisations discussions highlighted during the workshop indicated that while DMELs indicate a minimal effect level, for non-threshold substances there is no safe exposure level. The concern highlighted was that wider use of DMELs may send the message that use and exposure is ‘safe’. This may explain
why these two stakeholder categories in particular are against the wider use of DMELs (likely more in favour of full restriction/phase-out of all non-threshold hazardous substances).

Interestingly, again, reflecting the very mixed response to this question, public authorities had 51% of respondents strongly agree/agree in the wider use of DMELs, compared to 51% of business associations who strongly disagree/disagree. Feedback from the workshop indicated that the qualitative risk assessment can have variable quality and is challenging to assess and review. This was part of the reason that public authorities were in favour of wider use of DMELs for improved clarity. Industry (business/companies – 56% strongly disagree/disagree, business associations 51% strongly disagree/disagree), highlighted the technical and economic challenges to developing DMELs and posed the question over whether the assessment would add any additional value beyond the qualitative assessment. This perhaps reflects the outcome of the response to the survey question.

One further key point is that trade unions (who represent workers) were firmly in favour of wider use of DMELs, with 67% of respondents agreeing to the wider use of DMELs. This may further reflect some of the underlying details identified in the previous question. Figure B.3 highlighted that while the majority of respondents from businesses/companies were happy with the existing status quo, the micro-sized and small-sized companies had a bigger fraction that disagreed that is the case. For question 9g the trade unions stakeholder category are firmly in favour of wider use of DMELs. Taking these responses together along with feedback from the targeted consultation and workshop an underlying theme is the clarity, simplicity, and regulatory certainty in communicating risk. This is indicated where DMELs provide a clear threshold against which compliance can be assessed.
Figure B.4  Overall responses to question 9g
Figure B.5  Breakdown of responses to question 9g

- Trade union: 67% (Strongly agree), 11% (Agree), 22% (Neither agree nor disagree), 0% (Disagree), 0% (Strongly disagree)
- Public authority: 38% (Strongly agree), 23% (Agree), 12% (Neither agree nor disagree), 12% (Disagree), 8% (Strongly disagree)
- Other: 54% (Strongly agree), 38% (Agree), 8% (Neither agree nor disagree), 8% (Disagree), 0% (Strongly disagree)
- Non-governmental organisation (NGO): 23% (Strongly agree), 8% (Agree), 65% (Neither agree nor disagree), 3% (Disagree), 0% (Strongly disagree)
- Non-EU citizen: 33% (Strongly agree), 33% (Agree), 0% (Neither agree nor disagree), 3% (Disagree), 0% (Strongly disagree)
- EU citizen: 47% (Strongly agree), 10% (Agree), 25% (Neither agree nor disagree), 0% (Disagree), 8% (Strongly disagree)
- Environmental organisation: 50% (Strongly agree), 0% (Agree), 0% (Neither agree nor disagree), 50% (Disagree), 0% (Strongly disagree)
- Consumer organisation: 100% (Agree), 0% (Neither agree nor disagree), 0% (Disagree), 0% (Strongly disagree)
- Company/business organisation: 24% (Strongly agree), 41% (Agree), 15% (Neither agree nor disagree), 41% (Disagree), 0% (Strongly disagree)
- Business association: 18% (Strongly agree), 27% (Agree), 71% (Neither agree nor disagree), 0% (Disagree), 20% (Strongly disagree)
- Academic/research institution: 27% (Strongly agree), 6% (Agree), 72% (Neither agree nor disagree), 0% (Disagree), 0% (Strongly disagree)
Industry response by company size

Based on the survey results, 206 companies responded to the public consultation question 9g (including those who selected the ‘neither agree or disagree’ option). This included large companies (61% of the responses), as well as SMEs. The SME category is further broken down to include medium-sized companies (12% of the respondents), small-sized (13%) and micro-sized (14%).

Figure B.6 provides a further disaggregation of the responses to the survey question from the business/company stakeholder category. The overall response from this stakeholder category had 56% of all respondents select the disagree/strongly disagree option for the wider use of DMELs. The disaggregated version of the data (by company size) largely mirrors this position with the majority of respondents not in favour of the wider use of DMELs. However, for the micro and small sized companies ≥75% of respondents were not in favour of wider use for DMELs. In the micro-sized company set, those in favour of the wider use of DMELs is below 10% (only 3 respondents). The likely reason in this case is the highly technical nature of the work and associated costs, which SMEs would likely struggle to resource.

In terms of those respondents that selected ‘agree’ or ‘strongly agree’, the large company-size set has the highest proportion at 29% of responses, medium and small have 19%, and micro-sized falls below 10%. This would further suggest that larger sized companies perceive the potential benefits of wider use of DMELs to be greater. The public consultation did not include an open question to gather further explanation of why respondents picked a specific answer. The reasons are likely complex and varied. But one point is that with large volumes of substance produced, the workforce will also be larger as will the downstream user chain. Suggesting the greater use of risk data.

Figure B.6 Breakdown of responses to question 9g (company size)
Question 3 If such an approach were to be formalised in REACH, what do you think would be an appropriate benchmark for “politically acceptable risk”? (Based on an exposure period of 40 years for workers and 70 years for the general public): Workers. Question 9h in the PC

Overall response

The third question (question 9h in the PC) asked respondents to comment on what they considered an appropriate threshold for tolerable risk. This question was split into two halves, with first half covering thresholds for workers, and the second half covering thresholds for the general public (including consumers). This section covers the first half of the question on thresholds for workers.

Following the same approach as the previous two questions, the different stakeholder types have been collated. This has been completed on the basis of 771 respondents in total, a number of whom left question 9h blank. A total of 173 respondents completed question 9h selecting one of the four possible thresholds provided. A further 365 selected the ‘other/do not know’ option, and the remainder (233 respondents) left the question blank.

It can be noted that while question 9f received 537 responses, and 9g received 541, the two questions on thresholds received considerably fewer responses. This likely reflects that lack of strong feeling on what should be an appropriate threshold and also potentially the lack of engagement, i.e., respondents who are less familiar/have not attempted to use DMELs in the past.

<table>
<thead>
<tr>
<th>Stakeholder type</th>
<th>Number of respondents</th>
<th>Stakeholder type</th>
<th>Number of respondents</th>
<th>Stakeholder type</th>
<th>Number of respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academic/research institute</td>
<td>10</td>
<td>Environmental organisation</td>
<td>1</td>
<td>Public authorities</td>
<td>14</td>
</tr>
<tr>
<td>Business association</td>
<td>25</td>
<td>EU citizens</td>
<td>39</td>
<td>Trade unions</td>
<td>4</td>
</tr>
<tr>
<td>Company/Business</td>
<td>58</td>
<td>Non-EU-citizens</td>
<td>2</td>
<td>Other</td>
<td>8</td>
</tr>
<tr>
<td>Consumer organisation</td>
<td>0</td>
<td>NGOs</td>
<td>12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figures B.7 and B.8 provide the overall results to this survey question and a further disaggregation by stakeholder category. One caveat in this regard is that where question 9h received fewer responses overall it means that for some stakeholder categories there are very few (i.e., less than five) responses, and therefore care is needed when using Figure B.8 for further conclusions.

