

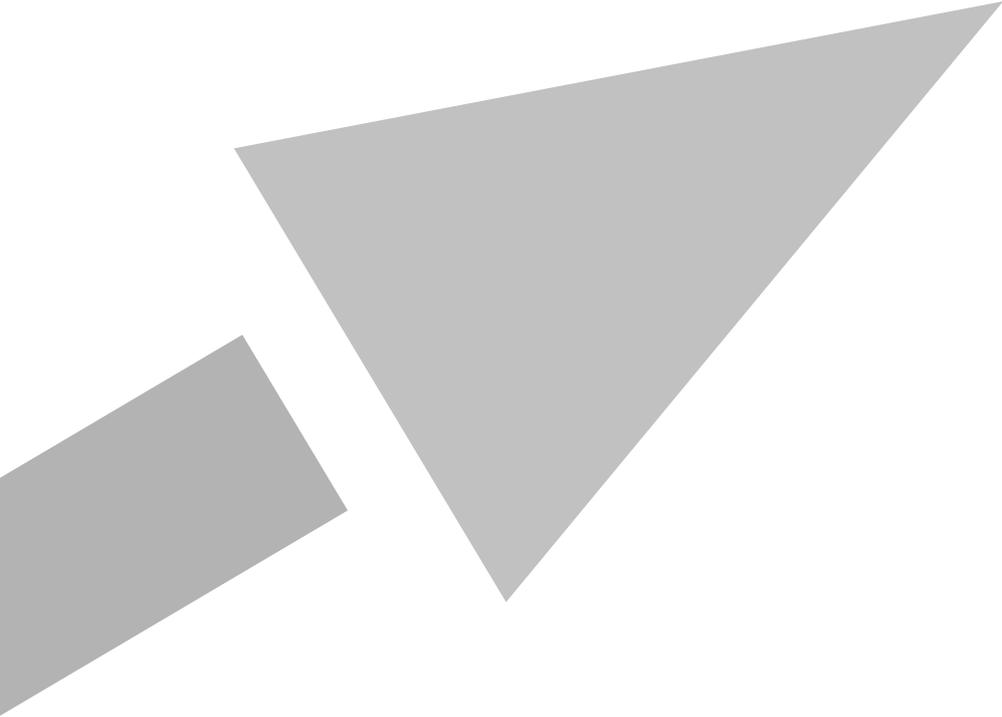
***Workshop on
Guidance on Assessment Factors to
Derive a DNEL***

25 March 2010, Barza d'Ispra

Workshop Report No. 20

Sponsored by the Cefic Long-range Research Initiative





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Guidance on Assessment Factors to Derive a DNEL

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1. EXECUTIVE SUMMARY

Under REACH, chemicals produced in or imported into the EU, in amounts of ≥ 10 tons/year, require detailed registration dossiers including a chemical safety assessment. One key element for the chemical safety assessment is the derived no-effect level (DNEL) which in turn depends upon the point of departure of the hazard assessment and the assessment factor (AF) applied. The REACH 'Guidance on information requirements and chemical safety assessment' (REACH TGD) contains in Chapter R.8 a number of AF for extrapolation of animal data to man that are based on previous experience and convention, and are thus proposed as default values.

Previous ECETOC Task Forces have developed concepts for so-called 'informed' AF based on animal data (TR 86) and for the use of human data (TR 104) to develop AF. A recently convened ECETOC Task Force looked at further published literature to substantiate the proposed informed AF. It also worked examples, based on SCOEL data, in order to show differences in DNEL when applying default or informed AF. The draft report from the Task Force was presented to the Workshop participants that came from regulatory bodies, academia and industry. This report summarises the presentations given at the workshop and the outcome of the discussions.

In conclusion, it was realised that there are some sensitivities regarding the suggestions made and the timing of the report. For some of the issues addressed in ECETOC's draft report, e.g. on the question of the necessary conservatism, it became evident that the positions taken by the different Workshop participants were not far apart and some common ground could be gained. However, for a number of approaches in the REACH TGD and those proposed by the ECETOC Task Force on the justification for the application of informed AF, e.g. the need for a residual AF of 2.5 for remaining overall uncertainty, some of the participants raised the need for more scientific evaluation.

