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Draft
GUIDANCE FOR THE SETTING AND APPLICATION OF ACCEPTABLE OPERATOR EXPOSURE LEVELS (AOELs)

This document has been conceived as a working document of the Commission Services, which was elaborated in co-operation with the Member States. It does not intend to produce legally binding effects and by its nature does not prejudice any measure taken by a Member State within the implementation prerogatives under Annex II, III and VI of Council Directive 91/414/EEC, nor any case law developed with regard to this provision. This document also does not preclude the possibility that the European Court of Justice may give one or another provision direct effect in Member States.

FOREWORD

This guidance document provides recommendations for the establishment of Acceptable Operator Exposure Levels (AOELs) for active substances in the context of Directive 91/414/EEC concerning the placing of plant protection products (PPPs) on the European market.

This guidance document is intended for use by Member State authorities and EC peer review groups for setting AOELs and to assist European Commission and Member States when making decisions about inclusion of an active substance in Annex I of Directive 91/414/EEC. It is also intended to provide applicants with advice on the drafting of a scientifically reasoned proposal for AOELs on the basis of the data submitted so as to enable the Member States to evaluate an application for authorisation without the need to refer back to the applicant except for occasional clarification or further information, thus improving the efficiency and cost-effectiveness of the authorisation process. The document is divided into two sections, the main text describing the setting of AOELs, with an Appendix outlining the applicability of the AOEL concept to groups other than professional operators i.e. amateur users, bystanders, re-entry workers and residents.

This guidance document has been elaborated in co-operation with the Member States and the European Food Safety Authority (EFSA) and represents a consensus of present knowledge; it will be updated on the basis of new data and/or policy. It is based largely on the documents "Recommended method for the establishment of acceptable operator exposure levels (AOELs)" and "Criteria to establish health-based occupational exposure limits for pesticides" which are result of a research project sponsored by the European Commission to develop a harmonised procedure to set AOELs within the European Union (see EU Project Group, 2000). The document does not, however, intend to produce legally binding effects.

CHAPTER 1 INTRODUCTION

1.1 Directive 91/414/EEC concerning the placing of plant protection products (PPPs) on the market provides in Article 5 (2) that for inclusion of an active substance in Annex I an acceptable operator exposure level (AOEL) shall, if necessary, be taken into account. In addition, Directive 94/79/EC requires a scientifically reasoned proposal for the establishment of an acceptable operator exposure level (AOEL) for an active substance. The following guidance is appropriate to chemical substances (micro-organisms have not been considered – see section 2.6 of SANCO/108/2002 rev3 of 14/10/2003).

1.2 The risk assessment process, in relation to operator health entails a sequence of actions which is outlined below:

(a) Assessment of effects, comprising

(i) hazard identification (identification of the intrinsic hazardous properties of the substance);

(ii) elucidation of the dose (concentration) - response (effects) characteristics, when appropriate and derivation of No Observed Adverse Effect Levels (NOAELs);

(iii) definition of the toxicity profile relevant for operator exposure (i.e. mixer/loaders, applicators, crop-workers, harvesters, residents and bystanders).

Exposure profiles will vary with the different categories defined above, these are described in more detail in Appendix 1.

The majority of the mammalian toxicity data on plant protection products and active substances are obtained using the oral route, yet most exposures to operators, workers, bystanders and residents will be *via* dermal and / or inhalation routes. This will necessitate route-to-route extrapolation techniques, where appropriate.

(b) Assessment of absorption characteristics

(i) estimation of the relevant oral absorption, when appropriate;

(ii) estimation of the relevant inhalation absorption, when appropriate;

(iii) estimation of the relevant dermal absorption, when appropriate.

This may lead to conclusions on the degree of absorption for the relevant routes of uptake, which are to be used in further risk assessment processes.

(c) Exposure assessment for the operator (i.e. mixer/loaders, applicators, crop-workers, harvesters and bystanders) for the different likely routes of exposure.

(d) Comparison of information on hazardous properties and hazardous dose levels/concentrations with exposure levels, taking into account local effects and the appropriate absorption levels for each relevant route of uptake into the body, in order to characterise the degree of risk posed by the plant protection product.

(e) Risk management, in cases where the risk assessment leads to a risk estimation that is considered unacceptable. By prescribing various measures leading to exposure reduction the estimated risk may be lowered sufficiently to support Annex 1 inclusion and re-registration.

On the basis of the risk assessment and risk management process, an authorization-decision may be taken on the use of plant protection products.

1.3 According to Directive 97/57/EC (establishing Annex VI to Directive 91/414/EEC), the AOEL is defined as "... the maximum amount of active substance to which the operator may be exposed without any adverse health effects. The AOEL is expressed as milligrams of the chemical per kilogram body weight of the operator." In this guidance document, AOELs relate to the internal (absorbed) dose available for systemic distribution from any route of absorption and are expressed as internal levels (mg/kg bw/d). According to Directive 97/57/EC, "... the AOEL is based on the highest level at which no adverse effect is observed in tests in the most sensitive relevant animal species or, if appropriate data are available, in humans". However, in some cases, serious findings requiring a large assessment factor may drive an AOEL even though less serious effects occur at lower doses in the "most sensitive species".

1.4 AOELs are health-based exposure limits to be used for a decision about the inclusion of an active substance in Annex I and in the context of the risk assessment and management process for the authorization of PPPs. AOELs should be set to ensure that the presence of an active substance in a PPP, used in a manner consistent with the label instructions and good plant protection practice, has no harmful effects on the health of operators, workers, bystanders or residents.