For Figure B.7 it can be noted that there is a broadly linear trend, with 1 in 1,000,000 (10^-6) receiving the highest number of responses, followed by 1 in 100,000 (10^-5), and 1 in 1,000 (10^-3) receiving the least responses. This broadly reflects the position that there is different consensus on what might be the appropriate threshold, with most respondents airing towards precautionary approaches and more strict thresholds, with 1 in 1,000,000 being the most strict.
Figure B.7 Overall responses to question 9h (workers) – tolerable risk thresholds for excess lifetime cancer (40 years)

Figure B.8 helps provide further context to the results with a disaggregation of different stakeholder categories. Only five stakeholder category types selected 1 in 1,000 (trade unions, EU citizens, business/companies, business associations and academic researchers). For the trade unions in particular only 1 in 1,000 and 1 in 10,000 are selected. Some care is needed here as there were only four respondents. It is however interesting that for the previous question (9g) 67% of trade union respondents were in favour of wider use of DMELs in the workplace (to protect workers), but for this question the two lower threshold levels were selected. This might suggest that the biggest driver is the clarity over a recognisable and enforceable threshold, rather than very strict/high levels of protection (such as $10^{-6}$).

Equally public authorities were broadly split between 1 in 10,000 (36% of responses) and 1 in 1,000,000 (50% of responses), suggesting that while the ideal situation would be 1 in 1,000,000, there may be flexibility or recognition of practical constraints that more relaxed thresholds may be the most pragmatic solution.

Only two stakeholder categories (NGOs, and non-EU-citizens) selected only 1 in 100,000 or 1,000,000, suggesting that they felt strongly that anything less than this level would not be appropriate or acceptable.

Business/companies and business associations had respondents that picked all four possible choices, with broadly even balance between categories. Again, this could well reflect the broader range of opinions. For both stakeholder categories 1 in 100,000 was the most selected option with 36% of business associations and 39% of business/companies (in relation to the overall responses for each stakeholder category, respectively).
Figure B.8  Breakdown of responses to question 9h (workers) – tolerable risk thresholds for excess lifetime cancer (40 years)
Industry response by company size

A total of 58 respondents from the business/company stakeholder category provided responses to question 9h. However, this category is heavily dominated by large-size companies (38 responses equivalent to 65% of the total). In particular only four micro-sized companies and five small-sized companies provided responses. This could well reflect the technical nature of the subject matter and less direct engagement with quantitative risk assessment for SMEs in particular.

This would have direct impacts if DMELs were made mandatory. A further consideration is that under the REACH approach using SIEFs and one substance; one dossier there is a high potential that SME SIEF members would rely on larger sized companies to carryout technical work. It is unclear whether this means that SME companies would have less say in selection of the DMEL threshold.

The large-sized companies illustrate broadly even numbers of responses in the 1 in 10,000 to 1 in 1,000,000 range, with the highest selected choice being 1 in 100,000. It is a similar picture for medium-sized companies with broadly similar frequency for all four options. Small-sized companies primarily selected 1 in 100,000 and 1 in 1,000,000, which is again a possible reflection of precautionary approaches and selection of the highest risk control levels. Micro-sized companies only included four respondents, the majority of whom selected 1 in 100,000, again reflecting a preference towards precautionary approaches.

Figure B.9  Breakdown of responses to question 9h (workers) (by company size)
Question 4 If such an approach were to be formalised in REACH, what do you think would be an appropriate benchmark for “politically acceptable risk”? (Based on an exposure period of 40 years for workers and 70 years for the general public): general public. Question 9h in the PC

Overall response

The fourth question covers the second half of question 9h from the public consultation, which asked respondents to comment on what they considered an appropriate threshold for tolerable risk for the general public (including consumers).

As with the previous questions, a total of 771 respondents from different stakeholder categories completed the survey in total. For this question specifically a total of 161 respondents selected one of the four thresholds, and a further 372 selected the do not know/no opinion option. The remainder (238) left the question blank.

The rate of response for the two halves of question 9h is broadly similar (173 for worker thresholds, and 161 for general public). The table below provides a breakdown by stakeholder category. As with the previous question note that for some stakeholder categories have very few responses (less than five). Therefore, care is needed when interpreting this data especially.

<table>
<thead>
<tr>
<th>Stakeholder type</th>
<th>Number of respondents</th>
<th>Stakeholder type</th>
<th>Number of respondents</th>
<th>Stakeholder type</th>
<th>Number of respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academic/research institute</td>
<td>10</td>
<td>Environmental organisation</td>
<td>1</td>
<td>Public authorities</td>
<td>11</td>
</tr>
<tr>
<td>Business association</td>
<td>23</td>
<td>EU citizens</td>
<td>39</td>
<td>Trade unions</td>
<td>3</td>
</tr>
<tr>
<td>Company/Business</td>
<td>54</td>
<td>Non-EU-citizens</td>
<td>2</td>
<td>Other</td>
<td>7</td>
</tr>
<tr>
<td>Consumer organisation</td>
<td>0</td>
<td>NGOs</td>
<td>11</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figures B.10 and B.11 provide the overview of results for this survey question and a disaggregation by stakeholder category. Figure 10 illustrates that more than half of all respondents selected the 1 in 1,000,000 ($10^{-6}$) option, with a clear message that for general public this is the most suitable level of protection. The next most frequently selected option 1 in 100,000 received one third of all responses, with the remaining two categories receiving far fewer responses ($\leq 10\%$ each). In this case the results provide a clear indication that the thresholds for the general public should provide a high level of protection.

Figure B.11 provides a further breakdown by stakeholder category. This reflects the overall picture with the majority of responses selecting the 1 in 100,000 or 1 in 1,000,000 (exampled by the yellow and orange in the graph). Respondents from public authorities, NGOs, non-EU Citizens, and other only selected one of these two options. There was a single respondent for environmental organisations who also selected the 1 in 100,000 threshold.

The remaining stakeholder categories (trade unions, EU citizens, business/companies, business associations, and academic/research institutes) selected a combination of all four thresholds.
As a further comment on the data presented in Figure B.11 some additional care is needed. For example, there were only three respondents in the trade union category, two of whom selected 1 in 10,000 and one who selected 1 in 1,000. In the graph this gives the 1 in 1,000 threshold 33% of the overall share of responses. This suggests that trade unions had the biggest proportion of respondents select the 1 in 1,000 threshold. However, where this category only has three respondents, it should be possible to recognise that it creates something of a false impression.

For the businesses/companies stakeholder group (which had 54 respondents) 17% selected either 1 in 1,000 or 1 in 10,000. Therefore, in terms of the different categories of stakeholders presented in Figure B.11 (excluding the issue identified above for trade unions), this stakeholder category proportionately had the highest number of respondents select the two highest risk thresholds. The PC did not include an open question to allow respondents to provide further explanation of why they selected a specific threshold. The reasons here are likely varied making it more challenging to comment.

One further finally interesting point is to note that a small number of EU citizens also selected the 1 in 1,000 and 1 in 10,000 threshold. This stakeholder category was made up of 39 respondents, two of which selected 1 in 1,000 and three of which selected 1 in 10,000. This is perhaps a little surprising given that end-use of chemicals and chemicals in articles covers a much larger cohort size than workers, and therefore the ramifications of 1 in 1,000 should be clear. Again, this question did not allow respondents to further elaborate on their selection choices so it is unclear the reasoning for why these thresholds were chosen.
Figure B.11  Breakdown of responses to question 9h (general public) – tolerable risk thresholds for excess lifetime cancer (70 years)
Industry response by company size

The business/company stakeholder group for this question was made up of 54 respondents. As with the other half of question 9h from the PC this category was dominated by large-sized companies. From the 54 responses received, 36 responses (66%) were from large sized companies, with the remainder from SMEs. This included nine medium sized companies, five small sized companies and four micro-sized companies.