The valuable discussions in the breakout sessions revealed a number of helpful suggestions for improvement of the draft report. Among those were:

- Registrants should be very precise when changing default AF.
- The ECETOC report should demonstrate better where the TGD AF are too conservative.
- The wording in the ECETOC report should also respect this, i.e. not to advise against the TGD default AF. The use of informed AF need to be put appropriately into context.
- A point estimate, i.e. a single AF, does not reflect the distribution of data. Several participants criticised the ECETOC approach since in deriving AF not only scientific considerations are to be taken into account. To decide on the proportion of the population to be protected by a given DNEL a political and societal agreement is required on the necessary level of confidence, or remaining uncertainty, and level of protection.
- Human data should be ranked and weighted in the light of the relevant animal data. Also negative human data can be of relevance, e.g. in the case of irritation and sensitisation.

All of these proposals were taken up into the final report of the Task Force (meanwhile published as Technical Report No. 110).

2. BACKGROUND

The REACH ‘Guidance on information requirements and chemical safety assessment’ (REACH TGD), Chapter R.8 ‘Characterisation of dose[concentration]-response for human health’ proposes a tiered and systematic approach for the delineation of Derived No Effect Levels (DNEL) (and Derived Minimal Effects Levels - DMEL) including the application of assessment factors for extrapolation from animal data to man (ECHA, 2008). A tiered and systematic approach to derive DNEL is supported by industry as a reasonable approach. Nevertheless, it is deemed advisable to provide additional scientific arguments and pragmatic recommendations, which in some cases may diverge from the standard procedure proposed in the REACH TGD.

Chapter R.8 recommends default assessment factors in absence of scientifically justified and chemical-specific ones. To complement these defaults, an ECETOC Task Force has prepared guidance on science-based factors that could be used based upon current knowledge. Examples have been developed on how this approach has been used by SCOEL (EU Scientific Committee on Occupational Exposure Limits) in the recent past.

A parallel project carried out by the Fraunhofer Institute for Toxicology and Experimental Medicine for the detergent’s industry initiative ERASM (Environmental Risk Assessment and Management) produced similar guidance (Batke *et al*, 2010). The ERASM project analysed the RepDose database that contains over 1700 repeat dose toxicology studies.

This Workshop was held to disseminate the approaches developed by the ECETOC Task Force and the ERASM project. Workshop participants were asked to discuss the proposals made and to assess where the science could be further developed in support of the implementation of REACH (EU, 2006a). The primary target audience of the Workshop were those in industry that are directly involved in the preparation of chemical safety dossiers under REACH. Regulators and academics were invited as observers and discussion partners.

The Workshop participants provided valuable feedback which has been incorporated into the final report of the Task Force: ‘Guidance on Assessment Factors to Drive a DNEL’ (published as ECETOC Technical Report No. 110, October 2010). The present report summarises the presentations given and the discussions in the breakout groups and in plenary.

3. PLENARY LECTURES

Hans-Jürgen Wiegand on the role of assessment factors in the REACH process:

REACH requires registration dossiers including chemical safety assessments (≥ 10 tons/year) (EU, 2006a). In these dossiers, exposure scenarios need to be justified against the DNEL based upon hazard assessments addressing:

- Acute or repeated exposure;
- different exposure routes (such as inhalation or skin contact);
- differentiation between systemic and local effects;
- and between workplace and general population exposure.

The publication of the REACH TGD triggered discussion within experts of the chemical industry on whether default assessment factors (AF) of Chapter R.8 may predominantly be applied for substances with limited information, or whether there is any scientific justification for more suitable, data-derived DNEL for substances with a broad information basis. This workshop presented for discussion a practical basis by which industry would be able to justify the application of 'informed' AF as an alternative to those in the REACH TGD, Chapter R.8.

The use of informed AF for hazard and risk assessment is well-established (e.g. Scientific Committee on Occupational Exposure Limits - SCOEL). The report from the ECETOC Task Force that was presented in draft form to the workshop participants contains a number of case studies drawn from SCOEL documentation, and compares the outcome of assessments based on default versus informed AF (ECETOC, 2010; also of interest: ECETOC, 2003; 2009a; 2009b).

The ECETOC approach leads to a scientifically justified procedure in deriving more practical orientated DNEL, whilst still providing the necessary conservatism for the safety of workers and the general public.

