ECHA
EUROPEAN CHEMICALS AGENCY

Technical Agreements for Biocides

Human Health (TOX)

Version 2.0, November 2018

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Preface

The Technical Agreements for Biocides (TAB) intends to provide in a concise format the general agreements of the Working Group (WG) which have not yet been included in any other BPR related guidance documents.

This document is intended to cover the technical/scientific WG agreements that have general relevance and to create a general database of questions where an agreement has already been reached. Only agreements of general relevance have been included.

The TAB is publicly available on the ECHA website and on the public S-CIRCABC Interest Group[1].

The answers presented in the document are those agreed by the WG. They are not the official view of ECHA, nor are they legally binding. It is not an authoritative source of information, and when in doubt, the original documents cited should always be consulted. The main sources for the TAB are the adopted minutes of the WG, and in all cases, a reference is given to the WG meeting or the Technical Meeting (TM) where the agreement was reached.

Starting from TAB Version 2.0 there is a separate document for each WG.

Procedure

TAB does not require a formal endorsement by the Biocidal Products Committee or the WG because the document records agreements made at the WG and included in their minutes. It is a living document that will be updated over time. Any suggestions on the need to change the content can be sent at any time to BPC-WGs@echa.europa.eu.

The text will be updated regularly by uploading a revised version in the Newsgroups of the BPC-WG S-CIRCABC site for a commenting period of 4 weeks for the WG members. After the commenting period, ECHA will revise the TAB if necessary, and publish it on the ECHA website. The procedure does not involve discussions at the WG. However, the TAB entry may be discussed at the WG if necessary.

[1] https://webgate.ec.europa.eu/s-circabc/w/browse/ae26a5d2-a19b-42b8-a173-19bef3375d49

Human Health

1 Dermal absorption

TOX 1 **If a biocidal product is applied directly on human skin, should other products that may be applied on the skin at the same time be taken into account? Such products could enhance the dermal absorption of the biocidal product.**

(TM I 2009)

Enhanced dermal absorption due to simultaneous application of a product other than the biocidal product in question should not be considered at active substance approval stage. If information of such interactions is available, it should be included in the CAR under *Elements to be taken into account by MSs when authorising products*.

TOX 2 **Derivation of dermal absorption values.**

(TM II 2012)

Detailed information should be provided by the Evaluating Competent Authority (eCA) on the dermal absorption value(s) in the LOEP. This should indicate how the value(s) was derived (in vitro and/or in vivo studies) and what exactly was tested (concentration of the a.s. and type of formulation). The text should also indicate the basis of the applicability of such values to the representative product (both the concentrate and the in-use dilution). This information is crucial at the product authorisation stage when a decision is required whether the dermal absorption values established in the LOEP can be extrapolated to other products.

TOX 3 **Dermal absorption value of dried dispersed residues**

(WG-III-2017)

The appropriate dermal absorption value of dried dispersed residues should be the higher of the values for the concentrate and the in-use dilution (EFSA Guidance on dermal absorption (2017)).
Note: The WG discussion referred to EFSA Guidance (2012) but the approach is identical in the guidance of 2017.

2 Reference values and assessment factors (AF)

TOX 4 **How should reference values be rounded?**

(WG-IV-2017)

For the rounding of reference values (AEL, AEC, ADI, ARfD), the principles should be applied that are presented on pages 24-25 of the EFSA Opinion *Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured Data*; EFSA Journal 2012;10(3):2579 (https://www.efsa.europa.eu/en/efsajournal/pub/2579): "*Derived values, such as health-based guidance values, should be rounded to a*

single significant figure if the impact of rounding is less than 10%, and to two significant figures if the impact of rounding to one significant figure exceeds that percentage. Rounding should happen as late as possible in the assessment process."
This agreement concerns reference values that are normally derived from NOAEL/NOAEC values by applying assessment factors. It does not concern measured values such as absorption values or NOAEC/LOAEC values used in e.g. local risk characterisation.

TOX 5 Is it acceptable to have different AELs for professionals and non-professionals?

(WG-IV-2014; TM III 2013)

It is in general not acceptable to have different AELs for professionals and non-professionals. However, when there is information related to age specific kinetic differences, different AELs can be set for professionals and non-professionals.

This exception was accepted in TM III 2013 for a specific substance for which it had been shown via PBTK modelling that variations in toxicokinetic dose metrics averaged during different life stages (from birth to 75 years of age) and were within a factor of 2 for all age groups (0-75 y) and within a factor of 1.2 for 5 to 75 years of age. The toxicokinetic AF of 3.2 was substituted with a chemical specific of AF 2 for the general population resulting, together with a toxicodynamic AF of 3.2, in an overall intraspecies AF of 6.4. Similarly for professional workers, a chemical specific AF of 1.2 resulted in an overall intraspecies AF of 3.8.