As with the previous question a general point can perhaps be made that SMEs were less likely to respond to the two questions on appropriate thresholds. This could be a reflection on being less familiar with DMELs, less likely to need to engage with the development of DMELs or a combination of both.

As with the overall results, the majority of respondents selected the 1 in 1,000,000 or 1 in 100,000 threshold level. For large-sized companies there is a clear rising trend in the frequency of responses going from 1 in 1,000 to 1 in 1,000,000. This again sends the clear message that the majority of these respondents believe that either 1 in 100,000 or 1 in 1,000,000 is appropriate. The micro and small sized companies also show a strong and clear preference for the 1 in 1,000,000 threshold with only a single response in other categories. The medium-sized companies are more evenly spread, but even here the highest frequency responses are under the 1 in 100,000 or 1 in 1,000,000 threshold levels.

This provides a clear steer on conclusions and broad agreement across all company sizes.

Figure B.12  Breakdown of responses to question 9h (general public) (by company size)
Appendix C
Feedback from study workshop and finalisation of sub-options (screening)
1. Introduction

1.1 Purpose of the workshop

The study workshop aimed to present and discuss the approach to the study, some preliminary findings, as well as development of policy options for impact assessment. The workshop also sought to gather inputs from participants on the preliminary work and findings related to tasks 1, 2 and 3 (see below), and helping to identify issues and data sources to shape the remainder of the work. The participants were asked to provide feedback on the current work as presented and help provide the basis to further shape the impact assessment more fully, including identification of sources of information and references that may help support the work.

The workshop participants included representatives from Member State authorities, industry, organisations representing civil society, and international organisations and agencies.

The workshop is included alongside a wider targeted consultation phase for the project with further opportunities to engage with the project during early 2022.

1.2 Workshop participants

A range of stakeholder types registered interest in the workshop, including companies, business associations, MSCA/national institutes, EU institutions and agencies, academic or research institutions, consultancies, and NGOs. Details on the level of attendance by each category are provided in the table below.

<table>
<thead>
<tr>
<th>Breakdown of participants by stakeholder type</th>
<th>% (full meeting)</th>
<th>% (break-out groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Business associations</td>
<td>27.7%</td>
<td>32.3%</td>
</tr>
<tr>
<td>MSCA/National institutions</td>
<td>46.4%</td>
<td>33.8%</td>
</tr>
<tr>
<td>EU institutions and agencies</td>
<td>6.3%</td>
<td>10.8%</td>
</tr>
<tr>
<td>Academic or Research Institutions</td>
<td>1.8%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Consultancies</td>
<td>0.9%</td>
<td>1.5%</td>
</tr>
<tr>
<td>NGOs</td>
<td>3.5%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Companies</td>
<td>13.4%</td>
<td>13.8%</td>
</tr>
<tr>
<td>Total</td>
<td>N = 112</td>
<td>N = 65</td>
</tr>
</tbody>
</table>

The workshop attracted a high level of interest with a total of 112 delegates in attendance. To help maximise the exchanges during the breakout sessions attendance was limited to one member per organisation (with 65 delegates split into three groups for the breakout sessions). Overall, there was a broadly even representation between Member State Competent Authorities (46.4%) and industry (business associations and companies’ combined, 41.4% of attendees). There was also
representation from NGOs (3.5%), academics and research organisations (1.8%), and consultancies (0.9%). The remaining attendance was made of EU level institutions and agencies, primarily the European Commission and European Chemicals Agency.
2 Summary of stakeholder feedback received through the session

2.1 Introduction
During the workshop break-out sessions a set of key questions were asked for each Task, with feedback requested from the delegates. This section provides a summary of the feedback received.

2.2 Task 1 – Types of hazard and estimated numbers of substances

2.2.1 Uptake and use of the DMEL approach for Cat 1A and 1B carcinogens/mutagens appears to be around 20%. Are there specific reasons why it is this low?

The delegates attending this session put forward a range of issues that underlined how and why DMELs are/are not used. Broadly these issues can be summarised by three main discussion points:

- Firstly, the decision-making process for when a DMEL should be used. The delegates noted that key role of DMELs is to help provide quantitative risk assessments for substances with no threshold values. However, determining whether a threshold can or cannot be determined is a process in its own right. The delegates highlighted that even for hazard classes where DMELs are used (i.e., primarily carcinogens and germ cell mutagens) it is possible to have threshold and non-threshold carcinogens. This means that even for carcinogens a DNEL might be a more appropriate approach to adopt for cases where thresholds can be derived. For example, a plausibility check would be needed to confirm whether a DNEL (compared to a DMEL) would also protect from the non-threshold effects. This issue is further exacerbated by data availability, noting that under REACH the assessments are primarily conducted using historical data for chemicals.

- The second possible issue is the availability of good guidance to help structure the approach to developing DMELs. The delegates highlighted that while other processes under REACH are relatively mature, the concept of DMELs is relatively new and the understanding and data is still evolving. A similar level of knowledge for DMELs does not yet exist compared to DNELs (i.e., there is insufficient data available). Delegates noted that developing data on exposure-risk relationships is a demanding process (taking a year to deliver). This could be too demanding for companies which need to gather a lot of data. It is also necessary to have a lot of expertise to know which studies to give more weight to. Furthermore, the large assessment factor approach, which is suggested for use in developing DMELs, was first introduced to find impurities in food, and therefore it has its own limitations depending on setting.

- As a related issue, which can exacerbate the points above. Selection of the threshold (e.g., 1 x10^-4) is open to discussion, with a general lack of agreement over what is a suitable threshold for tolerable risk. This lack of agreement can create uncertainty and
dissuade people from attempting to develop such thresholds where other approaches are available.

- Finally, the delegates highlighted that the use of DMELs is not currently a mandatory requirement under REACH but rather a recommendation. The delegates highlighted that they could see the benefit of having a DMEL in that it eliminates higher risk. However, there appears to be many open questions with regard to DMELs and there is no wide agreement on what tolerable or acceptable thresholds should be used under the DMEL process. From an industry perspective the preference would be to identify a DNEL if at all possible, first as the process is more well defined, and in practice should take precedence anyway. Part of the driver behind this is the regulatory certainty of the outcomes when selecting risk management options (safe use vs. SEA) and complexity (data, approaches, acceptance).

  - Concerns were also raised by industry representatives that DMEL thresholds under REACH guidance are very low, and very difficult for some companies to achieve such a low levels (depending on the substance and setting). If they would try to reach the DMEL set by guidance this could mean the substance can no longer be used. It could therefore make a qualitative approach to enable a continued use of the substance more attractive.

As a counter-factual some delegates posed the question, on whether one could consider that 20% uptake and use of DMELs is that low. One participant indicated that in their view 20% uptake of DMELs is not such a low rate of usage, and that actually the results indicate that DMELs are already being used where possible.

### 2.2.2 What might be needed to help increase uptake of the DMEL approach for carcinogens and mutagens specifically?

The use of DMELs is largely dependent on the data available. For a particular substance, there might be an official national binding exposure level. This would be a reason to further examine the data, and to assess whether this would make DMELs more beneficial.

Delegates also highlighted that it is important to consider who will prepare the DMEL, which is very demanding, assuming there is enough scientific research and information that can be used. If there is not sufficient data for companies to carry out this work, it presents further challenges and costs which are a barrier in themselves. This issue would be further exacerbated for substances found within the low tonnage brackets of REACH. In particularly, suggestions to include the need for DMELs as part of risk assessments under 1-10 tonnes would be very difficult to complete.