George Rusch on the ECETOC approach to assessment factors for DNEL derivation:

In deriving DNEL it is important to consider that they are more than exposure guidelines. In many cases they are comparative estimates of safety. For that reason, it is important to avoid misclassification of a substance as either more toxic or less toxic than it is. Over-classification can lead to choosing other less effective or more costly substances or unnecessary and expensive engineering control costs. When applied to land-use planning scenarios, over-classification could lead to unneeded restrictions. Under-classification can lead to possible exposures to toxic levels of the substance. The REACH TGD provides default AF that should be used when appropriate data is lacking or of limited reliability. Informed AF are based on a more robust data set. The ECETOC approach focuses on application of robust data sets to risk assessment. Most of the default factors were developed when our understanding of chemical toxicity was far more limited than it is today. As such, they were conservative by design.

The ECETOC Task Force reviewed the literature to derive informed AF based on current knowledge of toxicology and pharmacology. This information allowed the Task Force to refine some of the traditional AF. For example, today we know that a rat's metabolism is 4 times faster than a human's and that of a mouse is 7 times faster. Thus, on a mg/kg basis, the rat can metabolise a chemical 4 times faster than humans. We can therefore apply an allometric AF of 4 for rat or 7 for mouse data instead of 10 for both. Also studies of human responses have shown that the variation between normal and sensitive people is typically in the range of 2-5 and rarely more than 6. This again allows for a more precise application of an AF for sensitive members of the population.

In addition to these generalised approaches, having a better understanding of the mode (mechanisms) of action on a chemical-specific basis permits an even better basis for refining AF as does application of PBPK modelling and target tissue dosimetry. The table below on default AF from animal data provides a comparison of the default factors for extrapolation of toxicology data to human risk assessment as given in the REACH TGD and as developed by the ECETOC Task Force. In many cases, the default factors are similar. Where there are differences, the REACH TGD has presented the traditional approach while the ECETOC values are based on a current review of the literature.

Probably the area of greatest difference is the REACH TGD application of a 2.5 toxicodynamic AF for all other differences. The Task Force could not identify any support for this in the literature. Another area where different AF were considered was for simple direct-acting irritants in the area of exposure duration. The REACH TGD presents the same AF as are used for systemic effects while the Task Force recommends an AF of 1. The reason for the Task Force recommendation is that irritation is concentration-dependent and not dose-dependent. In fact, in cases of prolonged exposure, a person usually becomes more tolerant of the exposures. This has been observed in protracted single exposures as well as for workers exposed for many years to irritant gases. The final area where somewhat different values are derived is for intraspecies AF. Here the REACH TGD recommends 5 for workers and 10 for sensitive members of the population. The Task Force recommends 3 and 5, respectively. Many studies (e.g. Calabrese, 1985; Hattis *et al*, 1987; Glaubiger *et al*, 1982) have shown that, even for sensitive members of the population, the variation from the baseline population is rarely more than a factor of 3. Where large epidemiology studies are used, since they will contain sensitive members of the population, an AF of 1 could be used.

In the case of route-to-route extrapolation from oral to inhalation exposure, the REACH TGD would use 2:1. The ECETOC Task Force conducted a review to determine what the best values for this type of extrapolation should be. It also looked into the correct ratios for scaling from sub-acute to sub-chronic to chronic.

A final point that must be considered when combining adjustment factors is the resulting conservatism from multiplication of these numbers. Each uncertainty factor is designed to include sensitive members, who represent a minority of the population. As a result, these uncertainty factors are conservative. At the 95% confidence level, there is only a 5% chance that

the effect would not be covered by the factor. This does not mean that 5% of the population will develop the effect. If three AF, each at 95%, are combined, the chance that the effect will be covered is >99.99% and the chance that the effect will not be covered is 0.000125 (i.e. $0.05 \times 0.05 \times 0.05$). Likewise if two AF, each at only 90%, are combined, the chance that the effect will be covered will still be 99%. Therefore, even if one factor did not reach 95%, because the limits were too wide, the resulting risk assessment would still be conservative.

Default assessment factors from animal data (cited from: ECETOC, 2010)