TOX 6 Should developmental studies be used for AEL derivation if their NOAEL is the lowest available?

(MOTA v.6)

When valid developmental studies are available, all relevant critical effects should be evaluated together with other observations from other studies. If the NOAEL derived from relevant effects in a valid developmental toxicity study is lower than those from short-term and long-term studies, and this cannot be explained by dose spacing, the NOAEL from the developmental toxicity study should be used for the derivation of the AEL value. This will apply to the global population (thus protecting both pregnant and non-pregnant women).

Developmental studies are often the only studies to use gavage dosing with the aim of determining a NOAEL. This can give rise to C_{max} related effects, such as certain clinical signs, that might not be relevant to dermal exposures where a spike of absorption is not normally seen.

It should be noted that due to their inherent limitations, developmental studies cannot be considered as surrogates for other repeated-dose toxicity studies when these are missing or invalid.

TOX 7 In case where a risk characterisation is based on a maternal effect, should the intra-species factor remain at 10 or should it be reduced for taking into account the higher sensitivity of the pregnant subpopulation?

(MOTA v.6)

There is no evidence that pregnant women are always more sensitive than the rest of the population. The AEL derived from maternal effects will cover the whole population, and the intra-species factor is 10 unless there are specific reasons to deviate from this.

TOX 8 Should an extra AF be added for using a 1-year dog study in deriving the long-term AEL?

(TM IV 2009)

No extra AF is normally necessary, since a 1-year dog study should be considered sufficiently chronic for deriving the long-term AEL without additional AFs, unless there is a clear justification to the contrary.

TOX 9 PT 14: Which studies can be used in setting the acute AEL for anticoagulant rodenticides?

(TM II 2007)

The general problem in selecting the appropriate study for anticoagulants is that, in general, acute studies are not suitable for setting AELs due to the cumulative effect of anticoagulants. In terms of exposure and study duration, teratogenicity studies in the existing dossiers have been more relevant for AEL setting, and the developmental study in the most sensitive species should be used.

TOX 10 PT 14: If subchronic studies are used for chronic scenarios of anticoagulant rodenticides, will an extra assessment factor be needed? Which AF would then be appropriate?

(TM I 2007)

The AF will depend on the available data set, and the decision will have to be made case by case. If an extra AF is concluded to be necessary, a factor of 3 is considered sufficient to provide safe margins to cover for the use of subchronic studies for chronic exposure scenarios.

This agreement is maintained although the current default value is 2 for extrapolation from subchronic studies to chronic exposure (Guidance for Human Health Risk assessment part B).

TOX 11 Is there an agreement on using an extra AF for anti-vitamin K (AVK) anticoagulants for the severity of the effect?

(TM III 2006)

An extra AF of 3 will be used for all AVKs, while it was recognised that this factor is not scientifically derived.

TOX 12 How should the systemic AELs be derived for pyrethroids, given that there is extensive first pass metabolism following oral administration?

(TM III 2009)

When appropriate data exists for dermal and inhalation routes, this data should be used to derive route-specific systemic AELs, rather than using oral data and route-to-route extrapolation. Extrapolation would be problematic due to extensive hepatic first-pass metabolism.

This approach requires that 1) appropriate route-specific data is available, and 2) large first-pass metabolism is demonstrated or likely.

3 Local risk assessment

TOX 13 Is local risk assessment necessary for substances that are classified for local effects but are present at concentrations that do not trigger classification of the product?

(WG-II-2018)

According to ECHA Guidance Vol III Parts B+C, risk characterisation for local effects is triggered only when the biocidal product is classified for local effects. It is however considered that the assessment of local effects may be useful in several situations reflected below.

A qualitative local risk assessment (LRA) would not be required if classification is not triggered. However, if a relevant NOAEC/LOAEC is set for the active substance, a quantitative or semi-quantitative LRA may provide valuable information regarding the possible effects expected due to the use of a biocidal product. The following principles apply for each route of exposure, provided that the route is relevant for human exposure:

- For the inhalation route, a quantitative LRA should be performed whenever possible, i.e. whenever an inhalation AEC is derived for local effects.
- For the oral route, the possibility of performing a semi-quantitative or quantitative LRA should be considered for local effects on a case by case basis. The most relevant assessment would usually be expected to be either qualitative or semi-quantitative and not quantitative because the effects will depend on a number of parameters such as concentration, dosing system, exposure time and the frequency of exposure, and furthermore, the experimental design would most often not be corresponding to human oral exposure.
- For the dermal route, a semi-quantitative LRA should be performed. The assessment should include information regarding NOAEC/LOAEC for local effects and should also provide information regarding the expected dermal effects in the exposure situations, taking into account the amount and concentration to which exposure takes place, as well as the frequency and duration (descriptive approach). The nature of the expected effects should be considered together with exposure considerations in deciding whether PPE or RMMs are required to limit the effects.

