DNEL: multiple values for identical substances?

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REACH means a paradigm shift for the management of chemical substances. With the implementation of REACH the manufacturers/importers of chemical substances are responsible for assessing the risk for the environment and human health and, if necessary, to propose measures to reduce exposure. As part of the human health risk assessment, Derived No Effect Levels, DNELs are established based on the available data on the intrinsic toxicological properties of a substance. The DNEL describes the dose which is safe for humans, meaning that any exposure at or below the DNEL will not lead to adverse effects and can be regarded as a safe level for humans. For all possible exposure scenarios, including exposure at the workplace during production or use, the estimated exposure level will be compared with the DNEL. If the exposure equals or is below the DNEL, the identified use is safe and no additional measures have to be implemented. If the assessment for an identified workplace exposure scenario leads to the conclusion that there is no risk, then the producer and/or user can handle the chemical as intended, without having to implement additional measures. Under these conditions, no additional Occupational Exposure Limits are necessary, as long as the exposure conditions are covered by the Chemical Safety Report (CSR). This information is communicated through the value chain using the extended MSDS.

In an ideal world and following the initial hypothesis under REACH, only one unique DNEL is derived based on the same database for identical chemical substances. Forced data sharing (Art. 30) leads to a uniform set of NOAELs as starting points. NOAELs and DNELs are made public via the Internet (Art. 119) and are accessible to all potential registrants. The obligation to submit all relevant available information leads to common knowledge, which then leads to one unique assessment of the substance. In real practise, it can be expected that more than one DNEL will be derived for the same substance, e.g. for the workplace exposure scenario. One situation can be that a registrant can “opt out” from a REACH consortium for non-scientific reasons and develop its own chemical safety report including derivation of a DNEL. The option to leave a consortium for a given substance is important and necessary for industry, since there may be critical confidentiality or legal issues. Also, it may not be possible to reach agreement within a consortium on various issues including financial compensation or interpretation of data. It should be noted, that the individual use of default assessment factors, may lead to different conclusions on the value of the DNEL. In addition, different substance identity may be claimed based on different production processes or impurities. Substances with “dual use” may not be reported consistently via the Internet and registrants may fail to recognize the information. No harmonized inventory will be established according to the

REACH Regulation, therefore it can be foreseen that several DNELs will be established for identical substances.

The situation for the workplace is further complicated, since already today different Occupational Exposure Limits (OELs) exist across Europe. Again, in an ideal world, after risk assessments for the workplace, including DNELs, have been established for all chemical substances in Europe, OELs would no longer be necessary. Scenarios for safe use and handling would be described in the CSR and, if necessary, measures proposed to be established at the workplace to guarantee the safe use. All users or producers could rely on the described conditions and measures and there would be no need to set an OEL.

In the interim time, during the "Phase in Period", it has to be decided how existing and newly established OELs should be used and their role in the context of REACH has to be defined. Industry is conducting risk assessments and is establishing safe exposure scenarios, including for workplace exposure. Therefore, the role and value of OELs for the respective substances can be questioned. Setting of an OEL (DNEL for workplace exposure), is useful to control exposure, if it is not feasible to sufficiently describe all possible exposure scenarios in the CSR.

The relationship between a DNEL and an existing national OEL needs to be clarified. If the producer or importer derives a DNEL for the workplace, which differs from the existing national OEL, what are the consequences? If, e.g. the proposed DNEL is below an existing national OEL, can the user of the substance refer to the national OEL and not implement additional measures to reduce exposure, as may be required by the lower DNEL established by the manufacturer or importer?
These situations are especially difficult to deal with, if the national body or authority used the same data for the OEL setting but a different process, which may not be in line with the process described in the REACH guidance document. The draft RIP 3.2 guidance document on DNEL derivation proposes the use of several default assessment factors during extrapolation from animals to humans, which differ significantly from the extrapolation process used in several countries, including the process used by SCOEL to establish ILVs. Since the REACH registrant should follow the guidance document, DNELs will definitely differ from existing and newly established OELs, like e.g. the MAK values and AGW values in Germany. According to REACH, the DNEL has to be used to establish safe use or handling for identified exposure scenarios and is the basis for communication to downstream users. If DNELs differ from OELs in different EU countries, there is a conflict, which is difficult to communicate and in many cases will lead to confusion. The producer or importer may – as of today - have to communicate different information through Material Safety Data Sheets for different EU countries, depending on national OELs. On the other hand, he also has to communicate how the substance can be used safely, which is based on the DNEL, which have a different value than the OEL, complicating things further.