Assessment factors – accounting for differences in: (page numbers in brackets refer to the REACH TGD)		Systemic effects		Local effects (inhalation)	
		REACH TGD	ECETOC	REACH TGD	ECETOC
Route-to-route extrapolation (p. 24-28)	Oral to inhalation	2			
	Inhalation to oral	1	(no proposal)		
	Oral to dermal	1			
	Dermal to inhalation Inhalation to dermal	} case-by-case			
Interspecies (p. 29-33)	Correction for differences in metabolic rate (allometric factor) 'Remaining differences'		Rat → humans 4 Mice → humans 7 2.5	4 7 in total allometry	1 1 2.5
Intraspecies (p. 33-34)	Worker	5	3	5	3
	General population	10	5	10	5
Exposure duration (p. 34-35)	Sub-acute to sub-chronic*	3	3	3	1
	Sub-chronic to chronic	2	2	2	1
	Sub-acute to chronic	6	6	6	1
Dose-response (p. 35-36)	Reliability of dose-response, LOAEL/NAEL extrapolation and severity of effect	≥1 3 (in majority of cases) → 10 (in exceptional cases)	3	≥1	
Quality of whole database (p. 36-37)	Completeness and consistency of available data	≥1		≥1	
	Reliability of alternative data (e.g. read-across)	≥1		≥1	

* These factors are implied

In summary, it is felt that available data can be used to refine the approach to conducting robust risk assessments and developing science based AF. Also, even if the range covered by a single AF varies slightly from the 95% level, the result of multiplying AF will increase the conservatism of the final risk assessment and still be protective.

Inge Mangelsdorf on the outcome of the ERASM project:

Within the ERASM project, extrapolation factors (EF) were re-evaluated based on the Fraunhofer ITEM in-house database RepDose, initially sponsored by the Cefic Long-range Research Initiative (Batke *et al*, 2010; Escher and Mangelsdorf, 2009; Bitsch *et al*, 2006).

For the first time, a tiered approach was used to derive EF for time, species and route based on NOEL or, if not available, on LOEL ratios. The tiered approach started with a 'study level' that included all available studies meeting the general conditions, followed by a 'chemical level' with one EF per chemical based on the most sensitive and reliable studies. Finally an 'expert level' was set up based only on NOEL ratios of comparable studies with regard to dose-spacing, scope of examination, target organs and - if possible - strain and author. By applying this approach the amount of data was reduced in each step, while the reliability of the derived EF was increased.

Overall, the data sets derived in this project are robust, as narrow time frames close to the OECD guidelines were used for study durations, only the same routes of administration were compared, and either the same rodent species was used or allometric scaling was applied. Furthermore, the studies included are based on a variety of peer-reviewed sources, omitting a laboratory- or author-specific data set which would not reflect how risk assessment is often carried out.

For all distributions it was observed that the variance is reduced from the 'study level' to the 'expert level' as geometric standard deviations (GSD) as well as 90th percentiles decreased.

Time-EF for oral studies were 1.5, 3.1 and 1.4 for sub-acute to sub-chronic, sub-acute to chronic and sub-chronic to chronic based on the geometric means (GM) and 5, 13 and 3 based on the 90th percentiles, respectively. The results for time extrapolation for inhalation studies showed a trend to lower GM, geometric standard deviations (GSD) and 90th percentiles compared to oral exposure but more adequate studies are needed for refinement.

The results for interspecies extrapolation supported allometric scaling. The GM of the 'expert level' dataset of the comparison of oral rat and mouse studies could be transferred to factors of 4 for rat to human and 7 for mouse to human extrapolation. The GM of 1 observed for the distribution of inhalation studies of rats and mice was also expected, if only allometric differences have to be taken into account.

For route-to-route extrapolation, local toxicity is not comparable for oral and inhalation studies. Within the ERASM project, systemic NOEL were derived for all studies based on affected organs. The GM of oral-to-inhalation extrapolation was between 1.5 and 0.6 for the different

levels of the tiered approach. Within the tiered approach, the 90th percentiles decreased from 45 to 5. In the 'expert-level' data set it was observed that the EF depend on the toxicity of compounds: low toxic compounds would need a high factor (> 6), medium toxic compounds a medium factor (about 3) and toxic compounds no further factor (equally toxic in inhalation and oral studies). For a final decision on route-to-route extrapolation, more adequate studies are needed.

Overall, the factors derived with RepDose are lower than factors proposed for REACH. But still some questions remain: Is the GM the best measure? Can factors be specified depending on toxicity or physico-chemical parameters?

Dieter Beyer on default assessment factors versus expert evaluation (SCOEL):

The REACH TGD recognises that the use of 'informed' AF is preferred over 'default' AF wherever possible, whether supported by substance-specific data or, for example, by read-across to other chemicals or mechanisms of action. The use of informed AF for hazard and risk assessment is well-established and has been used for many years by organisations such as SCOEL and national competent authorities to set occupational exposure limits.