In selecting the most relevant study results for setting the NOAEC/LOAEC for local effects, considerations should be given to the dosing that should optimally resemble the expected human exposure in terms of amount, concentration, frequency and duration. The identification of a NOAEC/LOAEC in a given study may not be relevant for the risk characterisation if the study setup is such that the information is not useful for the assessment of human exposure situations. This could be the case if the effects are only seen in conditions that are not relevant for human exposure, such as repeated exposure at high concentrations under occlusive dressing. The assessment should take into account the differences in the formulation tested (usually the active substance in a vehicle) and the formulation of the product. The NOAEC seen in testing should be considered relevant for the product unless there is information to the contrary.

TOX 14 Should dermal AEC values be derived based on local dermal effects?

(WG-II-2018)

Local dermal effects seen in the studies and/or expected to take place in humans should be described and a NOAEC/LOAEC, usually expressed as a percentage concentration, should be provided.

A dermal AEC should normally not be derived, as it is preferable not to set a defined limit for acceptable exposure due to local dermal effects. An AEC would express a concentration above which the use would become unacceptable, and setting this level below a NOAEC could be questionable. Furthermore, the usefulness of the information available from animal studies may be limited because the study setup would not necessarily reflect the human exposure situation. However, where appropriate information is available regarding cumulative dermal effects and this information is considered relevant for humans, an AEC could be derived.

Normally the RC for dermal effects should be based on the NOAEC/LOAEC (usually expressed as a percentage concentration), and the acceptability of a scenario will be decided case by case using all the available information.

TOX 15 For the derivation of local reference values, is it possible to deviate from the default value in setting an assessment factor (AF) for intraspecies difference?

(WG-V-2015)

When reference values are set based on animal studies and there is no information of effects in humans at similar dose/concentration levels, the intraspecies AF should normally be 10.

When setting the intraspecies AF based on human data, normally the dynamic factor of 3.2 should not be changed. The kinetic factor 3.2 cannot be excluded if the study population is small and no sensitive populations are studied.

It is nevertheless possible to set an intraspecies AF lower than 10 (e.g. 3.2) even when dynamic and kinetic differences cannot be excluded, taking into account factors such as mode of action (e.g. pH-related irritancy at the first site of contact and no local metabolism involved) and low severity of the effects at LOAEC.

4 Specific toxicological effects

TOX 16 How should unpalatability be considered when the NOAEL is set based on reduced body weight gain?

(WG-II-2014)

Reduced body weight gain should usually be considered as an adverse effect and as a basis for setting the NOAEL. Although unpalatability may contribute to the reduced body weight gain, it should be clearly shown that there is a causal relationship between reduced palatability and reduced bodyweight gain/food consumption. If the effect is present also in e.g. gavage or inhalation studies, it cannot be explained by unpalatability.

TOX 17 Should emesis (e.g. in dogs) be considered as an adverse effect and used as a basis for setting the NOAEL?

(WG-V-2014)

Emesis is considered as an adverse effect and can be used as a basis for setting the NOAEL.

TOX 18 How should hepatocellular hypertrophy, enzyme induction and liver weight increases be interpreted in toxicological studies in rodents?

(WG-IV-2018)

Liver cell hypertrophy and liver weight increase should be considered as potentially adverse effects. However, on a case-by-case basis, hepatocellular hypertrophy leading to ≤15% increased mean absolute or relative liver weight, should not be regarded as adverse, and should not be used for the purpose of defining the LOAEL for that specific study, in the demonstrated absence of all of the following changes:

- other histopathological findings such as necrosis, inflammation, fibrosis, vacuolation, pigmentation, degeneration, hyperplasia, etc. but not limited to these,
- other effects that are indicative of specific liver toxicity, such as adverse clinical chemistry changes.

If relevant and comprehensive histopathological and clinical-chemistry investigations have not been performed or where there is insufficient information to determine whether the observed increase in liver weight is an adaptive or an adverse response, then the default is to assume that the effect is adverse. Mechanistic information such as enzyme induction can be used to support decision making.