If only the extrapolation procedure is different but the hazard assessment is the same for a given substance, different values are questionable and cannot be scientifically justified. Default extrapolation factors are only partly based on science and their use largely depends on the committee setting the OEL. Some of these committees do not publish details on the extrapolation process they are using, or they use expert judgement instead of assessment factors. Also, the use of default assessment factors is controversially discussed in the scientific community.

Goals of REACH are, to establish a transparent system, to enhance communication within the value chain and to harmonize management of dangerous chemical substances within the EU. Therefore, consideration should be given to the establishment of a harmonized DNEL inventory. In case of more than one Chemical Safety Report (CSR) for the same substance, resulting in different DNELs, ECHA should establish a procedure to harmonize the DNELs in consultation and cooperation with the responsible companies. Scientific principles should be used to decide on the correct DNEL and the harmonization process should be transparent, taking into account all available data and scientific arguments. Special consideration should be given to possible consequences of the use of the substances, to avoid competitive disadvantages while making sure, that the substance can be used safely. In order to achieve this, also limit values established in non-EU countries could be used as reference values. The use of default assessment factors should be strictly limited to cases where no supportive data or data from related substances exist. Grouping of substances and cross reading should be used whenever possible.

National authorities and scientific committees should evaluate their hazard and risk assessment processes and the criteria for using assessment factors in extrapolating toxicological effects from animals to humans. At least, the extrapolation procedure should be transparent and documented in such a way, that the reasons and the scientific basis for differences between different occupational exposure limit values for identical substances, can be clearly understood. This includes the scientific rationale for using or not using assessment factors, especially if default values are used. Each of the steps used in extrapolating data from animals to humans, should be addressed and explained, if no documented standard procedure is followed. It is important to note, that default assessment factors are based on experience and not strictly on science and that they may or may not be suitable for a given substance. Therefore, if supportive data are available, they should be taken into account and should be given priority over default factors. These data may also include data from other substances, which are e.g. structurally related, or have the same or similar mechanism of action.

The role of EU-wide and national OELs in the context of REACH should be clarified, especially during the “Phase in Period”, before all REACH substances are assessed and safe use and handling is established for identified exposure scenarios, including the workplace.

To build trust in the risk assessment procedure used under REACH, it is important that identical toxicological data lead to an identical DNEL for identical substances. One can point to the situation for Classification and Labelling (C&L) under REACH. Here, following article 113, an obligation exists to harmonize C&L and to establish a C&L inventory.

DNEL: multiple Values for identical Substances?

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The Chemical Company

Overview

- Presentation focuses on workplace exposure
- REACH paradigm shift and process for risk assessment
- Multiple values for identical substances
  - and identical exposure scenarios
- The ideal world: initial hypothesis for phase-in substances
- The role of OELs (national, EU) in the context of REACH
- Harmonization
  - DNEL and OEL
  - Multiple DNELs

REACH – The Paradigm Shift

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- Companies are responsible for the safe use of the chemical substances they are manufacturing/importing, including workplace exposure
- REACH risk assessment for a dangerous substance includes hazard assessment and exposure assessment
- During the process, exposure scenarios are identified, including scenarios for occupational exposure
- According to the draft DNEL guidance document (RIP 3.2), depending on the exposure situation, different assessment factors should be used
  - Higher default assessment factor for consumer exposure compared to exposure at the workplace
    - Less uncertainty for intraspecies variability at the workplace
  - Resulting in multiple DNELs for identical substances and different exposure situations/scenarios (consumer, workplace: production, professional user)