SCOEL evaluates the toxicological data on chemicals as requested by the EU Commission and proposes Occupational Exposure Levels (OEL). If the data base leads to the conclusion that it is possible to identify a clear threshold-dose below which exposure to the substance is not expected to lead to adverse effects, SCOEL is able to propose health-based indicative occupational exposure limit values (IOELV). A single informed uncertainty factor (UF) is applied based on a weight-of-evidence approach taking into account all data obtained for humans and experimental animals.

The Task Force examined 25 summary documents prepared by SCOEL (substances which are included in the second and third IOELV list; EU, 2006b; EU, 2009) and compared IOELV and UF proposed by SCOEL with DNEL derived by default AF as per the REACH TGD (ECHA, 2008; 2010) and DNEL derived by applying AF as per ECETOC TR 86 (2003).

For many substances (irritant chemicals as well as those with systemic effects) the hazard properties are systematically overestimated by DNEL derived using the REACH TGD default approach. The discrepancies between DNEL and IOELV were summarised and discussed.

The following approach was followed by the Task Force for each compound:

- Identify relevant dose descriptor as defined by SCOEL;
- modify starting point according to REACH TGD or ECETOC (no compound-specific information was considered in these steps);
- apply default assessment factors according to REACH TGD or ECETOC (no compound-specific information was considered in these steps);

- calculate AF and DNEL according to REACH TGD or ECETOC (long-term; worker) and compare to UF and IOELV.

SCOEL did not modify the starting point. Using the REACH TGD modification of starting point often resulted in a modified N(L)OAEC of approximately half the experimental value.

Six substances were identified, where the SCOEL IOELV was based upon systemic effects in animals, and a further six substances, where it was based upon local effects in animal studies. In nearly all cases, in which the IOELV was based upon systemic effects, the overall AF applied by SCOEL was lower than the recommended one by the REACH TGD. In only one of these cases, i.e. pyrethrum, it was higher than the one proposed by ECETOC. In the case of pyrethrum, there was no relevant inhalation study in humans or animals upon which to base the IOELV assessment. SCOEL was, however, able to apply an informed AF based upon substance-specific ADME data showing marked route-to-route differences. In all six cases, in which the IOELV was based upon local effects in animal studies, the overall AF applied was substantially lower (between 10- to 20-fold) than that of the REACH TGD and lower (1- to 3-fold) than those proposed by ECETOC.

In many examples, the SCOEL documentation does not enable the identification of the applied individual factors because they use an overall weight-of-evidence approach taking into account all data obtained for humans and experimental animals. But the comparison shows that applying the default AF of the REACH TGD to both local and systemic effects in a standardised manner often leads to a situation where the resulting DNEL would be one order of magnitude lower than the IOELV. Considering that IOELV have been established by an independent scientific expert committee and are meant to be protective of worker health, the REACH TGD approach appears conservative. There is a strong indication that the differences between IOELV and DNEL are in part due to differences in interpretation with respect to modification of the starting point and to how to apply the combined factors of inter- and intraspecies variability.

In addition to the modification of the starting point, a possible explanation for differences in the interpretation of health outcomes may be correlated to the residual factor of 2.5 and to the combined inter- and intraspecies AF of 12.5 (excluding allometry) proposed by REACH TGD. Since the overall UF applied by SCOEL are in the range of 1-4 for the majority of examples and an UF > 12.5 was applied for a single compound only, the Task Force concluded that SCOEL did not consider a factor for 'additional uncertainty' or 'intraspecies' for derivation of an IOELV. It may be argued that the IOELV were derived for data-rich chemicals using 'informed' AF. Generally, even for such substances no robust information is available that would allow omitting a combined AF of 12.5. The Task Force concluded that the approach of SCOEL argues against the use of this conservative combined AF irrespective of the completeness of the data base.

Overall, the Task Force concluded that modification of the starting point and REACH TGD's default AF result in DNEL which are substantially more conservative (average 20-fold) than the IOELV obtained from expert judgement after assessment of the whole database.

4. BREAKOUT SESSIONS

The Workshop participants discussed in breakout groups specific questions under three broader themes. The following provides their reporting as given in plenary.