Definitions

i. Operators are: persons who are involved in activities relating to the application of a plant protection product; such activities include mixing / loading the product into the application machinery, operation of the application machinery, repair of the application machinery whilst it contains the plant protection product, emptying / cleaning of the machinery / containers after use. Professional operators should be trained and will be expected to take steps to minimise exposures to themselves and others. Professional operators may have access to appropriate personal protective equipment (PPE). Amateur operators (that is home garden users) are considered not to have access to PPE

ii. Workers are: persons who, as part of their employment, enter an area that has been treated previously with a plant protection product or who handle a crop that has been treated with a plant protection product; for whom it is usually assumed that no protective clothing is worn. As a means of providing protection to workers, re-entry to a treated area can be prohibited for a period specified on the product label

iii. Bystanders are: persons who are located within or directly adjacent to the area where pesticide application or treatment is in process; whose presence is quite incidental and unrelated to work involving pesticides but whose position may put them at risk of potential exposure; who take no action to avoid or control exposure and for whom it is assumed that no protective clothing is worn and perhaps little ordinary clothing.

iv. Residents are: persons who live, work or attend school or any another institution adjacent to an area that has been treated with a plant protection product; whose presence is quite incidental and unrelated to work involving pesticides but whose position may put them at risk of potential exposure; who take no action to avoid or control exposure; for whom it is assumed that no protective clothing is worn and perhaps little ordinary clothing and who might be in the location for 24 hours per day.

1.5 The term "AOEL" under Directive 91/414/EEC implies particular reference to "operators" which are represented by mixers/loaders, applicators and re-entry workers. However, according to Directive 97/57/EC, the AOELs established shall also be used to evaluate the possible exposure of non-occupationally exposed groups (bystanders). Therefore, based on the current Community legislation, the AOELs set for operators and workers should be established in such a way that they are also applicable for all the groups defined in 1.4.

1.6 So far, no EC agreed procedure has been established for the assessment of combined exposure to active substances. For products containing different active substances with a common mechanism of toxicity, at dose levels similar to the NOAELs used to derive the AOELs,, this issue should be addressed by a correction in the exposure estimate rather than by application of a "formulation specific AOEL".

1.7 This document does not attempt to address the derivation of acceptable exposure levels for local effects (e.g. irritation and sensitisation) produced by exposure to plant protection products. For professional operators, it is envisaged that such effects will normally be addressed by classification and labelling and the use of appropriate personal protective equipment. However, the potential for acute local effects to occur in workers, amateur operators, bystanders and residents should be considered, for example if the spray dilution is classifiable as an irritant, and appropriate risk management measures taken. If local effects are produced in inhalation studies, these should be taken into account to ensure a systemic AOEL is adequately protective for the local effects.

CHAPTER 2 HAZARD CHARACTERISATION

2.1 The aim of this chapter is to provide a short reference to the general aspects of hazard characterisation for an active substance, which are extensively discussed in the documents of the co-operative research project (EU Project Group, 2000). Fundamental steps in hazard characterisation are:

- description of the toxicological profile of the substance;
- identification of the relevant critical effects in the most relevant and sensitive species; and
- dose-response evaluation, i.e. identification of the LOAEL (lowest-observed-adverse-effect level) and the NOAEL (no-observed-adverse-effect level) for the critical effects.

2.2 Precise information on the toxicological and metabolism data requirements and test methods for the inclusion of an active substance in Annex I and for an application for the authorisation of a PPP is provided by Directive 94/79/EC. The directive specifies that the information for the active substance, taken together with that provided for one or more preparations containing the active substance, must be sufficient to permit an evaluation to be made as to the risks for man, associated with the handling and use of PPPs containing the active substance. In addition, the information provided must be sufficient to establish an AOEL.

2.3 All mammalian toxicity and metabolism studies required under Directive 91/414/EEC should be considered when setting an AOEL. Though AOELs are usually based on oral short-term (i.e. repeat dose) studies, it may be appropriate to use other studies depending on the effects seen and the patterns of use of the PPP. Additional details of how the patterns of use might influence the choice of studies for the AOEL is presented in Appendix 1.

2.4 For most toxicological endpoints it is generally agreed that there is a threshold below which no toxic effect occurs. The highest dose level at which no statistically significant increases in frequency or severity of toxicologically relevant effects are observed between the exposed population and its appropriate controls is usually defined as the NOAEL. For some types of effects (e.g. direct interaction with DNA) no threshold is assumed, however it is possible that a threshold for the toxicological consequences of interaction with DNA might exist or could be demonstrated.

2.5 According to Directive 97/57/EC, the AOEL is based on the NOAEL in the most sensitive relevant animal species, or, if appropriate data are available, in humans (see also para. 2.9). Selection of the most appropriate NOAEL on which to base an AOEL needs to be assessed on a case-by-case basis, and requires expert judgement. To aid identification of the relevant NOAEL, a summary of the toxicity profile of the active substance is suggested in which all NOAELs and LOAELs, together with the critical effects on which these levels are based, should be listed. Such a list should be easy to read and some flexibility in design will be necessary, especially if a large number of toxicity studies are available. The required information may be given as part of a general overall summary table of the toxicity profile of an active substance, which could cover other reference doses as well (e.g. ADI and ARfD).