Delegates commented that for low threshold carcinogenic substances it is better to use a risk-based approach utilising qualitative risk approaches. The same approach is used with food and drinking water contaminants. This suggests that a case-by-case approach might be better than a blanket implementation of mandatory DMELs.

The delegates noted that DMELs could present one option to risk assessment, however, it should not be mandatory or the only option. The available data should include/detail exposure risk relationships. Sometimes, when there is limited data (e.g., only three doses are tested and they are
not properly spaced) it can be difficult to identify risks. For this reason, the greater flexibility in selection of approaches (quantitative / qualitative) was seen as a strength.

One delegate posed the question of why there was a desire to help increase the uptake of DMELs and whether this reflected a consensus that current approaches are not safe or appropriate. In this case the desire to increase the use of DMELs would be to improve detection of risk. DMELs seems to be used for substances where there is low action currently being taken and where there is little need for regulatory scrutiny. In such cases, it may be better to close the gap with data rather than insist wider uptake with the DMELs application.

Delegates agreed that it may be necessary to identify the data gaps and collectively address these first, potentially with ECHA facilitating. At the heart of this argument was a need for sufficient publicly available data to help draw conclusions. In this respect some of the delegates noted that in their opinion making the use of DMELs mandatory could act as a driver to close such data gaps.

### 2.2.3 What are the perceived benefits of the DMEL; would wider use significantly improve risk control compared to the current qualitative assessment?

The delegates provided a range of discussion points as to the merits of DMELs. In particular, a number of representatives were keen to stress that DMELs are used and are already providing benefit. This was seen as an important point to make, particularly after the previous question which perhaps suggests that a 20% uptake for carcinogens and mutagens is perceived as a low rate of application.

In terms of the benefits and potential wider use, the discussion focussed on:

- Firstly, the use of quantitative risk assessments over qualitative risk assessments for non-threshold substances, suggests a better understanding of the true risk, and therefore as a consequence improved health protections. The delegates argued that to truly understand whether this argument is correct it is essential to identify if the DMEL is correlated to an increased level of protection. It is sensible to therefore consider what other registrants have done instead of using DMELs (i.e., have they appropriately performed an appropriate risk assessment or done no risk assessment?); and additionally for those registrants that did make use of DMELs whether it resulted in the need for additional health protection measures.

- Delegates commented that there is awareness of the use of certain substances and need to appropriately manage risk. However, with the advent of the European Green Deal and zero pollution commitments for toxic substances to the environment there is a need to eliminate hazardous substances in our daily life, and this heightens the need to understand and control risks even further. The same delegate also stressed that this did not mean DMELs were not already in use, or that they cannot be used more (for example in remedial measures) but also that they should not be used as a standard approach on the basis that it is assumed we need to get rid of every hazardous substance.

- The other potential benefit for wider adoption of DMELs was noted to be an improved level playing field. In particular, industry representatives highlighted the need for predictability, with everyone having to do the same thing. DMELs could be utilised in such a fashion as to have equal targets to implement, rather than with a qualitative
Delegates suggested that the wider uptake of DMELs would also mean there is a need to introduce a level of acceptable risk. Benefits of this depend on what the baseline is, and what level of risk is agreed on.

2.2.4 **Based on the review of other endpoints, do you consider that other hazard classes than carcinogenicity/mutagenicity could readily adopt the DMEL approach?**

All of the delegates (national authority representatives, industry, NGOs, and academics) responding to this question were keen to highlight the complexity in developing quantitative risk assessments for non-threshold substances, the labour-intensive nature of the work, and heavy data requirements. In particular, a number of delegates highlighted that while good work had already been completed in helping to apply DMELs to non-threshold carcinogens and mutagens, this work was far from complete, and there may be concerns that looking at other hazard endpoints may be too early yet.

The delegates commented that in particular carcinogens represented the most promising application for DMELs. and to fully adopt and implement the use of DMELs for all non-threshold carcinogens would in itself be a significant achievement.

For other endpoints to consider for the implementation of DMELs, it is important to highlight that there is no validated methodology to establish these endpoints. **Lack of validated methodologies makes it very difficult to derive values** in order to populate such endpoints. If such methodologies are available, the wider implementation of DMELs for other hazard endpoints could be a possibility for the future. It is not possible to predict at this stage whether the successful implementation of DMELs for other non-threshold hazard properties is possible. Primarily, the delegates indicated that these decisions would depend on what data is available, and many delegates felt that not enough was known yet to start working on this.

The delegates noted that for endocrine disrupting chemicals there is still a disagreement on whether thresholds exist, making it difficult to move on to DMELs. Similarly, from a toxicology point of view for respiratory sensitisation, it may be possible to determine a threshold mechanism for respiratory mode of action however, currently it is not possible to quantify this threshold. However, from a mechanistic point of view, if hypothetically there is a threshold it would point towards the use of DNELs. Meaning that the use of DMELs could be seen as a lesser surrogate due to lack of knowledge on a mode of action (i.e., DMELs should not be used because there is a lack of data/knowledge to derive DNELs).

Regarding mutagens, one delegate commented that mutagens should be considered for use of DMELs, however, not for other endpoints. Differences in threshold for end points make this complicated.

Equally, delegates commented that to consider the use of DMELs for other hazard classes of risks requires better data. Current data is not suitable or in a manner that cannot be easily utilised to support the use of DMELs in many instances. This makes it very difficult to consider extending the scope of the use of DMELs. Its already challenging to implement DMELs in their current scope, so enlarging it is seen by participants as very difficult.
2.2.5 What are the practical limitations for using DMELs for non-threshold hazards beyond carcinogens and mutagens?

Availability of data and methodologies are the key limitations, noting also that many uncertainties exist. For example, it could be possible to attempt the use of DMELs for end points (other than carcinogens) where it is assumed there could be thresholds, but thresholds cannot be quantified. This could be seen as a misuse of the DMEL concept, and a proper approach would be to focus more on developing the threshold and applying DNELs.

2.2.6 Further comments received in writing

The narrative provided in the preceding sections is based on the discussions held during the workshop. However, as part of the proceedings, delegates were given the opportunity to provide further written comments. A high-level summary of the comments received is provided below:

- The delegates highlighted a number of issues which present possible barriers to wider use of DMELs: need for underlying data; appropriate guidance; personnel with high levels of scientific expertise (which REACH registrants may not have); and complexity of the issues faced in developing DMELs.

- An industry delegate commented there is a possible concern that if the underlying data is less complete, assumptions of linearity have to be applied and this could affect the quality of the DMEL. The delegate voiced concerns that making use of DMELs mandatory could have significant impacts on quality of the work and desired outcomes.

- Other industry delegates highlighted that the use of DMELs is still a relatively new concept and more data is needed to demonstrate their inherent value over qualitative approaches before advocating wider use.

- Another industry delegate commented that care is needed for all hazard classes to determine that they are truly non-threshold, and concerns about using DMELs as a surrogate where lack of data prevents derivation of a DNEL. The delegate highlighted EDCs as a possible example and need for a case-by-case assessment.

- A delegate from a regulatory body highlighted the benefits of DMELs to quantitatively better understand the risks presented, which would lead to the better selection of RMMs. This ultimately has benefits for both human health protection, but also management of RMMs and cost where needed.

