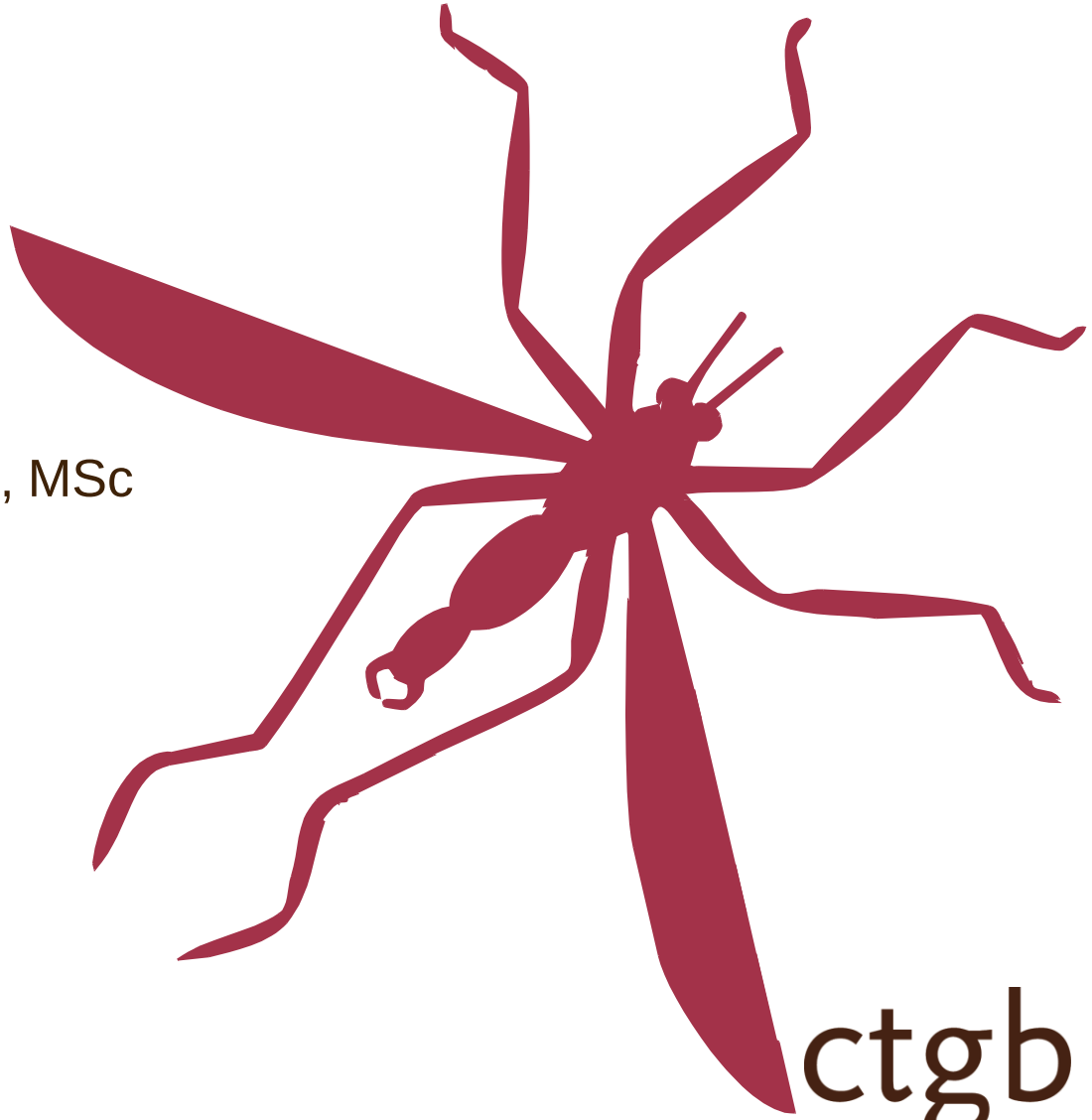
Introduction on reference values



Marloes Busschers, MSc

Board for the
Authorisation
of Plant Protection
Products and
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Outline

- Reference values
  - AOEL
  - ADI
  - ARfD
- Where to find them?