2.6 The principles behind the determination of the critical NOAEL and applicable assessment factor are the same for deriving an AOEL as for an ADI and ARfD (European Commission, 2001; IPCS, 1994, 1999, 2005*)*. The critical effect should reflect the most sensitive relevant endpoint for that particular compound. Should an active substance lead to more than one toxic effect, the adverse effect exhibiting the lowest NOAEL would normally be used as the relevant critical effect when establishing an AOEL. However, in cases where a severe effect with a higher NOAEL would require an assessment factor greater than 100 resulting in a lower AOEL, this should be used (see also para. 3.4).

2.7 If a substance is genotoxic in vivo and/or carcinogenic, a plausible mechanism of action should be proposed by the applicant to permit an assessment of its relevance to man. The proposal needs to be adequately justified including reference to experimental data for the substance. If the mechanism has not been determined but a threshold is likely, e.g. it is a non-DNA reactive genotoxin,, it may be possible to set an AOEL pending submission of mechanistic data. In general, it will not be possible to set an AOEL if a substance is genotoxic in vivo and/or carcinogenic unless a threshold based mechanism has been demonstrated.

2.8 With an animal study, it is necessary to consider whether the effects on which a NOAEL is based are relevant to humans. Relevance to humans is sometimes difficult to assess and it has to be assumed that the NOAEL for the most sensitive animal species is relevant to humans in the absence of data either for or against this.

2.9 According to Directive 91/414/EEC, the "... AOEL is based on the highest level at which no adverse effect is observed in tests in the most sensitive relevant animal species or, if

appropriate data are available, in humans". However toxicological studies conducted in humans with the purpose of determining a human No Observed Effect Level of an active substance have not been and will not be used per se to derive regulatory limit values (such as an Acceptable Daily Intake, an Acceptable Operator Exposure Level or an Acute Reference Dose) for the substance. Rather, such studies if they are scientifically and ethically valid, will be evaluated and used as supplementary information to confirm the validity of regulatory limit values which will continue to be derived from extrapolations from appropriate studies in laboratory model species.

In general, the relevant NOAEL on which to base an AOEL will be obtained from animal studies, but if appropriate scientifically valid and ethically generated human data are available and show that humans are more sensitive and lead to a lower AOEL value, these data should take precedence over animal data.

2.10 As a general principle, NOAELs for local skin effects are not considered relevant to setting an AOEL, since they often correlate closely with the concentration of the substance at the site of contact. Such effects should be addressed by hazard symbols / phrases and suitable PPE or technical/engineering controls. However, it may not always be possible to be certain whether a possible systemic effect is secondary to a local effect. Unless there is a scientifically based case to show an absence of relevance to human exposures, the possible systemic effect should be regarded as relevant for setting an AOEL. If local effects are produced in inhalation studies, these should be taken into account to ensure a systemic AOEL is adequately protective for the local effects.

CHAPTER 3 EXTRAPOLATION ISSUES

ASSESSMENT FACTORS

General considerations

3.1 To translate the selected NOAEL into an AOEL, assessment factors accounting for uncertainties in extrapolation from toxicity data to the exposed human population have to be applied. For the sake of clarity in this guidance document, the term assessment factor is used and is meant as a general term to cover all factors designated in the literature as safety factor, uncertainty factor, extrapolation factor, adjustment factor, etc. A detailed consideration of assessment factors can be found in IPCS, 2005

3.2 Assessment factors are also used for setting the acceptable daily intake (ADI) and the acute reference dose (ARfD) for pesticide active substances. Therefore, at least in general terms, it is important that the fundamental approach for the choice of assessment factors for an AOEL is compatible with that used for setting ADI and ARfD. At present, hazard assessment for most toxic endpoints is based on the assumption of a threshold and makes use of a default 100-fold uncertainty factor when considering risks to the general population. The basis for this approach is a 10-fold factor for interspecies variability and a 10-fold factor for inter-individual variability. It is probable that genetics will determine inter-individual variability to the same or a greater extent than age, gender or general health status, therefore the default inter-individual variability factor of 10 is applicable to all exposed groups.

Using non-default assessment factors

3.3 In deriving an AOEL the default position is to use assessment factors of 10-fold for interspecies variability and a 10-fold for inter-individual variability. In certain cases additional information might be available on interspecies and / or inter-individual differences to permit the use of a chemical specific assessment factor – see IPCS 2005.

Application of additional assessment factors

3.4 The biological significance of the critical adverse effect in terms of its presumable health consequence (including severity, frequency and reversibility) and its relevance to humans should be considered in the selection of assessment factors. When the critical effect is judged of particular significance (e.g. teratogenic or irreversible neuropathic effects), an increased margin of safety might be considered necessary. This can be achieved by the use of an additional assessment factor, which in current practice has not been greater than 10. Quantification of this factor cannot be justified by scientific considerations, but should rather be determined on a case-by-case basis taking into account the dose-response data.

3.5 As a general rule, where an AOEL is based on a NOAEL for a non-severe end-point, the margin between the AOEL and the NOAEL / LOAEL for a severe effect should be adequate based on the severity of the effect and the dose response relationship. The determination of an adequate margin will need to be determined by expert judgement.