- Delegates from different regulatory bodies indicated that they would like to see the sub-options on Cat 2 carcinogens and mutagens, non-enzyme respiratory sensitisers and EDCs included in the scope of the study. In the case of EDCs an argument was made that as this substance will soon have its own hazard class it is worth further analysis. For the other hazard endpoints, a concern was raised that looking only at Cat 1A/1B carcinogens and mutagens may be too narrow for a complete analysis.
2.3 Task 2 – Regulatory uses and dose-response relationships

2.3.1 Some Member States make use of a traffic-light / two-tier approaches, adopting both acceptable and tolerable risk thresholds. How useful is this approach in practice? How burdensome is it in terms of development? Could it be applied within the REACH chemical safety assessment process?

The majority of delegates felt that the application of two-tier systems could add benefits to the existing approaches. Participants highlighted that such a system adds flexibility and allows authorities to set a minimum boundary (tolerable risk threshold) and a target to work towards (acceptable risk threshold). In other words, it sets a direction of travel with the opportunity to improve over time towards the acceptable thresholds. Importantly the two-tier system lays down the thresholds for use by both industry and regulators, allowing a dialogue. The use of two-tier approaches could also be beneficial for Cat 2 carcinogens where currently there is less data.

While the idea of a two-tier system was broadly seen as a good idea, some delegates did express some concerns. The implementation of two-tier systems seems a good idea in principle, but a feasibility study is needed to look at how many substances might be included, how the approach would work in practice across different national legislation and how risk thresholds would align with related legislation, particularly occupational safety. It is recognised that two-tier systems are already in use for some Member States. There is at least one recent example (cobalt) where the use of a two-tier system under REACH allowed a pragmatic outcome. This is where the original threshold could not realistically be met. The opportunity to transition towards acceptable risk threshold with agreed timescales and commitments demonstrated quantified improvements without harming the competitiveness of the EU economy. A full roll out of the two-tier system for all EU countries could, however, be challenging for some.

Some delegates did further indicate that there needed to be greater clarity over what specifically is meant by ‘acceptable’ and ‘tolerable’ (i.e., need clear rules and enforcement to define at EU-level what is meant by acceptable and tolerable) particularly where these thresholds are selected based on judgement rather than scientific reasons. It is clear that tolerable risk thresholds should not be exceeded with measures needed to contain the risk, however, it is unclear what role the regulator has in reviewing and agreeing the thresholds fairly. This would need additional guidance from the Commission on how to assess the use of two-tier systems in practice. Also, it is less clear what obligations acceptable risk would place on operators.

There are also question marks over whether such a two-tier system would be applied at the substance, sector, or operator level. Note that operators will also have commitments under OSH, and regulatory alignment will be important. Furthermore, would the two-tier system be applied to consumer settings and how might the messaging be communicated to the general public.

One delegate indicated that the two-tier system had worked very well in Germany, for example, but there is some concern on wider EU-impacts for Member States that have not used it before. Non-threshold hazard substances are highly complex, including the development of risks for specific settings. Question marks remain over whether this is the appropriate time to introduce this two-tier system given all the other changes under REACH. Furthermore, given the existing data gaps and challenges that already exist with the use of DMELs, the two-tier system approach could be a step too far.
2.3.2 Some Member States and OECD countries already prescribe values for life-time excess cancer risks in different settings. How acceptable has this approach been?

In principle this approach could be useful for levelling the playing fields, but there is a question over how it aligns with related legislation, particularly occupational health and OELs / BOELVs. There is a risk that the DMEL may end up being less ambitious/strict than the limits set under occupational health.

The general application of a mandatory threshold value for specific hazards (e.g., carcinogenicity) could be a good way of helping to improve consistency. However, the complexity and risk of specific substances and settings can vary significantly. This means the threshold would need to be set at a less stringent level to allow for the more complex situations.

Delegates highlighted there are some possible concerns with mandatory DMELs, and backsliding i.e., that the minimum would become the default with less effort to exceed the minimum. Also, one would need clear instructions around minimal threshold and what might be needed to determine acceptable thresholds vs tolerable thresholds.

There were some comments that a ‘one size fits all’ approach would probably not be appropriate, and that there is a need for flexibility to allow for the specificity of issues to be properly considered. Greater clarity over expected minimum thresholds would be welcome and help improve consistency. However, the sheer complexity and variability of risks for different substances and settings could be a limiting factor for implementation.

2.3.3 ECHA already provides guidance for DMELs with suggested levels. Is this sufficient or should acceptable or tolerable risk levels be prescribed in law? If so, should it be a single risk level or a two-tier ‘traffic light’ system?

Delegates indicated that Appendix R.8-14 of the ECHA guidance\(^{41}\) already suggests possible values that could be compared to specific DMELs. However, the concepts for two-tier systems are not yet included. Nor is the concept of a harmonised/standardised DMEL. That being the case an update of the ECHA guidance for latest knowledge and development of such methodologies would be very valuable. It could be good practice to include a routine update cycle (e.g., every five years). This would make the guidance more effective and useful and allow for developments in what threshold values should be used in practice. Routine update would also allow greater validation for how and where DMELs have been used in practice.

One issue of concern was that the development of a methodology for different approaches for the ECHA guidance could be a labour-intensive process.

---

\(^{41}\) Guidance on information requirements and chemical safety assessment – Chapter R.8: Characterisation of dose [concentration]-response for human health.
2.3.4 Should the REACH registrant always be responsible for developing DMELs, or could things be improved e.g., by allowing Member State authorities to decide on harmonised DMELs under REACH evaluation procedures or under CLP harmonisation procedures?

Based on the discussions surrounding this question there were broadly three main topics discussed:

- Firstly, it was suggested that greater clarity was needed around what was meant by a ‘harmonised’ DMEL. The delegates agreed that greater standardisation in approach and the kinds of tolerable risk threshold in use was desirable but acknowledged that the nature of the topic is highly complex. It was noted that while for other hazard classification under CLP and REACH it may be possible to have a combination of harmonised classifications and self-classifications, the development of an EU-wide ‘harmonised’ threshold value for non-threshold hazards would be problematic, because of the highly specific nature to the substance and setting. The delegates highlighted in particularly that parallels to CLP may not be helpful and that DMELs should remain a REACH-centric issue.

- In particular, one concern was that assuming that harmonised DMELs could be developed they would likely only be updated every several years. They would then become the base level used by everyone, and therefore could ignore or by-pass developments in science.

- Secondly, delegates raised concerns around who would be responsible for developing such harmonised DMELs. Members from the RAC highlighted the expected obligations and workload of the RAC are already quite considerable and that introducing the role to create harmonised DMELs would therefore likely create resource issues as they could be very labour intensive. This could either limit progress or delay the production of harmonised DMELs for many years. A better solution may be to use the RAC as a review body rather than carrying the obligation for the development of harmonised DMELs. This would leave the obligation of developing DMELs with the REACH registrants. Another challenge for the RAC or any other centralised pool of experts in developing DMELs is that a harmonised methodology does not exist, reflecting the complexity and variability of the issues explored.

- Finally, concerns were raised around tasking specific regulators with obligations to develop standardised approaches under different legislation and the risk of incoherence. As an example of the incoherence trying to develop harmonised DMELs could create, it was noted that under OSH work has already been completed (and is ongoing) to prioritise the carcinogens of highest concern and set binding limit values. This suggests that this kind of work is already happening albeit under different legislation and for worker settings only.