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The REACH Process (1)

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- Hazard characterization using all available toxicological data and new data to be generated according to the REACH requirements
  - Based on tonnage level and identified uses
  - Includes calculation of DNEL values (consumer, worker)
- Identification of exposure scenarios (ES) and exposure assessment
- Risk assessment
  - ES workplace (ESW) < DNEL = safe use
    - No additional measures for ESW
      - As long as the exposure conditions are covered by the Chemical Safety Report (CSR)

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The REACH Process (2)

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- Is there still a need for workplace exposure limits and their communication throughout the value chain?
  - No
    - ESW describes the exposure at the workplace sufficiently
    - Use and handling under the conditions of the ESW is regarded as safe
  - Yes
    - The exposure at the workplace cannot be sufficiently described in the ESW

The ideal World: Initial Hypotheses for Phase-In Substances

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Forced data sharing (Art. 30) :
- **leads to uniform set of NOAELs as starting points**

NOAELs and DNELs made public via Internet (Art. 119) :
- **accessible to all potential registrants**

Obligation to submit all relevant available information (Annexes VII-X) :
- **common knowledge leads to common assessment**

Uniform DNELs for each substance : Consistent level of protection

The real World: Testing the initial Hypothesis

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Forced data sharing (Art. 30) :

- **leads to uniform set of NOAELs as starting points?**

No

- **registrant can opt-out for non-scientific reasons**
- **different substance identity may be claimed**

NOAELs and DNELs made public via Internet (Art. 119) :

- **accessible to all potential registrants?**

No

- **substances with "dual use" (e.g., biocides) may not be reported consistently**

Obligation to submit all relevant available information (Annexes VII-X) :

- **common knowledge leads to common assessment?**

No

- **individual choice of assessment factors (e.g., intra-species or nature and severity of effects) possible**

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Possible Consequences of multiple DNELs

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- Downstream user chooses the supplier with the „better"/higher DNEL
  - Lower technical requirements at the workplace
  - No need to reduce exposure
- Competitive advantages/disadvantages
- Different levels of protection
- Inconsistent communication in the value chain
- Difficult starting point for exposure scenarios, not covered by the CSR
  - Downstream users may have to decide on the „best" DNEL to assess their exposure situation

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DNEL and OEL

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- Derivation of a REACH-DNEL
  - REACH Guidance Document includes the use of default assessment factors
- EU and national OELs are derived following different procedures for extrapolating effects from animals to humans
  - Some scientific committees in Europe also use default assessment factors
    - but factors are not used consistently
  - Some scientific committees in Europe use mainly expert judgement (MAK, SCOEL)
    - or a combination of assessment factors and expert judgement

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Proposed REACH TGD Safety Factors

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Inter-species	Δ in metabolic rate / bw	allometric scaling
	remaining differences	1 to 2.5
Intra-species	worker	5
	general population	10
Exposure duration	subacute → sub/semi-chronic	3
	sub/semi-chronic → chronic	2
	subacute → chronic	6
Dose response	NOAEL, BMD5	1
	LOAEL	3 to 10
	Severity of the effect	expert judgment
Quality of data base	completeness and consistency	1
	reliability of alternative data	expert judgment

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Example for GOOD correlation (SCOEL/DNEL) VINYLACETAT

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NOAEC (rats, mice; 2 years) 50 ppm

For DNEL derivation to be divided by
5 for intra-species variation
2.5 for remaining differences (local effects)

DNEL=**4 ppm**

SCOEL value: **=5 ppm**

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Example for POOR correlation (SCOEL/DNEL) DIETHYLENE GLYCOL(MONO) BUTYLETHER

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NOAEC (rats, 90 days) 15 ppm; 100 mg/m³ (**vapour**)
LOAEC (rats, 90 days) 350 mg/m³ (**aerosol**)

For DNEL derivation to be divided by
2 for time-extrapolation
5 for intra-species variation
2.5 for remaining differences (local effects)

DNEL=**0.5 ppm**

SCOEL value: **=10 ppm**

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Differences between DNEL and OEL