3.6 If, having considered the overall database, an AOEL has to be based on a LOAEL rather than a NOAEL, an additional assessment factor has to be considered. The additional factor

will vary depending on the shape of the dose-response curve and the magnitude of the effect at the LOAEL. No science based factor for the extrapolation of a LOAEL to a NOAEL can be derived. This extrapolation step should therefore be based on expert judgement until other methods, such as the benchmark dose concept, are elaborated and validated for use in pesticide human health risk assessment practice. The use of LOAELs to set AOELs should be a last resort; however if the effects at the LOAEL are of moderate magnitude and not severe the use of a LOAEL and an appropriate factor can negate the need for additional animal studies.

Quality/extent of toxicity data

3.7 If there are limitations in the available toxicity data, it might still be possible to set a "provisional" AOEL until further data have been submitted. Such a situation might arise, for example in cases of:

a) deviations from official guidelines which are not properly substantiated;
b) low number of animals used;
c) inadequate number of dose levels tested;
d) inadequacy of haematological, biochemical, and pathological examinations;
e) indications for doubts regarding the confidence in the database:
    i. the absence of certain types of studies (e.g. route specific studies);
    ii. conflicting results between studies;

Where the conduct and/or reporting of crucial studies shows significant departures from modern standards the suitability of setting a "provisional" AOEL would need to be considered on a case-by-case basis, and an additional assessment factor should be applied to account for uncertainty in the database. The size of this additional factor depends on expert judgement and should tend to produce a conservative AOEL. If predicted exposures are below such a conservative AOEL additional studies might not be necessary.

Exposure duration

3.8 When oral data are used as starting point for an AOEL, in general no corrections are needed for the anticipated exposure scenario as the database will include studies with a range of durations. Similarly, for gaseous or volatile active substances, or those used to generate gases it is to be expected that an adequate database of inhalation studies will be available to permit the derivation of an AOEL.

3.9 If route-to-route extrapolation is not justifiable because there are route specific effects, an AOEL may be based on relevant route-specific (dermal and inhalation) repeated dose toxicity studies. Since these studies frequently cover only a relatively short period of time and / or only dose for 5 days per week, it might be necessary to extrapolate from short-term experimental data to an AOEL applicable to longer term exposures. This can be done by the use of assessment factors. These assessment factors can be derived from the oral toxicological profile, for example, by comparing NOAELs and LOAELs from acute, short-term (28- and 90-day) and long-term oral studies.

Overall assessment factor

3.10 In the default procedure for deriving AOELs, the overall assessment factor is established by multiplication of the separate factors described above. In many cases, the overall assessment factor is likely to be determined exclusively by multiplying the default 10-fold inter- and intraspecies assessment factors. If factors in addition to those for inter- and intraspecies differences are used (e.g. for severity of effect or quality of database), care should be taken to ensure that there is no undue compounding of conservative assumptions.

3.11 In all cases where a factor other than the default is used, the reasons must be clearly described.

ROUTE TO ROUTE EXTRAPOLATION

3.12 Pesticide operators are mainly exposed through skin contact and inhalation, whereas an AOEL will normally be derived from oral studies, since most of the toxicity studies specified in Annex II to Directive 91/414/EEC are performed through the oral route. Route-to-route extrapolation is defined as the prediction of an equivalent dose and dosing regime that produce the same response as that obtained for a given dose and dosing regime by another route. The general principle of route-to-route extrapolation is to convert the external dose of one exposure route to another one based on the equivalency of internal (systemic) dose achieved through the two routes under consideration while taking into account differences in metabolism and differences in kinetics (concentration achieved).

3.13 If there are indications that the type and extent of effects of the substance are essentially independent of the route of exposure, e.g. by comparing results from oral and dermal or inhalation toxicity studies or from results of toxicokinetic and/or mechanistic studies, route-to-route extrapolation is appropriate and the use of oral studies for AOEL setting is preferred.

3.14 Where there are indications that toxicity is dependent on the route of exposure, careful consideration should be paid towards the applicability of route-to-route extrapolation, and preference might then be given to the use of appropriate route-specific studies as a basis for AOEL setting (see 4.13 *et seq.*).

3.15 Route-to-route extrapolation is only applicable to systemic effects, since local effects often correlate closely with the concentration of the substance at the site of contact. In some cases, the inhalation exposure route, apart from delivering the substance to systemic distribution, may also cause specific toxicity to the lungs and the upper airways. Therefore, a specific assessment of lung toxicity is necessary if inhalation is a relevant exposure route (see 4.21).

3.16 Most databases for plant protection products will not contain sufficient information to permit the use of physiologically based pharmacokinetic (PBPK) modelling in risk assessments. However, if sufficient information is available, the use of PBPK modelling can reduce the uncertainty in route to route and interspecies extrapolation and could be used in the derivation of AOELs.

CHAPTER 4 RECOMMENDED METHOD FOR SETTING AN AOEL

General considerations

4.1 An AOEL is a health-based exposure limit and will be established on the basis of the toxicological properties of an active substance. The default AOEL represents the internal (absorbed) dose available for systemic distribution from any route of absorption and is expressed as an internal level (mg/kg bw/d). It is set on the basis of oral studies provided that there are no indications of significant route-specific differences.

4.2 The whole toxicological database must be considered, and all potentially adverse effects (e.g. genotoxic, carcinogenic, teratogenic, reproductive, neurological, immunological and endocrine effects) must be taken into account. For each critical adverse effect, mechanistic aspects (including toxicokinetic and toxicodynamic considerations) as well as the relevance of observed effects to humans should be carefully considered. On the basis of this evaluation the NOAEL from the most appropriate toxicological study is chosen as starting point for establishing an AOEL (see Chapter 2).

