ADI and ARfD derivation for biocidal active substances

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1. Background to ADI and ARfD setting

According to the ECHA Guidance Vol III part B (2015), if residues in food or feed are expected to arise from the use pattern of a biocidal product, an ADI and, if necessary, an ARfD should be derived.

ADI (acceptable daily intake) is an estimate of the amount of a substance in food or drinking water that can be consumed over a lifetime without presenting an appreciable risk to health (WHO, 1987).

ARfD (acute reference dose) is an estimate of the amount of a substance in food or drinking water that can be ingested over a short period of time, usually during one meal or one day, without appreciable health risk to the consumer (JMPR, 2002).

Both ADI and ARfD are external reference values and are expressed on a body weight basis.

According to ECHA Guidance Vol III Part B (2015), the principles for ADI and ARfD setting in plant protection products should be applied. For ADI setting there is no internationally agreed guidance but for pesticides the principles have been described in various publications (WHO 1990, 2009). For ARfD derivation, the OECD Guidance No. 124 should be followed, supported by the publication by Solecki *et al*. (2005). The ECHA Guidance Vol III Part B (2015) can be applied in support to the aforementioned guidance in selecting the critical dose descriptors and appropriate assessment factors.

2. When to set ADI and ARfD

Reference values must be derived for the most critical effect(s) if the substance exerts adverse systemic effects by a threshold mode of action, or local effects via the oral route. Reference values cannot be derived if the effects have entirely or partly a non-threshold mode of action (e.g. for mutagenicity, genotoxic carcinogenicity) or it is currently not possible to derive a threshold (e.g. local effects) (ECHA Guidance Vol III Part B, 2015).

According to the ECHA Guidance Vol III Part B (2015), "For certain PTs and use patterns, especially if the active substance can enter the food chain, ADI and, if necessary, ARfD should be derived". However, to align with the principles applied in the plant protection products framework, these reference values should always be derived if appropriate information is available, unless it is not scientifically justified (e.g. highly reactive substances where no residues are expected).

If an active substance is evaluated under several product types, ADI and ARfD should be reported in each assessment report, regardless of the PT. For clarity, a standard phrase could be included where relevant: "*The value was not used in the current assessment as no consumer exposure via food is expected in the PT/uses assessed*".

Already existing ADI and ARfD values from other European frameworks (e.g. food and feed additives, veterinary medicinal products, plant protection products) should be taken into consideration whenever possible (ECHA Guidance Vol III Part B, 2015). Conflict of scientific opinion should always be avoided, as recommended by Art. 95 of REACH Regulation and ECHA

Management Board (Decision 18/2013). Nevertheless, deviations from reference values already identified by other regulatory bodies would be possible on a case by case basis if different information or new methodology is available and a robust justification is provided.

3. What to consider in setting ADI and ARfD

The study in the most sensitive and relevant species resulting in the most appropriate dose descriptor (no observable adverse effect level; NOAEL) should be selected from the complete toxicology dataset.

The critical NOAEL should be based on the identification of the critical systemic effects.

In selecting the appropriate animal study, consideration needs to be given to relevance for human exposure in terms of duration and pattern of exposure. Generally, long-term oral studies are the basis for ADI derivation, because in these studies the test substance is normally incorporated in the diet and administered for the majority of the lifetime on a daily basis, reflecting the ADI concept.

Usually ADI and $AEL_{long\text{-}term}$ (AEL, acceptable exposure level) are derived on the basis of the same NOAEL from long-term or sub-chronic studies, and similarly, ARfD and AEL_{acute} are based on the same NOAEL from acute or short-term studies.

Short-term studies are more suitable for the derivation of the ARfD. If the critical effect has not been adequately evaluated in a single dose study, the endpoint from a repeated dose short-term toxicity study should be used (OECD, 2010; Solecki *et al.* 2005; ECHA Guidance Vol III Part B). Normally, all indications of acute toxicity observed in repeated dose studies should be considered as potentially relevant in setting an ARfD, in particular effects observed at the beginning of repeated dose studies. This also applies to developmental effects, which typically result from exposure during sensitive periods.

The route of administration should be considered carefully when evaluating the possible acute effects for ARfD derivation, and disregard effects not relevant for residue intake (Solecki *et al.* 2005).

Gavage administration may result in marked differences in kinetics following the bolus administration of a high dose compared to more frequent intakes of small amounts through the diet (WHO 1990). Furthermore, local gastrointestinal effects might not be relevant for ADI/ARfD derivation if it is shown that such effects are due to the gavage administration, and dietary administration does not produce the same effects (JMPR 2002, OECD 2010). For example, if diarrhoea and vomiting in dogs are due to local (irritant) effects and high active substance concentrations following specific dosing methods (e.g., capsule administration or gavage), then these effects should not be considered relevant for setting an ARfD (Solecki *et al*. 2005).

If an active substance administered via food/diet exerts local toxicological effects on the gastrointestinal tract, such effects may be considered relevant for ARfD derivation. For these direct effects, a reduction of the assessment factor may be considered (OECD 2010). It should be noted that the principles described in the Annex II of the plant protection products Regulation 1107/2009 require applying at least the default assessment factor of 100 for both ADI and ARfD derivation. However, when sufficient information is available and if justified, a deviation from the default assessment factor may be considered, thus applying an increased or decreased margin of safety. For ARfD derivation, a reduction of the assessment factor for human toxicokinetic differences may be justified if it can be assumed that the concentration of the active substance rather than the total intake would determine the effects (Solecki *et al*. 2005).

The rabbit is known to be sensitive to gastrointestinal disturbances due to a disruption in the balance of the caecal microflora. Some biocidal substances disturb the balance of the rabbit intestinal/caecal microflora leading to malnutrition and subsequent maternal toxicity, while humans might be exposed to higher doses without similar concern. For such substances, the information from prenatal developmental toxicity study might not be relevant for humans.

Multi-generation and teratogenicity studies provide information relevant for medium-term exposure, but in exceptional cases they have also been used in establishing ADIs and ARfD. For example, the NOAEL from a reproductive toxicity study may serve as a basis for ADI setting when a higher assessment factor is used that leads to an ADI lower than the ADI that would be derived when considering a NOAEL from a long term study and applying a default assessment factor of 100 (WHO 1990).

4. References

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