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- The extrapolation procedure used by the different committees in Europe should be transparent and each step should be explained and documented
  - This includes the scientific rationale for using or not using assessment factors, especially if default values are used.
- It is important to note, that default assessment factors are based on experience and not strictly on science and that they may or may not be suitable for a given substance. Therefore, if supportive data are available, they should be taken into account.
  - may also include data from other substances, which are e.g. structurally related, or have the same or similar mechanism of action.
- Only then comparison between an OEL and a DNEL is possible and existing OELs can be used as the basis for DNEL setting as part of the REACH risk assessment

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The Role of OELs in the context of REACH, example 1

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For substance X a new OEL of 5 ppm is established in one country
The exposure at the workplace ranges from 10 to 20 ppm
ESW1 = 10 ppm; ESW2 = 20 ppm

The DNEL established for substance X is 20 ppm
ESW1 and ESW2 are identified as safe use

Additional measures have to be implemented in one country only

Can companies using the substance rely on the information provided by M/I
Are companies not in compliance because of the lower OEL?

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The Role of OELs in the context of REACH, example 2

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For substance X an OEL (ILV) of 50 ppm exists
The maximal exposure at the workplace is 50 ppm

The DNEL established for substance X is 20 ppm
measures to reduce exposure are described

Some companies/users rely on the OEL which has been established by a scientific committee and was adopted by national law

As soon as a harmonized DNEL or safe exposure scenarios are established for a substance under REACH
Is there still a place for OELs?

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A better World: The Case of Classification & Labelling

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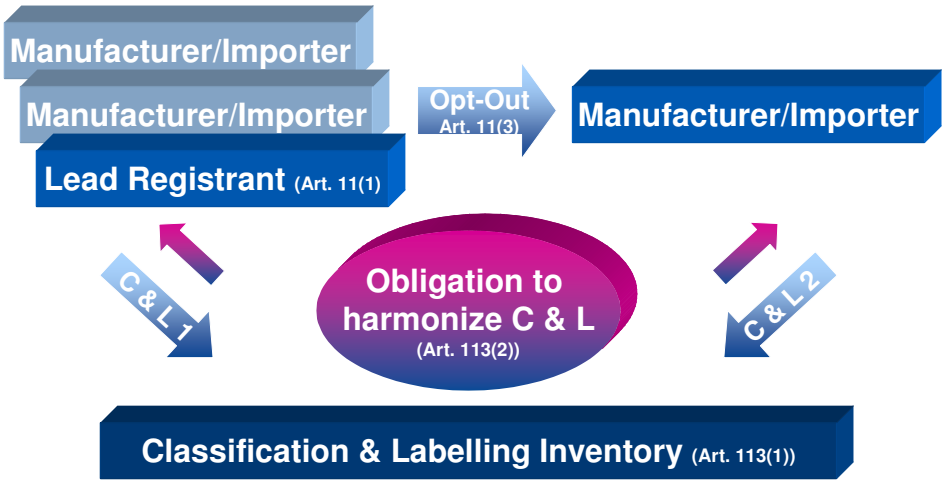

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OELs and REACH Conclusion

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Existing OELs have a role in the interim period before DNELs and safe exposure scenarios are established. They can also be used as basis for DNELs

There are situations where OELs can still be useful, e.g. < 10t, not-manufactured substances (dust, mixtures)

As soon as DNELs and/or safe exposure scenarios are established, OELs should be replaced

Multiple DNELs Summary

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Given the present conditions, no uniform DNELs are warranted under REACH

Situation with C & L is similar, but mechanism for harmonization in place

An Internet-based DNEL inventory could help to facilitate harmonization

Multiple DNELs
Conclusion

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- In case of more than one Chemical Safety Report (CSR) for identical substances, resulting in different DNELs, a process should be in place to harmonize the DNELs
  - In consultation and cooperation with the affected companies
  - Scientific principles should be used to decide on the correct DNEL
  - the harmonization process should be transparent, taking into account all available data and scientific arguments.

→ **There should only be one value for a given substance and exposure scenario in the EU**

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