4.4 Since targets, critical effects and NOAELs for an active substance may differ depending on the exposure period, more than one AOEL might in principle be established to allow for more flexibility and consistency in the risk assessment. For example, the exposure patterns for operators, re-entry workers and bystanders might be very different and justify the generation of separate AOELs for each group. However, as a default procedure, particularly to demonstrate that the requirements for the inclusion of an active substance in Annex I are fulfilled, only one AOEL should be established for an exposure period appropriate to the frequency and duration of exposure of operators (including contractors), re-entry workers, bystanders and residents for the use(s) supported in the DAR.

4.5 Since an AOEL is expressed as an internal dose, the external NOAEL (applied dose) has to be converted to an internal value by using a correction factor for systemic availability, especially if the absorbed dose at the NOAEL is significantly lower (in current practice <80 %) than the applied dose. For converting an external dose to an internal dose, adequate absorption data should be provided. Since absorption can be dose (or concentration) dependent, the correction factor should be based on the percentage of absorption most applicable to the NOAEL used to derive the AOEL. Although the critical parameter is bioavailability of the toxic component(s), adequate data are often not available on these and a surrogate of absorbed radiolabel is normally used. The extent of oral absorption can

be calculated from the proportion of the dose excreted in the urine, plus any of the faecal excretion that can be shown to result from compound that is absorbed and subsequently secreted into the gastrointestinal tract e.g. in the bile. However, where the critical target organ / tissue is not the liver or gastrointestinal tract and the biliary component is unlikely to have reached the target organ / tissue (i.e. is excreted very rapidly) exclusion of the biliary component from the estimate of the bioavailable systemic dose should be considered. The basis for the oral absorption value used to derive the AOEL must be explained in the accompanying text.

4.6 The relevant identified NOAEL must be divided by an overall assessment factor for the derivation of an AOEL. Different critical effects may require a different overall assessment factor (see Chapter 3). As a general rule, where an AOEL is based on a NOAEL for a non-severe end-point, the margin between the AOEL and the NOAEL / LOAEL for a severe effect should be adequate based on the severity of the effect and the dose response relationship. The determination of an adequate margin will need to be determined by expert judgement.

4.7 Specific considerations on likely exposure routes under the proposed conditions of use shall be taken into account when setting an AOEL, to assess the uncertainty of route-to-route extrapolations. If there are clear indications that toxicity is dependent on the route of exposure, preference should be given to the use of route-specific studies as a basis for an AOEL.

4.8 It should be clearly stated whether any AOEL proposal applies also to re-entry workers as well as to non-occupational operators (home/garden users), residents and bystanders. If it does not apply to all groups, an explanation and appropriate alternative AOELs should be provided (see Appendix 1). As a general rule for Annex 1 inclusion, a single AOEL applicable to all groups should be proposed.

USE OF NOAEL FROM ORAL STUDIES

4.9 Taking account of the typical exposure patterns to plant protection products (see Appendix 1), as a default procedure, an AOEL will be based on the NOAEL from an oral short-term toxicity study (typically 90-day study; or occasionally 1-year dog study) provided that:

- the critical endpoint(s) of the substance (e.g. reproductive/developmental toxicity) are covered;

- no irreversible effects occur at lower dose levels after chronic exposure;
- the number and type of parameters studied are considered adequate; and
- the number of animals examined and the animal species is adequate.
  [Data from the initial stages of longer term studies can also be relevant in clarifying the dose response relationship, particularly if the appropriate end-points have been determined at interim time-points]

4.10 If a more sensitive, relevant end-point has been determined in a study investigating specific end-points (e.g. neurotoxicity, reproductive toxicity or developmental toxicity) the respective NOAEL should be considered for AOEL setting.

4.11 If there are indications that effects only become evident in chronic toxicity studies but might be initiated by shorter term exposures, the NOAEL for these effects in the long-term studies (including 1 year dog) should be considered in AOEL setting.

4.12 In exceptional cases where the use of the above approach is clearly unrepresentative of the actual exposure scenario (e.g. very short-term or continuous) it might be more appropriately to derive an AOEL based on an alternative approach. Such an alternative approach could use NOAELs from shorter or longer duration studies. In all such instances full justification for the approach must be given.

USE OF DERMAL OR INHALATION STUDIES

4.13 When the results of the available toxicological and metabolism studies indicate the possibility of a relevant first pass effect and/or fundamental differences in metabolism or toxicity between routes (which might theoretically influence type and extent of effects), additional route-specific studies can be required according to Annex II of Directive 91/414/EEC. Decisions as to the need for supplementary studies should be based on expert judgement and a case-by-case evaluation of the overall toxicological database.

4.14 If relevant route specific studies are available they may be considered as the starting point for setting an AOEL. In practice, route-specific studies can only be considered for AOEL setting if:

- the number and type of parameters studied are considered adequate;
- the number of animals examined and the animal species is adequate; and

- the route-specific study is of adequate duration and covers the critical effects of the substance i.e. the most sensitive endpoints in the oral database have been evaluated in an appropriate route specific study.

AOEL based on a dermal study

4.15 Performance of dermal toxicity studies as basis for an AOEL should be considered when the results of toxicokinetic and/or mechanistic studies indicate that a relevant first pass effect and/or fundamental differences in metabolism exist between the oral and dermal route of exposure. However, it is recognised that the conduct of dermal studies to identify long-term or reproductive effects are not generally technically feasible. Therefore, if such effects are observed after oral administration, it has to be carefully considered whether these effects could also occur after dermal exposure.