4.1.1 Breakout Group I

Role of assessment factors in the process of chemical risk assessment and the consequences of default or informed factors

Chair: George Rusch

Rapporteur: Annette Wilschut

Other members of the breakout group: Ulrike Bernauer, Pauline Bingham, Laurent Bodin, Frans Christensen, Eliot Deag, Jeff Fowles, Bruno Hubesch, Sylvia Jacobi, Fritz Kalberlah, Reinhard Kreiling, Inge Mangelsdorf, Nils Krüger, Mandy Osterloh-Quiroz, Mark Pemberton, Sandra Schäfer, Dirk Schwartz, Steve Williams

Question: *Which are the areas of risk assessment where conservatism or default give rise to greatest concerns, and what can be done about them?*

- Exposure assessment is a major concern because for many substances measured data are not available.
 - Do not focus only on the default factors discussion.
 - Low-volume/data-limited substances will be considered as more highly toxic because of lack of data -> stop search for alternatives.
 - Perception of risk – if all substances were considered highly toxic, the real toxic ones will not be recognised (apathy).
 - Sensitive sub-populations (children) – industry should provide regulators with answers to these questions.
 - Start a multi-stakeholder process for development of revised assessment factors; agree on definitions (including how much protection we want to achieve); develop a common understanding of the process.
 - Benefit of developing a training protocol that should include both regulators and industry.
 - Acceptance of read-across: Looking at both hazard and exposure assessment.
- improve: we will ALL benefit!

Question: *What is the impact of the multiplicity of assessment factors (consider MLE vs. UCL, BMD vs. BMDL etc.)?*

- Only applicable for data-rich substances.

4.1.2 Breakout Group II

Derivation and application of assessment factors based on animal data

Chair: Dieter Beyer

Rapporteur: Erik Rushton

Other members of the breakout group: Marco Binaglia, Tialda Bouwman, Monica Dia-Ducruet, Aurelie Droissart-Long, Frederic Frère, Heinz-Peter Gelbke, Christa Hennes, Petra Kern, Mounq Sook Lee, Gary Minsavage, Daria Pakulska, Marja Pronk, Marion Schütte, Gerrit Schüürmann, Claudia Sehner, Hans-Jürgen Wiegand

Question: *Which assessment factors are going to be most useful in deviating from default assumptions and why?*

- The issue is not only the assessment factors but also the method of combining them.
 - Multiplication introduces variability much greater than the variability/uncertainty in the actual value.
 - A probabilistic approach should be applied to derive an empirical value – one simplistic approach may be to apply the geometric mean to help normalise differences.
- The position was discussed that the remaining difference of 2.5 is not scientifically justified. Likewise is the applicability of the value of 5 for workers.
 - This factor of 2.5 is arbitrary and its value could range from 1 to much greater.
- Another issue that needs to be addressed is what level of safety we are willing to accept – which impacts the AF.

Question: *How much data are needed to be able to deviate from default assessment factors?*

- Two approaches:
 - Evaluate the data used by ECETOC to derive defaults; if they are appropriate for the substance in question, then some justification for these values.
 - A probabilistic evaluation is needed to determine the quality of the data, in addition to quantity.

Question: *Should a DNEL be derived if there are no adverse treatment-related findings in animals up to the limit dose? Should the limit dose be taken as the NOAEL/NOAEC, or should it be concluded that a DNEL cannot be quantified?*

- A DNEL may be required for the substance; however for the endpoint in question at the limit dose, it does not appear scientifically appropriate to derive a DNEL.

4.1.3 Breakout Group III

Derivation and application of assessment factors based on human data and on use of existing exposure limits

Chair: Peter Boogaard

Rapporteur: Marie-Louise Meisters

Other members of the breakout group: Pauline Bingham, Sophie Duhayon, Andreas Flückiger, Rudolf Jäckh, Gary Jepson, Paul Bo Larsen, Bernd Märker, Reuben Mascarenhas, Chris Money, Christoph Müller, Benoit Nihoul, Dirk Pallapies, Iona Pratt, Carlos Rodriguez, Katrin Schmallenbach, Volker Soballa

Question: *Why are human data different to animal data, and is all of industry well positioned to judge human data?*

- Are they different?
- Data are not really different but are treated differently in the guidance.
- Should we consider ‘soft human data’ to be used in regulations? Also when used at low concentrations?
- For prominent effects ‘soft data’ are sufficient (e.g. sensitisation) but not for more subtle effects.
- ‘Soft data’ in humans cannot overrule animal data. The same applies for carcinogenicity data.
- With good knowledge of mode of action even ‘soft human data’ can be useful.

