

Appendix IV Guideline triggers for consideration of the need for additional toxicity information to assess equivalence of a new source compared to the reference source

Important notes:

- a) These guidelines indicate the need for additional consideration. They are not automatic triggers for conducting additional toxicity studies. A reasoned case may be acceptable in place of a further study, particularly if a further study involves animal testing.
- b) If there are new or increased levels of impurities (increased levels are defined in 5.2) in the new source compared with the reference source, additional toxicity data may be needed if the currently available information is insufficient. For large differences (e.g. 5-fold and above) in impurity levels between the reference source (or the material tested) and the new source, the need for a convincing case and/or data increases.
- c) These guidelines are not intended to apply where the new source contains an increased level of a relevant impurity. The applicant will need to provide a very strong case to support this and it will require very careful case-by-case assessment.
- d) The initial trigger for considering the need for further toxicity testing relates to a comparison of the technical specification of the new source with the technical specification of the reference source. However, ideally, a more refined assessment of the need for further testing should be based on a comparison of the technical specification of the new source with the technical specification of the material used in the relevant toxicity study(ies) to support the reference source. A more refined assessment such as this may not be possible if information on the technical specification of material tested in studies to support the reference source is not readily available.

The following approach is recommended for consideration of the need for additional toxicity information:

1. In all cases of new/increased levels of impurities, need:

- toxicology (Q)SAR analysis, if a reliable prediction is possible and can be supported scientifically. If there is an SAR alert for the impurity, it should be considered if this alert is also present in the active substance (and hence whether the potential concern is addressed by studies on the active substance). It might be considered appropriate to having a closer look at the alert and the structure triggering the alert or to investigate further to determine the validity of the alert in this particular case, e.g., by conducting a study.

2. For a new/increased impurity present at >0.1-< 1% in the technical specification for the new source, need:

- an Ames test either with technical material from the new source or the respective impurity, unless there are clear indications that another type of genotoxicity test might be a more appropriate (e.g. SAR evidence for an effect on the mitotic spindle). If the Ames (or other) test result is not clearly negative further *in vitro* genotoxicity testing is required.
[No Ames study is needed if the impurity is present at a satisfactory level in all other genotoxicity studies with the a.s]
If technical material from the new source is tested, the highest dose (micrograms technical material/plate) needs to be high enough to adequately investigate the

mutagenic potential of a low level of impurity. This should take into account the limit dose and the extent of toxicity at the highest dose tested.

3. For a new/increased impurity present at >1% in the technical specification for the new source, need:

- 3 *in vitro* genotoxicity assays with the technical material from the new source or the respective impurity (further genotoxicity testing *in vivo*, see data requirements for regulation 1107/2009, if the *in vitro* genotoxicity assays are not all clearly negative)

If technical material from the new source is tested, the highest dose (micrograms technical material/plate or mg technical material/mL medium) needs to be high enough to adequately investigate the mutagenic potential of a low level of impurity. This should take into account the limit doses for the tests and the extent of toxicity at the highest dose tested.

and consider¹³ need for:

- acute oral study*
- and/or skin sensitisation study (local lymph node assay normally preferred)
- and/or developmental toxicity study (typically an oral developmental toxicity study in one species should be sufficient; alternatively OECD reproduction/developmental toxicity screening test may be appropriate)
- and/or neurotoxicity study (if there is a concern that the impurity could be more neurotoxic than the a.s.).

[*Acute toxicity data would only be required if the evidence suggests that the presence of the impurity could result in a more severe hazard label for the a.s.. To decide on this in the absence of data, assume an extreme worse case oral LD50 of 1 mg/kg bw for the impurity.]

4. Other information to be considered on a case-by-case basis for a new/increased impurity present at >5% in the technical specification for the new source, notably:

- A 28-day or 90-day bridging study (with technical material from the new source) for repeat-dose effects to assess ability of the available data to predict the toxicity of the technical specification for the new source.
- In very special cases, other studies that are crucial for coming to a conclusion might be requested.

¹³ Inter alia, taking into account the predicted operator/worker and/or consumer exposure level