4.16 For converting a dermal NOAEL to an internal dose, adequate dermal absorption data should be provided for the test species, from appropriate *in vivo* or *in vitro* studies (de Heer et al., 1999; OECD, 2000). The correction factor should be based on the percentage of dermal absorption relevant the application rate used at the NOAEL. Alternatively, toxicokinetic data generated from dermal exposures using appropriate vehicles or formulations can be used to determine equivalence to results from oral studies. Possible differences between the dermal absorption values for the technical active substance or the material used in the dermal toxicity study used to derive the AOEL and the formulated product (and in-use dilutions) should be considered. If there are differences these must be taken in to account at the exposure estimation stage.

4.17 Local skin effects such as irritation and sensitisation are not appropriate for setting an AOEL. The dermal NOAEL used to derive an AOEL should be based on systemic effects.

AOEL based on an inhalation study

4.18 According to Directive 94/79/EEC, "… for volatile substances (vapour pressure > 10-2 Pascal), expert judgement is required to decide whether the short-term studies have to be performed by oral or inhalation exposure". In the case of gaseous substances, only inhalation studies are normally technically feasible. Therefore, for gaseous substances the toxicokinetic, metabolism and toxicity studies that are required under Annexes II and III of

Directive 91/414/EEC will normally be performed via the route of inhalation. Inhalation studies used in the deriving AOELs should use the nose only route to avoid confounding effects due to dermal absorption and ingestion following grooming.

4.19 For converting an inhalation NOAEC (expressed as mg/l) to an internal dose (mg/kg bw/d), the respiration rate of the test species, the duration of daily inhalation exposure in the study and the extent of respiratory absorption have to be taken into account. The default assumption is that respiratory absorption is 100%. For non-gaseous substances, the extent to which the size distribution of droplets/particles in an inhalation toxicity study is relevant to human inhalation exposure to the active substance (as product concentrate or in-use dilution) should be considered. In rat inhalation studies, particles of diameter <3μm will be deposited in the alveolar region and absorption will be across the alveolar wall; particles with diameter <6μm will be deposited in the tracheobronchial region and absorption will tend to be via the oral route following mucocilliary clearance; larger particles will tend not to pass the nasal turbinates / larynx and may not be absorbed. Therefore inhalation studies should aim to produce the majority of particles with diameters of <6μm. In humans, the equivalent diameters are <8μm for alveolar deposition and <15μm for tracheobronchial deposition. (For a more detailed consideration see USEPA, 1994; or Schlesinger, 1995.)

Alternatively, toxicokinetic data generated using inhalation exposures, if available, can be used to determine equivalence to results from oral studies.

4.20 To calculate the NOAEL in mg/kg bw/d for a rat study with daily inhalation exposure of 6 hours, the following assumption should be used (Lundehn et al., 1992):
$NOAEL_{internal}$ (mg/kg bw/d) = $NOAEC_{inhalation}$ (mg/l) x 45 l/kg bw/h (rat respiration rate) x 6h (daily inhalation exposure) x 1 (default respiratory absorption: 100 %). Additional correction will be needed if exposures were only for 5 days per week.

4.21 For some substances, certain toxic effects, for example on the lung, only occur during inhalation exposure. In cases where local effects to the respiratory tract are produced in the absence of systemic toxicity, an internal AOEL value cannot be established from the inhalation study. However, there is a need to provide protection against such local effects The risk management for such substances may be best addressed by establishing occupational exposure limit values (which are normally as ppm or mg/m^3). The setting of occupational exposure levels should be based on case-by-case assessments and is not addressed in this document. The fact that it is not addressed by this document does not

preclude the need to perform an appropriate assessment of operator, worker and bystander exposures in respect of both systemic and local effects.

CHAPTER 5 SUMMARY AND CONCLUSION

5.1 An AOEL is a health-based exposure limit and will be established on the basis of the toxicological properties of an active substance. The default AOEL represents the internal (absorbed) dose available for systemic distribution from any route of absorption and is expressed as an internal level (mg/kg bw/d). It is set on the basis of oral studies provided that no indications of route-specific differences.. Although establishment of an AOEL relies heavily on expert judgement, its derivation needs to be reported as transparently as possible. Any agreed AOEL may need to be reassessed in the light of new data.

5.2 Since the targets and critical effects and the NOAELs may differ depending on the exposure time, more than one AOEL might in principle be established to allow for flexibility considering the anticipated exposure situations. However, as a default procedure, particularly to demonstrate that the requirements for the inclusion of an active substance in Annex I are fulfilled, only one AOEL should be set for an exposure period appropriate to the frequency and duration of exposure of operators (including contractors), re-entry workers, bystanders and residents for the uses supported in the DAR. This is typically short-term exposure, e.g. repeated exposure during a 3 month period. Hence, the default AOEL will be a systemic AOEL based on the most sensitive, relevant NOAEL from an oral short-term toxicity study or studies investigating specific end-points e.g. reproductive toxicity, developmental toxicity or neurotoxicity. Where an AOEL is based on a NOAEL for a non-severe end-point, the margin between the AOEL and the NOAEL / LOAEL for any severe /irreversible effect should be adequate based on the severity of the effect and the dose response relationship.