Further information was provided by UK in an annex that was not endorsed as such, but the Human Health WG generally agreed with the principles presented therein. This non-endorsed annex is available in S-CIRCABC: https://webgate.ec.europa.eu/s-circabc/d/a/workspace/SpacesStore/3733c8dc-419c-4c58-ad1c-af18c4f333af/Interpretation%20of%20liver%20effects_annex.pdf

5 Corrosive substances

TOX 19 For active substance approval, is systemic risk characterisation necessary for corrosive concentrations?

(WG-III-2016)

Dermal and oral routes. The use of appropriate personal protective equipment and risk mitigation measures will always be required for corrosive concentrations, resulting in no direct contact with the corrosive substances. Exposure to corrosive concentrations would thus be negligible. Therefore, exposure to corrosive concentrations can be excluded and systemic risk assessment would not be necessary for such concentrations.

It should be mentioned in the CAR that for corrosive concentrations the systemic risks are covered by the local risk characterisation.

Inhalation route. If inhalation exposure is possible following the use of a corrosive concentration of the active substance, systemic risk characterisation should be performed, independently of whether or not the substance is corrosive as inhaled.

TOX 20 How should corrosivity be estimated for formulations that have not been tested?

(WG-III-2016)

For formulations that have not been tested, bridging principles and the calculation method should be applied where relevant in estimating corrosivity. For the calculation method, specific or generic concentration limits should be applied.

TOX 21 How should dermal absorption values be derived for corrosive concentrations of the active substance?

(WG-III-2016)

A default dermal absorption of 100 % should be indicated for corrosive concentrations unless there is data indicating lower dermal absorption. This value would normally not be used in the risk assessment because dermal exposure should be avoided using risk mitigation measures.

6 Exposure assessment

6.1 General issues

TOX 22 Can exposure assessment be performed by averaging the exposure e.g. over a year, if this information is needed?

(TM III 2007, TM IV 2009)

As a general rule, averaging of exposures will not be attempted unless there is sufficient justification and a Working Group agreement. It should be noted that in ConsExpo the chronic exposure is defined as a year average dose, which would not accurately describe a situation where exposure occurs seldom or sporadically.

TOX 23 What is the most relevant exposure determinant in the spray application scenario?

(TM III 2011)

The application duration of 120 minutes is the most relevant exposure determinant and should be used as default for spraying applications in stables. According to minutes from TM III 2011 (2b.10 Spray application in animal house scenario) animal house scenario was obtained from the median of wall and roof area of all types of stables.

TOX 24 Should exposure assessment for non-professionals be performed with the use of gloves as Tier II?

(WG-IV-2014, WG-I-2015)

The exposure assessment for non-professionals should be performed in light of both the CA meeting document *Authorisation of biocidal products classified as skin sensitizers requiring PPE for non-professional users* (CA-Sept13-Doc.6.2.a – Final.Rev1, amended by CA-May14 – Doc.5.2.a) and the guidance on local risk characterisation (ECHA Guidance for Human Health Assessment, Vol III part B).

Where an applicant has proposed the use of a sensitising active substance for non-professionals or, in the case of PT 21 an unacceptable systemic risk has been identified for non-professionals, the exposure assessment should be performed both with and without assuming gloves.

The CAR should state whether the eCA considers it acceptable to perform the risk characterisation assuming the use of gloves, clearly justifying the proposal. The BPC will then conclude on the acceptability of the RMMs.

In systemic risk characterisation, default protection factors for gloves can be applied. Local risk characterisation should be performed in a qualitative way and no numerical protection factor is thus needed.

For PT 21 substances, the CA document *Approach for antifoulings PT 21* (CA-March14-Doc.4.2) states that "Persons making products containing [the substance] available on the market for non-professional users shall make sure that the products are supplied with appropriate gloves".

TOX 25 Which protection factor for coveralls should be used in low pressure (1-3 bar) spraying or wiping applications?

(WG-III-2014)

According to HEEG opinion "impermeable" coveralls should provide a high degree of protection (95 %) against heavy contamination. It was considered that a low

pressure (1-3 bar) spraying or wiping does not cause such a heavy contamination and therefore the default 90 % protection factor of a coated coverall applies.

6.2 PT 1

TOX 26 PT 1: What retention factor value in hand wash should be used?

(WG-I-2015)

The default value of 1 % from the SCCS's Notes of Guidance for testing of cosmetics ingredients and their safety evaluation (7th Revision) should be used until a recommendation of the HEAdhoc is developed.

TOX 27 PT 1: How is sufficient contact time determined for disinfection of hands?

(WG-V-2014)

It is important that efficacy is demonstrated with the contact time used for the exposure scenario. In addition, there must be practical considerations as to whether the disinfection can in practice be performed during the time indicated. A contact time of 30 seconds would usually be considered sufficient for hand disinfection, provided that efficacy of the product after a 30-second contact is demonstrated. Default values can thus be replaced in the assessment when relevant information is available.