- GRAS system not useful for REACH because if you never looked for effects then you do not find them.
- Amount of human data is usually less than animal data.
- Monitoring data on workforce are useful for RA if you are aware of exposure levels, and if you monitor well you can also use negative human data.
- Some human effects are not picked up in the workforce because development is too slow.
- Asbestos: should we test always the human route of exposure?
- Oversight of REACH is that it does not provide anything on exposure characterisation.
- Registry of epidemiology studies, also negative ones, with Klimisch codes: strong bias as no negative data are reported. Should be improved human data.
- Can human data be more exploited? What about read-across? Not discussed. Pointing out that it works one way but not the other way?

- Strict design for animal data, not for human data. It is a shortcoming and PEG should focus on how to use human data.
- In animal studies, the most sensitive endpoint is defined. For human data, it is the most visual and obvious one, not the most subtle.
- Way forward is to investigate proactively possible effects in workforce and consumers.
- Better use of occupational medicine data if available and accessible.

Question: *What approach should be taken to use SCOEL values or existing exposure limits, the individual exposure limits and/or the underlying science?*

- SCOEL is comparing OEL and DNEL.
- Implementing DNEL would induce a change in technology due to their low levels.
- Underlying science can be useful as point of departure for DNEL_{general population}.

Question: *Can occupational exposure limits as derived by SCOEL also be used as point of departure to derive DNELs for the general population and, if so, how?*

- It is mostly not possible. OEL are focussed on inhalation, not so useful for general public.
- Not only applicable to occupational setting since you can use arguments in both directions. SCOEL is point of departure.
- If there are substance-specific data you should use them. With workers you have a recovery period but not with general public. You need to justify if doable.
- Guidance allows for extrapolation between routes. Air quality standards could be used.

- Specific chemicals with OEL can end up in consumer products, therefore important for general public too (e.g. solvents).
- OEL have limited analysis, e.g. reprotox is underexplored in SCOEL but big issue in REACH.
- Always make distinction between variability and uncertainty.
- AF are convenient, AF describe variability and uncertainty; AF are substance-dependent; idea influenced by dataset. Boundary conditions need to be more clearly set.

- Can you address all these points in reality? Goal of REACH is to eliminate bad substances otherwise you should classify everything; for benzene, the only problem is in humans.
- We have to use OEL. REACH requests all available data to be used. Current guidance is deficient in this respect, therefore new draft. Human data are very different in quality but still very useful. Look at human data in weight of evidence approach for REACH.
- Use data that are available, also human data.
- New IUCLID 5 which better reports human data.
- Incidences in humans should be followed up with better data; also information from light incidences (irritation) should be reported and published for a better use.

4.1.4 Question posed to each of the groups:

What should be the process of the future review and updating of assessment factors in light of new information, e.g. from REACH?

- Use and analyse in multi-stakeholder process.
- Both for exposure assessment as well as for hazard assessment.
- NB. Specific comments to improve report, especially SCOEL.
- Who decides on revision of guidance? ECHA should have this overview.
- More data available to work with after first REACH registrations.
- Applying REACH approach for every chemical at RAC will create a problem? Scientific knowledge needs interpretation. Is it ECHA's responsibility to signal problems?
- What kind of data do we need in order to modify AF? More focussed way by ERASM.
- More targeted would be to group substances as in the analysis shown by ERASM.
- How do you know when you are above the DNEL compared to exposure levels?
- We don't because there is no legal requirement. Is risk communication the challenge?

4.1.5 Discussion

The following key points were made during the discussions in plenary, i.e. following the presentations and the reports from the breakout groups.

- Registrants should be very precise when changing default AF. This would only be possible with chemical-specific data and after consultation with authorities.
- The ECETOC report should demonstrate better where the TGD AF are too conservative. It might have been useful to raise such arguments at the time of the writing of the REACH TGD when industry was present.
- It is important to ensure a sufficient level of conservatism. The wording in the ECETOC report should also respect this, i.e. not to advise against the TGD default AF. The use of informed AF need to be put appropriately into context. The response was that misleading phrasing in the report would be changed.
- For data-rich chemicals, the factor 2.5 for remaining uncertainties is not needed. But this needs to be evaluated more closely. Also the AF of 5 for worker intraspecies variability should not be needed, compared to SCOEL.
- A point estimate, i.e. a single AF, does not reflect the distribution of data. Several participants criticised the ECETOC approach since in deriving AF not only scientific considerations are to be taken into account. To decide on the proportion of the population to be protected by a given DNEL a political and societal agreement is required on the necessary level of confidence, or remaining uncertainty, and level of protection.
- Human data should be ranked and weighted in the light of the relevant animal data. Also negative human data can be of relevance, e.g. in the case of irritation and sensitisation.