5.3 If there are indications that effects only become evident in chronic toxicity studies but might be initiated by shorter term exposures, the NOAEL for these effects in the long-term studies (including 1 year dog) should be considered in AOEL setting. In exceptional cases where the default approach is clearly unrepresentative of the actual exposure scenario (e.g. very short-term or continuous) it might be more appropriately to derive an AOEL based on NOAELs from shorter or longer duration studies. In all such instances full justification for the approach must be given.

5.4 When the results of the toxicological studies indicate that a relevant first pass effect and/or fundamental differences in metabolism or toxicity between the oral and dermal or inhalative route of exposure exist, route-specific studies should be considered for AOEL setting. Since an AOEL is defined as an internal value, the external NOAEL from a route-specific study must be converted into an internal value, using appropriate conversion techniques. The uncertainties introduced by the use of route-specific studies (normally with a limited range of investigations) should be carefully weighed against the uncertainties associated with route-to-route extrapolation.

5.5 An AOEL cannot be established for an active substance that is genotoxic in vivo and/or carcinogenic unless a threshold mechanism has been demonstrated.

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APPENDIX 1

APPLICABILITY OF DIFFERENT EXPOSURE SCENARIOS TO THE AOEL CONCEPT

Toxicology studies normally considered for deriving AOELs

1. The toxicology studies normally considered in the derivation of an AOEL are described in table 1. From these studies the highest NOAEL in the most sensitive relevant species will normally be used to derive the AOEL . Therefore animal studies involving dosing every day for periods up to and including 90 days will be considered. Other study types (e.g. investigating particular findings) might be considered if available.

Table 1 Toxicology studies routinely used in deriving AOELs , their dosing duration and main observations

Study type	Route	Dosing details	End points normally monitored
Acute neurotoxicity (rat)	Gavage	Once	Clinical signs; body weight; behaviour; motor activity; reflexes; brain and nerve pathology. Observations at several times to day 15.
Repeat dose neurotoxicity (rat)	Diet	Treated diet available 24h/day for 90 days	Clinical signs; body weight; behaviour; motor activity; reflexes; brain and nerve pathology.
28 day (rat, mouse, dog)	Diet	Treated diet available 24h/day for 28 days	clinical signs; haematology; blood chemistry; body weight; tissue / organ pathology
28 day (rat, mouse, dog)	Gavage or capsule	Once every day for 28 days	clinical signs; haematology; blood chemistry; body weight; tissue / organ pathology
90 day (rat, dog)	Diet	Treated diet available 24h/day for 90 days	clinical signs; haematology; blood chemistry; body weight; tissue / organ pathology
90 day (rat, dog)	Gavage or capsule	Once every day for 90 days	clinical signs; haematology; blood chemistry; body weight; tissue / organ pathology
Reproduction (rat)	Diet	Treated diet available 24h/day for about 10 weeks before mating and then during pregnancy, lactation and weaning.	Mating performance; body weight; fertility; litter size; pup weight; pup development.
Developmental (rat, rabbit)	Gavage or capsule	Once every day from day 6 of pregnancy to day 15 (rats) /19 (rabbits) modern studies dose from day 6 to 19 (rats) or 29 (rabbits)	Maternal body weight; clinical signs; litter size; pup weight; pup abnormalities and skeletal development

2. In terms of the proportion of an animal's lifespan, 90 days represents approximately 12% of the lifespan of a laboratory rat or mouse, approximately 2% of the lifespan of a dog and <1% of the working life of a human.

Definitions and exposure scenarios for different groups

Definitions of the different groups derived from EUROPOEM, 1992 and EUROPOEM II 2002, are:

Definitions

i. Operators

Operators are persons who are involved in activities relating to the application of a plant protection product; such activities include mixing / loading the product into the application machinery, operation of the application machinery, repair of the application machinery whilst it contains the plant protection product, emptying / cleaning of the machinery / containers after use. Professional operators should be trained and will be expected to take steps to minimise exposures to themselves and others. Professional operators may have access to appropriate personal protective equipment (PPE). Amateur operators (that is home garden users) are considered not to have access to PPE

ii. Workers

Workers are persons who, as part of their employment, enter an area that has been treated previously with a plant protection product or who handle a crop that has been treated with a plant protection product; for whom it is usually assumed that no protective clothing is worn. As a means of providing protection to workers, re-entry to a treated area can be prohibited for a period specified on the product label .

iii. Bystanders

Bystanders are persons who are located within or directly adjacent to the area where pesticide application or treatment is in process; whose presence is quite incidental and unrelated to work involving pesticides but whose position may put them at risk of potential exposure; who take no action to avoid or control exposure and for whom it is assumed that no protective clothing is worn and perhaps little ordinary clothing.

iv. Residents

Residents are persons who live, work or attend school or another institution adjacent to an area that has been treated with a plant protection product; whose presence is quite incidental and unrelated to work involving pesticides but whose position may put them at risk of potential exposure; who take no action to avoid or control exposure; for whom it is assumed that no protective clothing is worn and perhaps little ordinary clothing and who might be in the location for 24 hours per day.

Exposure scenarios

i. Professional operators

3. Professional operators might be exposed to a plant protection product when they are involved in activities relating to the application of a plant protection product including:

- opening the container;
- making a dilution and mixing (if necessary) ;
- loading into the application machinery;
- operation of the application machinery / applying the product;
- repair of the application machinery whilst it contains the plant protection product,
- emptying / cleaning of the machinery / containers after use.