TOX 28 PT 1: How many facial tissues can be considered adequate for the estimation of acute and chronic exposure for non-professionals?

(WG-IV-2014)

For the acute exposure scenario a use of 15 tissues per day is assumed, and 4 tissues a day over one year for chronic scenario. This should be considered as a temporary agreement in the absence of appropriate guidance.

TOX 29 PT 1: Which is the adequate transfer efficiency of an active substance from a facial tissue (PT 1) to hand?

(WG-IV-2014)

A transfer efficiency of 50 % is considered a realistic worst case scenario based on the value of transfer efficiency of cotton substrate to wet hands (30 %), described in the Biocides Human Health Exposure Methodology[2] (2015). This should be considered as a temporary agreement in the absence of appropriate guidance.

[2] Available here: http://echa.europa.eu/about-us/who-we-are/biocidal-products-committee/working-groups/human-exposure.

6.3 PT 2

TOX 30 PT 2, swimming pool: What exposure duration should be used for swimming in a pool?

(WG-I-2015)

The duration of exposure should be 1 h, in line with the values indicated in the ConsExpo Fact Sheet for Disinfectants.

TOX 31 PT 2, swimming pool: What is the thickness of the product layer around the swimmer?

(WG-I-2015)

The thickness of the product layer on the skin is assumed to be 0.1 cm for liquids (Biocides Human Health Exposure Methodology[3], 2015). The value of 1 cm, as given in the ConsExpo Disinfectant Fact Sheet, is considered overly conservative. This should be considered as a temporary agreement in the absence of appropriate guidance.

TOX 32 PT 2, swimming pool: Which model should be used for inhalation exposure of consumers in swimming pools?

(WG-IV-2016)

Inhalation exposure assessment for consumers in swimming pools should be performed by assessing exposure to vapour using ConsExpo 4.1 evaporation model. Exposure to aerosol does not need to be assessed due to the lack of a suitable model.

6.4 PT 6

TOX 33 PT 6: Which model should be used to estimate exposure associated with the cleaning and maintenance operations of dispersing pumps as the post-application phase?

(WG-I-2015)

In the absence of more appropriate models, the "*Cleaning of spray equipment*" scenario in the BEAT database should be used.

TOX 34 PT 6: Which work phases will be considered when performing the exposure assessment for an in-can preservative?

(TM II 2008)

Exposure should be assessed from mixing the in-can preservative into the product which is to then to be used (for example, the addition of the in-can preservative to a formulation which is to be marketed as a laundry-washing detergent). This operation will usually be undertaken during the factory manufacture of the laundry-washing detergent. This should be considered as a 'primary exposure' scenario.

Details are sometimes given of exposure during the production of an intermediate product which is then placed on the market. It was agreed that the following situation will not be assessed since it can be considered equivalent to manufacture/formulation: *Solution containing 50 % of in-can preservative active Z DILUTED TO a solution containing 20 % in-can preservative active.*

6.5 PT 8

TOX 35 PT 8: What wood density should be used? This will have an effect in the exposure assessment of cutting and sanding treated wood.

(TM III 2008)

A wood density of 0.4 g/cm^3 will be used as a worst case scenario. This is an average value for softwoods given in the website www.csudh.edu/oliver/chemdata/woods.htm.

TOX 36 PT 8: Should secondary exposure of professionals handling treated dried wood be assessed?

(WG-V-2016)

Secondary exposure of professionals handling treated dried wood does not need to be assessed as it is covered by the exposure during the handling of wet wood after the application of the biocidal product. However, other types of secondary exposure to professionals (e.g. sanding treated wood) should still be assessed.

TOX 37 PT 8: Does exposure for application and post-application need to be combined for professional uses?

(WG-IV-2017)

The application tasks are daily tasks and are compared to the $AEL_{long\text{-}term}$ while some post-application tasks are not necessarily performed on a daily basis and can be considered as an acute exposure scenario. Therefore, exposure during application and post-application tasks should be assessed but not combined in those cases where the post-application scenario is not a long-term exposure scenario.

6.6 PT 18

TOX 38 PT 18: Which models should be used to assess exposure of professional users (farmers) during watering/pouring application?

(WG-I-2015)

The *Mixing and Loading model 5* from TNsG 2007 ("Model for pouring into a portable reservoir") should be used for the mixing and loading phase. The TNsG 2007 model for watering cans should be used as Tier 1 for the application phase. A reverse reference scenario, focused on duration exposure, can be performed as Tier 2 if necessary.