The general conclusions were that the complexity of the issues and variations between different substances means a single harmonised DMEL threshold value on a substance-by-substance basis is probably inappropriate. However, greater harmonisation for DMELs across substances within similar families or MOA could have beneficial impacts for consistency. There was, however, general feedback from delegates that existing approaches are probably better suited and more support should be given to existing work rather than new approaches.
One delegate did suggest that the idea of a harmonised DMEL in principle could be useful, particularly if it could be used as a benchmark for comparison setting, but it would need careful prioritisation and the levels of work required could mean that in practice very few harmonised DMELs would be developed in the coming years. Prior to the development of a harmonised DMEL one would firstly need an impact assessment study to consider the socio-economic aspects of the threshold. This could be very involved and entail detailed discussions with industry and between different regulatory bodies.

2.3.5 If use of the DMEL approach were extended, and increased information requirements for 1-10t substances were introduced (including a requirement for CSR), do you envisage any specific problems with applying the DMEL approach to 1-10t substances?

Delegates highlighted that without the obligation to develop a CSR the necessary data needed to even attempt DMELs would be missing, and therefore the wider CSA/CSR would need to include the 1-10t bracket first. This suggests that the use of DMELs at this tonnage bracket is some years away and that other changes are needed first.

As a further point, the delegates indicated that developing DMELs at the 1-10t threshold would be extremely challenging due to the current lack of data and likely technical capability within companies working at the 1-10t bracket. In reality this lack of data would almost certainly result in the need for more animal testing. It is also likely that many REACH registrants would have to use a qualitative approach.

Another concern is that many of the 1-10t substances are emerging chemicals and the data requirements could have quite negative impacts on innovation and competitiveness for EU companies with non-EU competitors.

Grouping and read-across would be important techniques to help bridge some of the gaps but substances would need to be structurally similar, which is unlikely. Read-across from other substances could help limit the effort for 1-10t, but it is less clear how readily this could be completed.

2.3.6 Further comments received in writing

A high-level summary of these comments is provided as follows:

- The written comments highlighted positive and negative issues for a wider adoption of two-tier or traffic light systems for adoption of DMELs. On the one hand a regulatory delegate highlighted the greater flexibility, possibility for improvement, and the fact that a two-tier system could allow room for consideration of socio-economic issues. Conversely, an industry delegate commented that while the traffic-light approach had worked well in their Member State, its usefulness cannot be considered without a more thorough analysis of the costs and benefits. In practice it is likely that each substance/use will need to be reviewed one by one, including the feasibility of measures that can be implemented, and costs would likely vary widely. This would mean an EU-wide implementation for all uses is not really feasible and a case-by-case approach would be better.
• Another regulatory delegate commented that they would welcome the wider EU implementation of a two-tier system for DMELs in worker settings but noted that a discussion was yet to be had about the possible application in consumer settings, and therefore this should be held first rather than moving to directly implementing systems.

• A regulatory delegate agreed that they favoured a two-tier system, but that this approach should make use of the values derived already (i.e., need for regulatory continuity For example, the RACs opinions on cobalt or tattoo inks. While the thresholds in these cases were low a two-tier system would allow more flexibility and use of use values agreed by the RAC would be aligned with reduced risk and protection aims.

• In terms of different settings, one delegate highlighted concerns with using different thresholds for different populations (workers/consumers). The delegate commented a greater degree of harmonisation in thresholds were needed, and perhaps the two-tier system could allow for different settings.

• A regulatory delegate also echoed the need for greater harmonisation/standardisation of thresholds in use. They commented that this was needed to make residual BOELVs for carcinogens more transparent (noting the wide range of thresholds in use). As a further comment on whether DMELs should be made mandatory, the same delegate commented that currently a legal definition of acceptable and tolerable thresholds was missing. If it remains voluntary there is no impetus to define these terms formally under REACH. This could be a driver for making the DMELs mandatory but a wider discussion was needed.

• An NGO delegate raised further concerns that if DMELs were made mandatory with standardised thresholds, the work and effort to develop such thresholds would be considerable. This would mean that once in use, an update of DMELs would not happen for several years and new science would be omitted. A case-by-case approach allows the flexibility in making use of the best data available.

• Other delegates agreed with this position commenting that the existing case-by-case approach provided the best situation and highlighted this is also reflected in the current ECHA guidance.

• One delegate commented that their preference would be non-regulatory encouragement for wider use of the DMEL approach. In their opinion the main issue was a need for better guidance and training of experts. This could include as a minimum a mandatory update cycle of the guidance every five years.

• Multiple delegates (from all stakeholder types) urged caution over attempting to develop DMELs for substances in the 1-10t bracket. This was on the basis of lack of data, and technical expertise. One delegate suggested that in these cases large assessment factor approaches could be used to read-across from LOAELs or NOAELs, but the necessary assumptions could mean the derived thresholds were equal to or worse than qualitative approaches.
Another delegate concurred and suggested that efforts should be given over to prioritising carcinogen/mutagen substances at higher tonnages currently without a DMEL rather than focussing on 1-10 tonnes.

2.4 Task 3 – Policy options and assessment of their impact

2.4.1 Do you agree that making the use of DMELs mandatory (where scientifically practicable) would help to improve consistency and ensuring a level playing field in REACH registration for non-threshold substances? Please explain.

Based on the comments from delegates at the workshop, there is some support from several participants for making the DMEL approach mandatory as it would improve consistency but participants also highlighted that the substance specific nature of the hazards would need to be taken into consideration also (e.g., different MoA should be treated differently).

One delegate commented that it could be useful to have a mandatory requirement for DMELs to achieve a more precautious measure. This would be an improvement from the current situation however, it needs to be accompanied with information on minimum risk level. Adopting a mandatory level (DMEL or DNEL) needs an impact assessment. To simply change current REACH from optional to mandatory DMEL is not feasible. Also, it would be complicated to adopt DMELs as it is now. Other changes would be required as well.

Another delegate commented that current guidance is lacking. A challenge in its practical application is the need for expert judgement. A policy decision would be required to facilitate this, e.g., as was decided for EDCs. If there is a clear effect for neurotoxicants you can use DMELs. The issue for carcinogens (CAT 1A and 1B), is that it is possible to have threshold and non-threshold substances, and this means that two assessments might be needed. One determine if a threshold exists (and use of DNELs), or a threshold does not exist and DMELs/qualitative risk assessment. Often these decision can be based on expert judgement, and predictability of the outcome is challenging.

The threshold values in use can range widely substance to substance. For example, the current REACH guidance suggests a target threshold of $10^{-5}$ is an “acceptable” risk level. If we look at existing authorisations (e.g., trivalent chromium) the risk levels in the RAC and SEAC opinion are higher than the current guidance (e.g., $8 \times 10^{-3}$). For some substances, it is impossible to set these acceptable risk levels.

One delegate posed the question of what the enhanced use of DMELs aims to achieve? Is it to minimise risk as far as possible, or where the EU Green Deal is now in place is the aim for full elimination? The requirements placed upon REACH Registrants in terms of risk management may conflict with the wider need for competitiveness and innovation.

A general point was made to the delegates that there is a need to investigate whether the introduction of DMELs will lead to a better protection of health. The outcome of the study should help address this question.

An industry delegate commented that the use of the DMEL approach may not always lead to better health protection. The delegate stated that DMELs may be more precautionary than the qualitative approach, but from an industry perspective – it is not clear why DMEL would be a better approach than a qualitative assessment in terms of risk assessment.
A more general point made by several delegates (of all stakeholder types) was the recognition that **data do not exist to allow making DMELs mandatory for all substances.** The industry perspective is that a case-by-case approach makes more sense, especially for EDCs. The mode of action and endpoint are very important to consider. Delegates agreed that for endpoints covering non-threshold carcinogens and germ cell mutagens use of DMELs is more plausible, in part because the ECHA Guidance documents help support their use. However, more work is needed to understand substance specific mode of action (for respiratory sensitisers and EDCs at least).