Exposures would be *via* dermal and / or inhalation routes. These activities are taken into account in the exposure assessment

4. A professional operator might use the same product more than once per day, or possibly for an entire working day (8 – 10 hours) and might use the same or a similar product repeatedly during a growing season. However, for most products it is considered very unlikely that an operator (even as a specialist contractor) will use the same or similar product for more than 3 months in any one year. Therefore the use of toxicity studies of up to 90 days duration is normally appropriate for deriving the default AOELs for professional operator exposures.

ii. Amateur operators

5. Amateur operators might be exposed to a plant protection product when they are involved in activities relating to the application of a plant protection product including:

- opening the container;
- making a dilution and mixing (if necessary) ;
- loading into the application equipment;
- operation of the application equipment / applying the product;
- repair of the application equipment whilst it contains the plant protection product,
- emptying / cleaning of the equipment / containers after use.

Exposures would be *via* dermal and / or inhalation routes.

6. An amateur operator might use the same product more than once per day and might use the same or a similar product several times during the year. However, for most products it is considered very probable that when compared with a professional operator an amateur operator will use far less of the product on any

one day over a shorter timescale and is very unlikely to use the same or similar product for 90 days in a year. Therefore the use of toxicity studies of up to 90 days duration for deriving default AOELs for amateur operator exposures will be protective.

7. Unlike professional operators, amateur operators are considered not to be trained or have access to personal protective equipment (PPE). This could result in amateur operators receiving proportionately higher exposures relative to the amount of product used. However, the differences between professional and amateur exposures in terms of work rate and availability of PPE are taken into account in the assessment of amateur operator exposures.

iii. Re-entry workers / harvesters

8. Re-entry workers / harvesters might be exposed to a plant protection product when they enter an area (indoors or outdoors) that has been treated previously with a plant protection product or by handling a crop that has been treated with a plant protection product. This could be related to a number of different types of activity:

    - inspection (e.g. for disease or readiness for harvest);
    - thinning;
    - pruning;
    - weeding;
    - harvesting / cutting;
    - sorting;
    - handling crops treated prior to / during storage;

    There is evidence (EUROPOEM II, 2002) to indicate that the clothes worn and use of gloves is very variable thus it is assumed that re-entry workers /harvesters usually have no protective equipment. Work periods can be up to 8 hours per day. Exposures would be *via* dermal and / or inhalation routes. The use of the default AOELs are considered adequate for re-entry workers.

9. A member of the public such as a walker who moves through an area treated with a plant protection product can be considered to be exposed in a manner similar to a re-entry worker entering a treated crop. It is possible that the member of the public could cross several treated fields in a day and go walking regularly. However, because of crop growth / harvesting, disease / pest pressures varying through the year due to it is very unlikely that they will come into contact with crops treated with the same or a similar products for more than 90 days in a year. Exposures would be via dermal and / or inhalation routes. Because the first tier exposure model for re-entry workers assume no protective clothing this is equivalent to a member of the

public entering a crop. The use of the default AOELs are considered adequate for members of the public entering a treated area.

iv. Bystanders

10. Bystanders can be exposed to a plant protection product due to being present in or adjacent to the area being treated at the time of application. Activities that could result in bystander exposure include:

- walking into a crop during application;
- walking / travelling adjacent to an area being treated;
- being in a garden next to a field / orchard being treated;

Exposures could be by dermal or inhalation routes, from spray drift and / or vapour and would occur over a short period of time. Bystanders would be assumed to have no PPE and potentially be wearing minimal clothing.

11. Bystander exposures maybe acute if they relate only to the time of application. It could be argued that it is appropriate to compare bystander exposures with an acute reference dose equivalent to the ARfD. However, it is possible that a bystander who resides adjacent to a treated area or who regularly walks around areas treated with plant protection products could receive repeated exposures. There is also the potential for bystanders to be 'residents' and be subject to longer-term exposure. Therefore the use of the default AOEL, based on studies up to 90 days duration is considered protective of bystanders.

v. Residents

12. Resident exposures could result from several scenarios related to residing adjacent to an area that has been treated with a plant protection product, including:

- contact with surfaces that have been subject to spray drift e.g. turf or that have been directly treated;
- breathing air containing volatile active substances;

Exposures to contaminated surfaces could occur daily; inhalation of volatile components could be for 24 hours per day.

13. The magnitude of resident exposure is likely to be greatest immediately following application (or venting) and then reduce over time as the residue declines or is dispersed. It is possible that residents could be adjacent to areas that are treated repeatedly. However, because of crop growth / harvesting, disease / pest pressures varying through the year due to it is very unlikely that they will be exposed to significant levels, compared with the initial exposure (which should used in exposure estimation), of the same or a similar

products for more than 90 days in a year. Therefore the use of the default AOEL, based on studies up to 90 days duration is considered protective of bystanders.

Summary

14. For the range of scenarios described above, it is considered that the use of the AOEL concept is appropriate and that for most patterns of use the default for deriving the AOEL based on toxicity studies of up to 90 days duration is adequately protective. For specific products where use patterns will be outside the norm, the derivation of a long-term AOEL for use in operator exposure determinations will also be applicable to other exposed groups.

15. The related aspect of ensuring that the exposure assessments are appropriate for the exposed groups is outside the scope of this document and requires separate guidance.