TOX 39 PT 18: Which model should be used to assess exposure of non-professional users during hand-held pump sprayer applications?

(WG-I-2015)

The *Consumer spraying and dusting model 1 – hand-held pumped spray for handheld applications* (TNsG 2002, page 194) should be used. In a higher tier assessment, ConsExpo 4.1 may be used for the specific consumer product, using the spray model and product specific defaults (where available).

TOX 40 PT 18: Does primary and secondary exposure for professional users need to be combined?

(WG-II-2017)

A combined assessment should performed for the primary and secondary exposures, since the operator might be exposed to the same active substance at the workplace and at home. This applies to cases where both primary and secondary exposure are of the same time frame (e.g. short-term, mid-term or long-term).

TOX 41 PT 18: For general public exposure to active substance-releasing mats, how many mats should be considered per day in the exposure assessment as representative for a household scenario?

(WG-III-2017)

A number of 2 mats per day and per household is considered appropriate, also for long-term scenarios, in the human exposure assessment.

6.7 PT 19

TOX 42 PT 19: Should the simultaneous use of sun lotions be considered in the exposure/risk assessment?

(WG-IV-2016)

For the purpose of risk assessment for active substance approval in PT 19, the possible simultaneous use of sun lotions does not need to be considered.

6.8 PT 21

TOX 43 PT 21: Does the scenario of a toddler touching wet and dry paint need to be assessed for non-professional applications of PT 21 active substances?

(WG-II-2014)

This scenario needs to be assessed in line with the recommendation of the HEAdhoc Recommendation no. 5 "*Non-professional use of antifouling paints: exposure assessment for a toddler*".

TOX 44 PT 21: Does exposure during cleaning of spray equipment for antifoulings (PT 21) need to be assessed?

(WG-IV-2014)

The scenario of cleaning of spraying equipment need to be assessed according to the HEAdhoc Recommendation no. 4 "*Cleaning of spray equipment in antifouling use (PT 21)*".

7 Dietary risk assessment

TOX 45 Should the transfer of biocidal active substance into food from food or feed packaging be estimated?

WG-III-2017

The estimation of the transfer of a biocidal active substance residues from paper used for food/feed packaging (PT 12) into food should be assessed. The following approaches were agreed:

- **Biocidal residues in food packaging**: it is proposed to estimate the biocidal active substance transfer from food packaging to food using data if available, and otherwise by a theoretical worst case scenario. This proposal should be seen as an interim approach until a more clear procedure is defined by the Commission.

- **Biocidal residues in feed packaging**: it is proposed to estimate the biocidal active substance transfer from packaging to feed using data if available, and otherwise by a theoretical worst case scenario.

8 Waiving

TOX 46 Can extra assessment factors be used to cover the lack of data in waiving cases?

(TM I 2007)

In a case where there was scientific justification for waiving the 2-generation study, it was decided that an extra assessment factor (AF) of 3 should be used. Using an extra AF of 10, as was suggested, was considered over-conservative. An extra AF was however considered necessary since, although waiving was scientifically based, the data that was to be lacking could not be covered by other studies. Furthermore, there was not a possibility for reading across from a 2-generation study of another substance.

Applying extra assessment factors to cover for lack of data cannot be considered a general rule, but will be assessed on a case-by-case basis.

TOX 47 Is it possible to waive mutagenicity studies?

(TM IV 2012)

Waiving of genotoxicity data will not be possible by default, since no other types of studies than studies employing test methods specifically designed to detect genotoxic effects can provide the required information. However, under certain circumstances studies could be waived on a case-by case basis. In such cases a weight of evidence approach could be adopted, including all relevant information and data, e.g. (Q)SAR, grouping, read across, carcinogenicity data and reproductive toxicity data.

Mutagenicity is a toxicological endpoint per se and cancer data cannot replace mutagenicity data in the evaluation of the mutagenic potential of a substance. Negative carcinogenicity studies can however be used to judge the relevance of testing site of contact genotoxicity.

Note: As stated in the minutes of TM IV 2012, SE did not agree with the view suggesting that carcinogenicity studies could be used to inform on local genotoxicity.

See also the text on mutagenicity resulting from a refinement based on agreed version at the TM IV 2012 (Annex 1).

9 Companion animals

TOX 48 Should risks to companion animals be taken into account in the assessment? How should this be done?

(TM IV 2009)

Risks to companion animals (pets) should be considered at the member state level, at the product authorisation stage. The predominant approach should be to use appropriate risk management measures, e.g. labelling instructions.