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ABBREVIATIONS

ADME	Adsorption, distribution, metabolism, excretion
AF	Assessment factor
BMD	Benchmark dose
BMDL	Benchmark dose, lower confidence level
DMEL	Derived minimal-effect level
DNEL	Derived no-effect level
EEC	European Economic Community
ECHA	European Chemicals Agency
EEC	European Economic Community
EF	Extrapolation factor
ERASM	Environmental Risk Assessment and Management
EU	European Union
GM	Geometric mean
GRAS	Generally recognised as safe
GSD	Geometric standard deviation
IOELV	(EU) Indicative occupational exposure limit value
IUCLID	International Uniform Chemical Information Database
L(O)AEL	Lowest (observed) adverse effect level
MLE	Maximum-likelihood estimation
N(O)AEC	No (observed) adverse effect concentration
N(O)AEL	No (observed) adverse effect level
OECD	Organisation for Economic Co-operation and Development
OEL	Occupational exposure limit
OELV	Occupational exposure limit value
RAC	(ECHA) Risk Assessment Committee
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SCOEL	Scientific Committee on Occupational Exposure Limits
TGD	Technical guidance document
UCL	Upper concentration limit
UF	Uncertainty factor

APPENDIX 1: WORKSHOP PROGRAMME

8.30-9.00	Registration	
9.00-9.10	Welcome	Christa Hennes, ECETOC
9.10-9.30	Introduction on the Role of Assessment Factors in the REACH process	Hans-Jürgen Wiegand, Evonik Industries
9.30-10.00	Assessment factors for DNEL Derivation: An ECETOC Approach	George Rusch, Honeywell
10.00-10.30	Scientific Basis for Safety Factors – Re-Evaluation with RepDose	Inge Mangelsdorf, Fraunhofer ITEM
10.30-11.00	Coffee break	
11.00-11.30	Default Assessment Factors versus Expert Evaluation: What can we learn from SCOEL?	Dieter Beyer, Bayer Schering Pharma
11.30-12.00	Plenary Discussion / Introduction to Breakout Groups	Moderator: Mark Pemberton, Lucite International
12.00-13.00	Lunch	
13:00-14:30	Breakout group sessions	
	Group I	Role of assessment factors in the process of chemical risk assessment and the consequences of default or informed factors Chair: George Rusch / Rapporteur: Annette Wilschut
	Group II	Derivation and application of assessment factors based on animal data Chair: Dieter Beyer / Rapporteur: Erik Rushton
	Group III	Derivation and application of assessment factors based on human data and on use of existing exposure limits Chair: Peter Boogaard / Rapporteur: Marie-Louise Meisters
14.30-14.45	Coffee break	
14.45-15.45	Reports from the three breakout groups/ Plenary discussion	Moderator: Mark Pemberton, Lucite International
15.45-16.00	Outlook and Close of the workshop	Hans-Jürgen Wiegand, Evonik Industries

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No. 3	Use of Human Data in Risk Assessment. 23-24 February 2004, Cardiff
No. 4	Influence of Maternal Toxicity in Studies on Developmental Toxicity. 2 March 2004, Berlin
No. 5	Alternative Testing Approaches in Environmental Risk Assessment. 7-9 July 2004, Crécy-la-Chapelle
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No. 17	Significance of Bound Residues in Environmental Risk Assessment. 14-15 October 2009, Brussels
No. 18	The Enhancement of the Scientific Process and Transparency of Observational Epidemiology Studies. 24-25 September 2009, London
No. 19	'Omics in (Eco)toxicology: Case Studies and Risk Assessment. 22-23 February 2010, Malaga
No. 20	Guidance on Assessment Factors to a Derive DNEL. 25 March 2010, Barza d'Ispra

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Established in 1978, ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) is Europe's leading industry association for developing and promoting top quality science in human and environmental risk assessment of chemicals. Members include the main companies with interests in the manufacture and use of chemicals, biomaterials and pharmaceuticals, and organisations active in these fields. ECETOC is the scientific forum where member company experts meet and co-operate with government and academic scientists, to evaluate and assess the available data, identify gaps in knowledge and recommend research, and publish critical reviews on the ecotoxicology and toxicology of chemicals, biomaterials and pharmaceuticals.