For some substances DMELs will not be possible due to the lack of data. This applies to all types of substances. **A general point was that there needed to be an understanding of what specific data might be needed for different endpoints? And whether this data is currently provided as an obligation of developing the REACH dossier.**

### 2.4.2 What do you expect the key impacts to be (costs for industry, practicality, improved health protection) of applying more extensive use of the DMEL approach?

The delegates identified both potential positive and negative impacts depending on how the wider implementation of DMELs would be incorporated into REACH.

Briefly summarised the main positive impacts from wider use of DMELs were:

- The use of DMELs can help quantify the risks more accurately than qualitative approaches. This could mean that where precautionary steps are needed under risk assessments based on qualitative assessments; the use of DMELs could help better understand the risk and limit the use of unnecessary measures.

- The two-tier system of DMELs used in some Member States has been an effective means of target setting and allowing industry to improve over time.

- Potential benefits from the work developed on DMELs to other policy areas. However, some delegates did note that care needed to avoid regulatory inconsistencies (particularly with OSH), and that better co-ordination on these topics is needed.

- Some delegates believed that DMELs would lead to better health and environmental protections based on quantitative assessment of the risk. However, this needed to be weighed against the cost and effort to develop DMELs.

  - Briefly summarised the main negative impacts from wider use of DMELs were identified as:

- There were multiple comments from all stakeholder types, that the development of DMELs is a complex process requiring both good technical experts and good underlying data. If the use of DMELs were made mandatory, even for only (non-threshold) carcinogens and mutagens, there could be significant challenges for SMEs. Anticipated costs include increased costs for importers/producers/downstream users. Mandatory DMELs might also lead to global disadvantage for EU manufacturers due to different requirements for non-EU manufacturers which may produce chemicals at a lower cost. There may also be costs to customers if prices increase to absorb the extra cost. In terms of benefits, there will potentially be greater protection of workers.
• Concerns also highlighted the possible impacts on the quality of the DMELs developed if the process was made mandatory and necessary data was lacking.

• A number of delegates highlighted that there are already some binding OEL levels for CMR 1A and 1B (approximately 30 substances) and questioned that additional benefits would be reached from the DMEL approach.

  ▶ Beyond possible positive and negative impacts, much of the focus during the discussion of this question related to how the possible value of DMELs could be better demonstrated to understand what the wider benefits might look like.

  ▶ In particular, one delegate commented that case studies on specific chemicals/industries are required and will be important. This includes determining at what tolerable risk level different companies would be affected. In developing such case studies care would also be needed to cover the full range of possible situations and settings.

  ▶ A key question would be around whether mandatory DMELs will improve protection – this depends on the quality of the data and the DMEL derivation.

Another suggestion has been to look at existing authorisations and restrictions. The current acceptable risk concentration limits should be reviewed to gauge practicality. For the EU binding OELs there are large discrepancies in terms of risk associated with each OEL. They are set as low as possible based on feasibility and socio-economic implications. In comparison to REACH authorisation for Cr(VI) substances there were low tolerable risk levels implied under the REACH guidance.

### 2.4.3 Do you expect any different impacts depending on whether the approach is applied more extensively for (a) Workers (Occupational settings); (b) Humans exposed via the environment; (c) Consumers? What information sources could help to understand these impacts?

The delegates highlighted that when looking across different settings it is important to differentiate between firstly the derivation of the DMEL and secondly, how the concept is used in the regulatory approach. DMELs should be defined on a scientific basis, but for use/implementation in policy there are many other considerations. Their application to different groups (workers, consumers) is based on practical and socio-economic considerations.

Delegates highlighted that the DMEL concept in itself is quite generic, meaning it is more open to interpretation than other quantitative risk assessment processes. This suggests that applying assumptions based on entire hazard classes may not be suitable. As an example, Sensitisation is very likely non-threshold, but substance specificity should be maintained for the objective to protect health and safety. Therefore, the delegates suggested that the setting itself (worker, consumer, environment) may be partly a driver to what risk assessment method can be applied.

Delegates questioned whether the toxicity study data used is appropriate to calculate dose-response curves? Mode of action studies are not typical under REACH requirements but would help. Finding reliable dose-response functions is key. For Cr(VI) excess lifetime risk for cancer was assumed.
One delegate suggested that rather than focus on extending the use of DMELs from worker settings to other settings (consumers / environment etc.), a better option may be to focus on the relationships for different occupational legislation. In particular, there could be an increase in the overlap between REACH and OSH. REACH was seen as working well for the hazard aspects, while OSH was seen as needing to move to risk assessment.

**For consumers settings, predictability of exposure especially for substances in articles is essential to consider.** It has been noted that registrants often have less information on how consumers are exposed as there is less data on uses and exposure. More effort is thus needed from a public health perspective, and to see something that is practically implementable.

Additionally, one delegate noted that it is not clear if different levels of acceptable risk are needed.

Overall, the delegates concluded that a primary issue across different settings is a combination of data availability, and what can / should be achieved as part of risk assessments. There is significant work needed on deriving limits for non-threshold substances, but also a highlighted need to act consistently across different legislation and settings.

### 2.4.4 In terms of applying DMELs are specific industry sectors more affected than others?

The delegates commented that to better answer this question it is necessary to look at real-world examples. Therefore, as with responses to other questions, case studies across sectors would be important to identify whether impacts along the supply chain are on manufacturers/ producers or further along.

**It is anticipated that primary production (e.g., of metals) may be most affected.** This was on the basis that it is challenging to use closed systems / risk management for this sector specifically.

Classification and Labelling (C&L) may have more implications than DMELs in terms of restriction of chemical use.

### 2.4.5 Further comments received in writing

A high-level summary of these comments is provided as follows:

- Multiple industry delegates highlighted concerns around making the use of DMELs mandatory, highlighting the complexity of the issues and the substance specific issues. A case-by-case approach was argued as being more appropriate with flexibility over when a DMEL could or should be used.

- An industry delegate highlighted that their preference would be to see greater collaboration and use of data between OSH and REACH, in particular the use of BOELVs could be valuable to orientate risk assessments for non-threshold substances.

- In terms of sectors that may be most affected delegates identified the metal working and textiles industry sectors.

- One delegate also further commented that acceptable and tolerable risk as a two-tier system is not legally defined and this could create problems for communication of risk if implemented Europe wide without further clarifications.
3 Summary conclusions

3.1 Introduction

Tasks 1 and 2 of the study were intended to provide a state of play for how and where DMELs are currently used under REACH (as well as national legislation in the EU and OECD). This included further considerations for the wider use of DMELs to other hazard endpoints and different systems of implementation. The culmination of the outputs from Tasks 1 and 2 resulted in the development of preliminary options and sub-options to form the basis of an impact assessment.

The sub-options were grouped by different elements and assigned following a traffic light system (green – in scope, amber – potentially out of scope, and red – out of scope). Only sub-option marked as ‘green’ will be taken forward to the impact assessment phase.

Therefore, the workshop was intended to provide a critical communication with stakeholders to discuss and finalise the sub-options for the impact assessment.

3.2 Finalisation of policy options

This section provides a brief narrative for changes made to the sub-options with the finalised sub-options.

Which endpoints are covered?

