

## **Special tool: acceptable operator exposure level (AOEL)**

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The Acceptable Operator Exposure Level (AOEL) is applied in the assessment and review of pesticides and biocides within Europe. The AOEL is a health-based limit-value and is established on the basis of the full toxicological package required for pesticides respectively biocides. The default AOEL represents the internal (absorbed) dose available for systemic distribution from any route of absorption and is expressed as an internal level (in milligrams/kilogram body weight/day). The concept of the AOEL as such has relevant legislative consequences and serves primarily as an important tool for operator risk assessment. Exposure estimates exceeding the AOEL do e.g. not allow an inclusion of active substances in Annex I of Directive 91/414/EC.

Although a draft guidance was published in 2005, there is no formal harmonized method for the derivation of AOEL in Europe yet. A number of aspects in the AOEL approach are still subject to discussion at the EU-level. Major points of discussion are the number of AOELs to be set in a default procedure (one or three (acute, short-term, and long-term AOELs), whether external route specific AOELs should be set (such as an AOELinhalatory or an AOELlocal dermal), and which assessment factors to be used for the working population. Similar discussions take place at the moment in REACH Implementation Project 3.2 where the Derived No Effect Level (DNEL) approach is being developed for risk assessment under REACH. The presentation will highlight the similarities and differences between the AOEL, DNEL and OEL approach as the three 'types' of limit values set for workers within Europe.

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Special tool:  
Acceptable Operator Exposure Level (AOEL)



This presentation is about...

- Acceptable Operator Exposure Level (AOEL)
- Operators, i.e. those who use products
- The methodology
- The (scientific) difficulties
- AOEL vs OEL vs DNEL



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...but not about...

- Non-threshold substances
- Bystanders, producers, residential users
- ADI (Acceptable Daily Intake): toxicological standard for chronic intake of pesticides
- ARfD (Acute Reference Dose): for acute intake
- Margin of Safety (MOS)



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## The AOEL (Dir. 91/414/EEC)

- Definition: The acceptable operator exposure level is the maximum amount of active substance to which the operator may be exposed without any adverse health effects.
- One part of the procedure for the authorisation of pesticides (and biocides). The Uniform Principles apply!



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## Starting point

- 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.
- Not necessarily the lowest NOAEL in the most sensitive species (expert judgement).
- The critical endpoints of the substance (including reproductive/developmental toxicity, neurotoxicity and non-genotoxic carcinogenicity) should be covered.

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## Substance dossier

- The AOEL is a health-based limit-value and is established on the basis of the full toxicological package required for Annex I inclusion.
- NOAEL based on substance dossier
  - Acute studies (acute toxicity/irritation)
  - Subacute studies (28 days)
  - Semichronic studies (90 days)
  - Chronic studies (lifetime)
  - Multi-generation studies
  - Developmental toxicity studies
  - Sensitisation
- Different routes: oral, dermal, inhalation



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## Substance dossier (2)

- Usually only adequate oral studies with repeated dosing are available. Therefore, oral studies are often the starting point for the calculation of the AOEL.
- If toxicokinetic or mechanistic studies provide strong indications for route-specific effects and/or fundamental route-specific differences in metabolism (e.g. first pass), route-specific studies should be considered for AOEL setting (expert judgement).
- The most relevant routes for exposure to pesticides/biocides are the dermal and, to a lesser extent, the inhalatory route.

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## Systemic AOEL

- 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).
- External NOAEL from route-specific study should be converted to an internal value (except for some inhalatory and dermal effects).



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## Selection of starting point

- Default: Short-term toxicity study as a starting point because it is assumed that exposure occurs in a period  $\leq 3$  mo/yr
- If longer exposure cannot be excluded, a chronic study is preferably used as a starting point.
- More than one AOEL may be established to allow for flexibility considering the anticipated exposure situations.

- Exposure duration
- Exposure frequency
- Toxicokinetics (excretion)
- Reversibility of effects



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## Procedure

- Select relevant NOAEL (study)
- Select absorption data
- Define the Assessment Factors (AF) to be used.
- Derive AOEL value (default for PPP is short term, systemic value)



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## Correction for absorption

- Data on toxicokinetics shall be used to assess the bioavailability after oral, dermal, and/or inhalatory administration of the substance.
- Uptake after oral exposure
- Based on toxicokinetic/ADME study (OECD 417)
- Absorption may be dose dependent!
- If the absorbed dose at a relevant dose level is significantly lower (<80%) than the applied dose, the dose is corrected with a factor equalling the percentage absorption.

## Assessment factors

- 'Safety factor' to 'correct' the selected NOAEL
- Conform Acceptable Daily Intake (ADI) principle
- Total factor: 100
  - Interspecies differences: 10
  - Intraspecies differences: 10
- From average rat to sensitive human.....

## AOEL calculation

$$\text{AOEL}_{\text{systemic}} \text{ (mg/kg lg/dag)} = (\text{NOAEL}_{\text{oral}} \times A) : 100$$

Where:

- NOAEL<sub>oral</sub> is the No-Observed-Adverse-Effect-Level from the most relevant oral study.
- A is the fraction of the substance that is taken up by the body after oral administration (e.g. 60% oral absorption: A = 0,6).
- 100 is the assessment factor (10x10)

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## Transparency

- Although establishment of an AOEL relies heavily on expert judgement, its derivation needs to be reported as transparently as possible. Any agreed AOEL might need to be reassessed in the light of new data.



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## Local effects

- Local effects not used as a starting point for the derivation of a systemic AOEL.
- Local effects are supposed to be controlled within the framework of the risk management proces (R-phrases, PPE, etc.)
- AOEL for local effects is possible

## Guidance

- Not yet a harmonized method for the derivation of AOEL in Europe (draft guidance 2005).
- EU Draft Guidance Document. Guidance for the setting of Acceptable Operator Exposure Levels (AOELs). Sanco/10182/2005 rev. 9, d.d. 5 July 2005.
- Opinion of the Scientific Panel on Plant health, Plant protection products and their Residues on a request from the Commission on the Guidance Document (GD) for the establishment of acceptable operator exposure levels (AOELs). (Question N° EFSA-Q-2005-271) adopted on 06 April 2006. *The EFSA Journal* (2004) 345, 1-12

## Major points of discussion at EU level

- The use of human data
- The number of AOELs to be set in a default procedure (one or three (acute, short-term, and long-term AOELs))
- External route specific AOELs (such as an AOEL<sub>inhalatory</sub> or an AOEL<sub>local dermal</sub>)
- Assessment factors to be used (allometric scaling, working population)

## AOEL vs OEL vs DNEL

	AOEL	OEL	DNEL
Basis	Health based	Health based	Health based
Database	Full data package	Available public literature	Tonnage dependent
Population	Workers	Workers	Workers, general population
Route	Inhalation, oral, dermal	Inhalation	Inhalation, oral, dermal

## AOEL vs OEL vs DNEL

	AOEL	OEL	DNEL
Default exposure period	Short term ( $\leq 3$ mo/yr )	Chronic	Chronic?
Internal vs external	Internal (External)	External	External
AF	10x10	Case-by-case	Default values
Local effects	Included?	Important endpoint	Included

## Conclusion

Differences exist

- Different frameworks
- Different starting points and agreements

But.....

Basically the same principles apply



Thank you for your attention



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