The underlying assumption is that the hazard assessment, which is performed for humans, will cover the companion animals as well, while the exposure patterns will differ. It would not be sensible to try to perform an exposure assessment and risk characterisation for all companion animal species, especially given that suitable methodology is lacking. Risks to companion animals will therefore be left for the member state authorities to consider at product authorisation.

10 Appendices to the Human health section

Appendix 1. Mutagenicity

The importance of following data requirements and accomplishing appropriate weight of evidence analyses when assessing mutagenicity

(Agreed at TM IV 2012)

Effects of mutation

It is important to remember that mutagenicity is an endpoint that may lead to severe consequences, since it can cause (i) heritable mutations, i.e. changes in the DNA of germ cells that may be transmitted from a parent to a child in which they may result in malformations or genetic disorders, and (ii) mutations in somatic cells, which may lead to cancer.

Overall conclusion on mutagenicity

Overall conclusions from the evaluation of mutagenicity studies in a dossier should be based on overall weight of evidence analyses that should be done separately for the genotoxic endpoints for which information is required according to the Biocidal Products Directive (i.e. gene mutations in bacterial cells, structural chromosome aberrations in mammalian cells, numerical chromosome aberrations in mammalian cells, gene mutations in mammalian cells and, where required, the relevant endpoint *in vivo*). In the guidance for the implementation of REACH (Guidance on information requirements and chemical safety assessment, Chapter R.7a: Endpoint specific guidance) this generally applied approach is explained by the following text:

"For each test type and each genotoxic endpoint, there should be a separate *Weight of Evidence* analysis. It is not unusual for positive evidence of mutagenicity to be found in just one test type or for only one endpoint. In such cases the positive and negative results for different endpoints are not conflicting, but illustrate the advantage of using test methods for a variety of genetic alterations to increase the probability of identifying substances with mutagenic potential. Hence, results from methods testing different genotoxic endpoints should not be combined in an overall *Weight of Evidence* analysis, but should be subjected to such analysis separately."

Consequently, a data package of, for example, 12 in vitro studies (all of acceptable quality) including six negative gene mutation studies in bacteria, five negative gene mutation studies in mammalian cells, and one positive chromosome aberration study in mammalian cells would support an overall conclusion that the test substance has mutagenic potential in vitro, since the study on chromosome aberrations was positive. Furthermore, it can be concluded that the test substance does not have potential to induce gene mutations in vitro, neither in bacterial cells, nor in mammalian cells. It would be incorrect to draw the overall conclusion that the substance has no mutagenic potential in vitro by taking into consideration the inappropriate weight of evidence analysis based on the observation that only one of twelve mutagenicity studies was positive. In a real case it is likely that the results of the available data will be more complex, making it more demanding to analyse the results. However, in order to arrive at a relevant overall conclusion, the above considerations must be taken into account during the evaluation of genotoxicity test data.

Waiving of genotoxicity data

The TM is of the opinion that waiving of mutagenicity data requirements in the common core data set would not be possible by default, since no other types of studies than studies employing test methods specifically designed to detect genotoxic effects can provide the required information. In addition, results from a gene mutation test in bacteria are not sufficient to predict the potential of a substance to induce gene mutations in mammalian cells in vitro, since results from both types of studies are required according to the mutagenicity data requirements of the Biocidal Products Directive. Therefore, data could be waved on a case-by-case basis only, i.e. where it is technically not possible or where it is scientifically not justified to perform a mutagenicity study, as mentioned in the legal text of the Biocidal Products Regulation (BPR) 528/2012 and in the Technical Notes for Guidance on Data Requirements. A WoE evaluation may include data from other than actual standard test data, (Q)SAR data, grouping and read across, carcinogenicity data and others.

In particular, (Q)SARs are explicitly mentioned in the BPR 528/2012 (Annex IV, General rules for the adaption of the data requirements), where it is stated that (Q)SARs may be used to indicate the presence, but not the absence of a given dangerous property. However, this limitation is not stated for the grouping and read-across approach. The OECD toolbox provides (Q)SARs but also grouping and read-across approaches for the AMES test, in vitro UDS, in vitro chromosomal aberration test, in vitro COMET assay, in vitro sister chromatid exchange assay, mouse lymphoma assay, in vivo dominant lethal assay, in vivo drosophila SLRL test, in vivo micronucleus test – and in vivo carcinogenicity models as well as TD50. In the public VEGA software also AMES and carcinogenicity QSAR is available and it contains a combination of QSAR and an independent read-across tool. The OECD toolbox as well as VEGA contains also a user friendly possibility to evaluate the applicability domain, i.e. the suitability of the model for the specific substance. (Q)SARs are developed from a large database of substances and thereby may also overcome uncertainties from borderline or uncertain single testing results. They may be considered more objective compared to read across and grouping approaches. However all three non-testing approaches, i.e. (Q)SAR, read across and grouping are explicitly recommended for consideration in the BP Regulation 528/2112 (Annex IV).