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AOEL (acceptable operator exposure levels)

- Acceptable operator exposure levels (AOEL) is a health based limit-value
  - Maximum amount of active substance to which the operator may be exposed without adverse health effects.
  - Based on the full toxicological dossier.
  - Represents the systemic dose.

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Deriving an AOEL

- Step 1: select relevant NOAEL
  - Based on short-term toxicity studies
    - In some cases chronic toxicity more appropriate (e.g. exposure > 3 months/yr)
  - Most sensitive species
  - Generally only oral studies with repeated dose available

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Deriving an AOEL

- Step 2: determine oral absorption value
  - From toxicokinetics studies
  - If absorbed dose is <80% than the NOAEL will be adjusted.

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Deriving an AOEL

- Step 3: define the safety factor
  - Standard factor: 100
    - Interspecies differences: 10
    - Intraspecies differences: 10
  - Additional factor:
    - ‘special’ effects, eg if critical effect is reproduction or tumours, or based on LOAEL.

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Deriving an AOEL

- Step 4: derive the AOEL

AOELsystemic (mg/kg bw/day) =
(NOAEL x Absorption): safety factor

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ADI

- The amount of a substance that can be consumed on a daily basis over a lifetime without appreciable health risk.
  - Based on chronic exposure studies

$ADI = NOAEL_{chronic}$ / safety factor (100)

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ARfD

- “An estimate of a chemical substance in food (or drinking water), expressed on a bodyweight basis, that can be ingested over a short period of time, usually during one meal or one day, without appreciable health risk to the consumer.”

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ARfD

- The following categories of toxicological alerts should suggest the need to establish an ARfD:
  - Lethality after administration of a single low dose orally
  - Developmental effects
  - Clinical signs, other pharmacological effects, or effects on target organs observed early in studies with repeated doses
  - Acute neurotoxicity
  - Hormonal or other biochemical alterations observed in studies with repeated doses, which might conceivably be elicited by a single dose.

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ARfD

- Generally based on subacute (14-28 days) or short-term (90-day) studies
  - Acute studies are usually not appropriate to determine NOAELs for critical effects as currently performed.
  - Other studies also possible, e.g. neurotoxicity studies

ARfD = NOAEL / safety factor (100)

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Sources for AOELs/ADI/ARfD

- Pesticide Properties DataBase:
  - Establish by the EU-project Footprint
  - Contains 650 active substances and 200 metabolites
  - Updated regularly
  - Contains EU harmonised reference values

http://sitem.herts.ac.uk/aeru/footprint/en/index.htm

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Pesticide Properties DataBase

- Data sources:
  - Annex 1 data supplemented with databases and documents from government departments, online databases (e.g. EXTOXNET), MSDS, peer reviewed data.
  - Each data item tagged with code that allows source of data to be identified.
  - Tag also includes quality score from 1 (low) to 5 (high)

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Sources for AOELs/ADI/ARfD

- Pesticide Properties DataBase
  http://sitem.herts.ac.uk/aeru/footprint/en/index.htm
- EU Review reports
  http://ec.europa.eu/sanco_pesticides/public/index.cfm?event=activesubstance.selection&a=1
- EFSA conclusions
  http://www.efsa.europa.eu/en/pesticides/pesticidesscdocs.htm
- JMPRs

  http://www.inchem.org/pages/jmpr.html

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Background information

- Guidance document for the setting an AOEL:
  http://ec.europa.eu/food/plant/protection/resources/7531_rev_10.pdf
- Guidance document for the setting an ARfD:
  http://ec.europa.eu/food/plant/protection/resources/7199_vi_99.pdf

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