

WHO Prequalification of Vector Control Products

Considerations for fulfilling the acute 6-pack requirement for insecticide-treated nets

PURPOSE

For the WHO prequalification assessment of insecticide treated nets (ITNs), the standard 6-pack mammalian acute toxicity studies are included in the dossier requirements.

The purpose of this document is to provide guidance and explanations of criteria which will be considered in waiving the mammalian acute toxicity data requirement (single exposure via the oral, dermal and inhalation route, eye and skin irritation and skin sensitization) for ITNs.

BACKGROUND

Mammalian acute toxicity studies (acute 6-pack)

The short-term toxicity testing battery consists of the following six acute toxicity studies, commonly referred to as the acute 6-pack:

- Acute oral LD50 – Rat
- Acute dermal LD50 – Rat or rabbit
- Acute inhalation LC50 – Rat
- Primary eye irritation – Rabbit
- Primary dermal irritation – Rat or rabbit
- Dermal sensitization (local lymph node assay, guinea pig maximization test, or Buehler test).

For regulatory purposes, acute 6-packs may be required for technical materials, intermediate formulants, and end use products.

Purpose of acute toxicity studies in the evaluation of pesticides

Hazard categorization

The acute oral, dermal, and inhalation studies are used to determine the toxicity of the product following a single exposure to determine the LD50 (lethal dose 50) via the designated route of exposure. The primary eye irritation and primary skin irritation studies measure the severity of irritation or corrosivity upon exposure to the product. The dermal sensitization study determines whether a product can cause an allergic/sensitization reaction. Based on the acute toxicity data, pesticide products (technical and end use) are assigned toxicity categories established by the Globally Harmonized System (GHS, 2017) or the WHO Classification of Pesticide by Hazard (WHO 2019).¹

Labeling and classification of chemicals

National regulatory authorities rely on acute toxicity data to serve as a basis for precautionary labeling which includes the signal word, hazard symbol, personal protective equipment, statements of practical treatment, identification of child-resistant packaging, and designation of pesticides which may be applied only by certified applicators.

¹ International code of conduct on the distribution and use of pesticides: Guidelines on data requirements for the registration of pesticides. <https://www.fao.org/3/i3167e/I3167E.pdf>

Fulfilling the ITN dossier requirement for acute 6-pack

As an ITN is both the formulation and the delivery mechanism of the active ingredient (AI), direct testing of the ITN may not be possible using common methods for the acute toxicity studies.

Conducting the acute toxicity 6-pack on the ITN by physically altering the ITN (e.g., shredding the final product and using it as the test material, or extracting the total AI content from a portion of ITN and using the eluent as the test material) is not recommended as it does not represent actual acute exposure scenarios.

Generally, waivers are considered when a toxicity endpoint is not relevant to an end-use product based on the use scenarios and exposure potential. Based on the formulation characteristics of ITNs (e.g., low concentrations of AI, bound/biologically unavailable reservoir of AI, and low toxicity levels of typical formulants [binders and polyethylene]), manufacturers are encouraged to consider submitting waiver requests for all, or some, of the acute toxicity studies relying on the following guidance.

WAIVER PRINCIPLES

According to the European Union (EU) Biocidal Products Regulation (BPR) requirements, testing on the biocidal product does not need to be conducted, if there are valid data available on each of the components in the mixture sufficient to allow classification of the mixture according to the rules laid down in the Classification, Labeling, and Packaging (CLP) Regulation 1272/2008 and synergistic effects between the components are not to be expected (EU, 2012).

According to OECD (2016), testing on an end-use product may not need to be conducted if there are valid data available on each of the components in the product sufficient to allow classification of the product according to recognized calculation approaches, and synergistic effects among any of the components are not expected. Data demonstrating the toxic potential of the components would need to be made available to support such a waiver.

Review of Waiver Requests for Acute Toxicity ITN Applications

All waiver requests will be considered on a case-by-case basis following a weight-of-evidence approach. Waiver requests should be submitted with the initial submission of the product dossier in Module 4: Safety.

A valid scientific rationale including sufficient explanation and documentation to support the request for each acute toxicity study must be included. Waivers may be submitted for all or individual studies of the acute 6-pack. The burden of proof lies entirely with the party requesting the waiver. Citation of the above principles will not, by themselves, be considered.

Information and/or data which will be considered in waiving the product-specific acute toxicity requirement include the acute toxicity data of the AI(s), other formulants, formulated intermediates, and any other integral component of the formulation. The waiver request will be considered based on the nature of the effects observed, the routes of potential exposure, the doses at which the effects occurred, and the severity of the observed effects. Generally, waivers are considered when there is little or no significant human exposure potential by a given route of exposure.

REFERENCES

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