The delegates highlighted the complexity of the issues, substance specificity, and need for case-by-case analysis. While use of DMELs for a range of non-threshold hazards would be welcome, multiple obstacles could make this unfeasible at the current time. Furthermore, one delegate highlighted that for substances where a theoretical threshold could be determined, but lack of data made determination of the threshold challenging (e.g., due to very low concentrations), DMELs should not be used as a surrogate to the development of DNELs. Where much of the focus to date has been on carcinogens and mutagens, the scope of the study has been included Cat 1A/1B and Cat 2 non-threshold carcinogens and mutagens (currently CAT 2 is excluded). All other potential hazard classes have been excluded.

Who develops the DMEL?

The sub-options in the background paper include registrants only (sub-option i) and exclude regulatory bodies only (sub-option ii). These sub-options remain unchanged. Additionally, there was a third option related to the development of harmonised DMELs, but only for selected high priority substances. The RAC members highlighted the limited resources to develop such DMELs which could delay the outcome of the work as well as impact other work streams. On that basis sub-option iii has been moved to excluded. Sub-option iv has been re-instated. This sub-option provides the possibility for RAC to act in a review capacity during regulatory processes such as evaluation and powers to overturn the DMEL developed in the CSR.
Is the quantitative DMEL approach mandatory?

Sub-option ii on the mandatory development of DMELs where read-across approaches are possible is excluded on the basis that it has been merged with sub-option i (DMELs are mandatory where data is available).

How many quantitative risk thresholds are applied?

The sub-option ii on the possible wider implementation of two-tier or traffic light approaches has been included in the scope. The discussion around two-tier systems was significantly detailed during the workshop and in the written comments with arguments both for and against its wider use. However, where many delegates (from all stakeholder types) highlighted the possible flexibility of approach and value in setting a direction of continuous improvement meant that further exploration of the topic was warranted.
# 4. Workshop Agenda

<table>
<thead>
<tr>
<th>Time (CET)</th>
<th>Type of session</th>
<th>Sessions</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:30 – 09:45</td>
<td>Plenary</td>
<td>Welcome (Commission)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presentation of structure of workshop and desired outcomes (WSP)</td>
</tr>
<tr>
<td>09:45 – 10:15</td>
<td>Plenary</td>
<td>Task 1 - Hazard types for coverage by DMELs (Ramboll)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(20 min presentation + 10 min Q&amp;A / clarifications)</td>
</tr>
<tr>
<td>10.15 – 10.45</td>
<td>Plenary</td>
<td>Task 2 - Quantitative measures of acceptable or tolerable risk for DMELs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(WSP/Ramboll)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(20 min presentation + 10 min Q&amp;A / clarifications)</td>
</tr>
<tr>
<td>10.45 – 11.30</td>
<td>Plenary</td>
<td>Task 3 - Policy options to enhance use of DMEL concept in REACH (WSP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(20 min presentation + 10 min Q&amp;A / clarifications)</td>
</tr>
<tr>
<td>11.30 – 11.45</td>
<td></td>
<td>Break</td>
</tr>
<tr>
<td>11.45 – 12.15</td>
<td>Break-out</td>
<td>Breakout group sessions – World Café format</td>
</tr>
<tr>
<td>12.15 – 12.45</td>
<td>Break-out</td>
<td>Breakout group sessions – World Café format</td>
</tr>
<tr>
<td>12.45 – 13.15</td>
<td></td>
<td>Lunch</td>
</tr>
<tr>
<td>13.15 – 13.45</td>
<td>Break-out</td>
<td>Breakout group sessions – World Café format</td>
</tr>
<tr>
<td>13.45 – 14.00</td>
<td></td>
<td>Break</td>
</tr>
<tr>
<td>14.00 – 14.25</td>
<td>Plenary</td>
<td>Feedback from breakout group sessions (WSP / Ramboll)</td>
</tr>
<tr>
<td>14.25 – 14.30</td>
<td>Plenary</td>
<td>Workshop summary and closure (Commission)</td>
</tr>
</tbody>
</table>
Appendix D
Further analysis of chemical safety reports [confidential]
Appendix F
References
EU-Based references


https://www.echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258


EFSA, (2005). Opinion of the Scientific Committee on a request from EFSA related to a Harmonised Approach for Risk Assessment of Substances Which are both Genotoxic and Carcinogenic. 
EFSA, (2012). *Statement on the applicability of the Margin of Exposure approach for the safety assessment of impurities which are both genotoxic and carcinogenic in substances added to food/feed.*


Health Council of the Netherlands (DECOS) (NL) (2014). *Overview of methodologies for the derivation of Occupational Exposure Limits for non-threshold carcinogens in the EU.*


https://inchem.org/documents/ehc/ehc/ehc210.htm#PartNumber:4


OECD, (2018). *Considerations for assessing the risks of combined exposure to multiple chemicals*

https://www.rivm.nl/bibliotheek/rapporten/090013001.pdf

https://www.rivm.nl/bibliotheek/rapporten/320002001.pdf


RIVM, (2014). *Overview of methodologies for the derivation of Occupational Exposure Limits for non-threshold carcinogens in the EU.*


Social and Economic Council of NL (2021) Towards a harmonized risk-based approach for OELs in the EU for carcinogens without a threshold.

KEMI 2019. Future chemical risk management Accounting for combination effects and assessing chemicals in groups.

https://www.government.se/4adb1a/contentassets/ee36b3e49c354bb8967f3a33a2d5ca50/future-chemical-risk-management---accounting-for-combination-effects-and-assessing-chemicals-in-groups-sou-201945


UK COC, (2019). COC set of principles for consideration of risk due to less than lifetime exposure.


UK COC, (2020). Risk assessment of the effects of combined exposure to multiple chemicals on carcinogenicity.


http://www.fao.org/3/ae922e/ae922e06.htm

https://apps.who.int/iris/bitstream/handle/10665/43940/9789241572392_eng.pdf?sequence=1&isAllowed=y


**OECD-Based references**


Centre for Food Safety Food and Environmental Hygiene Department. The Government of the Hong Kong Special Administrative Region, (2012). *Endocrine Disrupting Chemicals in Food.* CFS Hong Kong

CETESB (2001). *Relatório de estabelecimento de Valores Orientadores para Solos e Águas Subterrâneas no Estado de São Paulo (CETESB SÃO PAULO 2001)* CETESB

Commonwealth of Massachusetts Department of Environmental Protection, (1990). *The chemical health effects assessment methodology and the method to derive allowable ambient limits.* Downloaded


HC (1998). *Assessment and Management of Cancer Risks from Radiological and Chemical Hazards* Health Canada

HC (2018). *Advancing consideration of endocrine-disrupting chemicals under the Canadian Environmental Protection Act, 1999.* Health Canada


Health Canada (2021). *Follow-up report to the Standing Committee on the Canadian Environmental Protection Act: chapter 3* Health Canada


Ministry of Labor and Employment (1978). *In Brazil, the Brazilian Regulatory Standards (NR) set occupational standards for chemical hazards cited in Chapter V, Title II of the Consolidation of Labor Laws (CLT) approved in*
1978 are obligatory for all Brazilian companies governed by the Labor Law. Exposure limits are provided in Tabela de Limites de Tolerância in Annex No.11 of Regulatory Standard NR N-15, MoLE.


National Health and Medical Research Council (2021). Australian Drinking Water Guidelines (NHMRC 2011 with updates in March 2021) NHMRC


NIOSH (2020). CURRENT INTELLIGENCE BULLETIN 69: NIOSH Practices in Occupational Risk Assessment CDC


