SciRAP items and guidance for evaluating relevance of in vivo toxicity studies for human health hazard and risk assessment.

Please consider whether the following five aspects of the study are directly relevant, indirectly relevant or not relevant for human health hazard or risk assessment. Direct, indirect and insufficient relevance has been defined by the European Commission Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR 2012).

Relevance item	Guidance
1. The identity of the tested substance	Consider if, based on the information given, i.e. CAS-number or similar, it can be concluded that the substance being investigated is the same as the substance subject to assessment. Consideration should also be given to the purity of the test substance and whether there may be impurities present that could significantly affect the identity of the substance. How to judge this item: **Directly relevant** - the study addresses the substance or agent (stressor) of interest for the hazard or risk assessment being conducted. **Indirectly relevant** - the study addresses a related substance or agent (stressor) to the one of direct interest for the hazard or risk assessment being conducted. **Not relevant** - the study addresses a substance or agent (stressor) that is not relevant for the specific hazard or risk assessment being conducted
2. The animal model used	Is the animal model relevant for human health outcomes? Consider the motivation behind the choice of animal model (species and strain) given, i.e. why one species or strain was preferred above another. Take into account factors such as species and strain differences in kinetics, metabolism, receptors, etc. Note that the default assumption is that effects observed in the animal model are relevant for human health unless there is evidence supporting otherwise. How to judge this item: **Directly relevant** - there is no evidence that the animal model is irrelevant for the hazard or risk assessment being conducted. **Indirectly relevant** - there is no clear evidence that the animal model is irrelevant for the hazard or risk assessment being conducted. However, there may be a suspicion of species and/or strain differences affecting the sensitivity of the model. **Not relevant** - there is evidence that the animal model is not relevant for the hazard or risk assessment being conducted.

Relevance item	Guidance
3. The endpoint studied	Are the endpoints relevant for human health outcomes? Consider the rationale given for the selection of endpoints. Note that several endpoints may have been investigated. The study should be evaluated based on each individual endpoint, i.e. the reliability and relevance of a study may have to be evaluated several times based on different endpoints. Also consider that even if an endpoint is not (directly) relevant to humans it may be related to another relevant endpoint that was not measured in the study. How to judge this item: **Directly relevant** - the study addresses the endpoint of interest for the hazard or risk assessment being conducted. **Indirectly relevant** - the study addresses a related endpoint to the one of direct interest for the hazard or risk assessment being conducted. **Not relevant** - the study addresses an endpoint that is not relevant for the specific hazard or risk assessment being conducted
4. The route of administration	Is the route of administration relevant to human exposure? Consider the rationale behind choosing the route of administration; is it described and valid. Note that, even if a route that is not directly relevant was used in the study, the data may still be used for risk assessment after considering the kinetics of the substance. How to judge this item: **Directly relevant** - the route of administration is the same (e.g. oral) as the route of exposure of interest for the hazard or risk assessment being conducted. **Indirectly relevant** - the route of administration is not the same as the route of exposure of interest for the hazard or risk assessment being conducted but the kinetics of the substance are sufficiently known to support extrapolations between different exposure routes. **Not relevant** - the route of administration is not the same as the route of exposure of interest for the hazard or risk assessment being conducted and the kinetics of the substance are not sufficiently known to support extrapolations between different exposure routes. Or knowledge of the kinetics do not support extrapolations between different exposure routes.

Relevance item	Guidance
5. The dose levels and resulting tissue levels	Are the dose levels relevant for measured or predicted human exposure? Dose levels should preferably be motivated and based on available information, e.g. data on toxicity and toxicokinetics, or dose-finding studies. Specifically consider species differences in metabolism, toxicokinetics and toxicodynamics. Also consider any effects that may be secondary to other toxicity (that may not occur at lower doses). How to judge this item: **Directly relevant** - the study addresses dose and/or tissue levels of interest for predicted human exposure in the hazard or risk assessment being conducted. **Indirectly relevant** - the study addresses dose and/or tissue levels that are not directly relevant for predicted human exposure in the hazard or risk assessment being conducted but the characteristics of the dose-response are sufficiently known to support extrapolations. **Not relevant** - the dose and/or tissue levels addressed in the study are clearly not relevant for predicted human exposure in the hazard or risk assessment being conducted. Knowledge about the characteristics of the dose-response are do not support extrapolations between the doses tested and human exposure levels.

SCENIHR. 2012. Memorandum on the use of the scientific literature for human health risk assessment purposes – weighing of evidence and expression of uncertainty. Available on-line: https://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_s_001.pdf