As regards exposure-based waiving of mutagenicity data, this would be very rarely possible, since mutagenic effects resulting from direct interaction of a substance with the DNA are considered to show a no-threshold dose-response relationship. However, in very specific cases of extremely low exposure the (Q)SAR based approach "Toxicological Threshold of Concern (TTC)" approach may be considered.

Use of Cancer data for the evaluation of mutagenicity in the frame of a Weight of Evidence approach

In evaluations of the mutagenic potential of active substances, data from cancer studies are frequently referred to, particularly when the results from the available mutagenicity studies are not fully conclusive, e.g. some studies may not have produced reliable results due to inadequate quality, or studies on one of the genotoxicity endpoints for which data is required may be missing. However, carcinogenicity data are not sufficient to determine whether a substance is mutagenic or not; for this, results from studies employing test methods specifically designed to detect genotoxic effects are required. Even though there is a certain concordance between mutagenicity and carcinogenicity, carcinogenicity studies are neither sensitive enough, nor discriminating enough to discern between a mutagenic substance and a non-mutagenic substance. However, in an overall weight of evidence approach for the evaluation of mutagenicity, all available relevant data should be included.

For a number of different reasons, for example interspecies- and animal to animal variability in metabolism, toxicokinetics and toxicodynamics, a mutagenic substance may not give rise to cancer in a particular carcinogenicity study. However, according to Billington et al. 2010 (Critical Reviews in Toxicology 40(1), 35-49), "Assessment of 202 pesticide evaluations from the European Union review programme under Directive 91/414/EEC indicated that the mouse carcinogenicity study contributed little or nothing to either derivation of an acceptable daily intake (ADI) for assessment of chronic risk to humans, or hazard classification for labelling purposes". From this study Billington et al. concluded that there were practically no mouse to rat interspecies differences that appeared relevant for a regulatory decision.

EFSA 2011 (EFSA Journal 2011, 9(9):2379) addressed the issue of a weight-of-evidence approach which takes into account all the available relevant data with the following conclusion: "The Scientific Committee recommends a documented weight-of-evidence approach to the evaluation and interpretation of genotoxicity data. Such an approach should not only consider the quality and reliability of the data on genotoxicity itself, but also take into account other relevant data that may be available, such as physico-chemical characteristics, structure-activity relationships (including structural alerts for genotoxicity and 'read-across' from structurally related substances), bioavailability, toxicokinetics and metabolism, and the outcomes of any repeated-dose toxicity and carcinogenicity studies." It also is acknowledged that there is practically no evidence for genotoxicity to germ cells without genotoxicity to somatic cells. This consideration is relevant when integrating negative carcinogenicity data in a WoE evaluation for genotoxicity.

The potential WoE based use of negative carcinogenicity data for the evaluation of genotoxicity is further supported by an actual evaluation of Annex VI (Harmonised classification and labelling for certain hazardous substances) of the CLP Regulation. Among all the 4138 entries there are 3068 entries without Carcinogenicity classification. Only 6 of those are classified for mutagenicity Cat 1A/1B. However, for these 6 entries the following information was retrieved from CCRIS, CPDB, HSDB Database (accessed via TOXNET): For one entry (CAS 17804-35-2) 2 positive mouse carcinogenicity studies and 2 US conclusions on positive carcinogenicity are available. For the other entries no carcinogenicity studies could be identified in these databases (CAS: 2040-90-6, 10605-21-7, 64-86-8, 2451-62-9, 59653-74-6). This analysis supports that at the CLP level there is no evidence for non-carcinogenic substances with clear genotoxicity.

A non-mutagenic substance may induce tumours in a carcinogenicity study because it has other modes of action in carcinogenesis than genotoxicity. On the other hand, some genotoxic mechanisms lead to developmental toxicity rather than to carcinogenicity (e.g. inhibition of mitotic spindle). Mutation is a toxicological endpoint *per se* and it is generally recognised that a substance which is considered to be mutagenic also causes concern for a possible carcinogenic potential, i.e. mutagenicity is a predictor of carcinogenicity.

In conclusion, cancer data cannot replace mutagenicity data in the evaluation of the mutagenic potential of a substance, but they should be used in a careful Weight of Evidence evaluation carried out on a case-by-case basis.

Note: As stated in the minutes of TM IV 2012, SE did not agree with the principle that carcinogenicity data are adequate for the evaluation of the mutagenic potential of a substance and, hence, SE did not agree with the parts of the document presenting views aiming to support this principle.