Guidance for Waiving or Bridging of Mammalian Acute Toxicity Tests for Pesticides

Pest Management Regulatory Agency
Health Evaluation Directorate

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1.0 Introduction

The objective of the following document is to provide guidance and criteria to pesticide applicants and registrants concerning the waiving of acute toxicity data, as well as the extrapolation of data from one product to another (often referred to as bridging). Clarification of these two concepts is important to ensure that the Pest Management Regulatory Agency (PMRA) is provided with the appropriate data required for decision-making and that unnecessary animal testing is avoided.

In 2011, the Office of Pesticide Programs (OPP) of the United States Environmental Protection Agency (EPA) issued a document titled "Guidance for Waiving or Bridging of Mammalian Acute Toxicity Tests for Pesticides and Pesticide Products (Acute Oral, Acute Dermal, Acute Inhalation, Primary Eye, Primary Dermal, and Dermal Sensitization)". A revision to EPA's document was subsequently released in 2012. As part of ongoing alignment efforts, the PMRA has considered this guidance and is issuing relevant and applicable guidance for Canadian applicants and registrants of pesticide products. Accordingly, portions of the text in this document have been excerpted from the EPA's guidance document. It should be noted that much of the guidance articulated in the current document reflects ongoing practice at the PMRA.

This guidance document is intended to complement toxicology data requirements set out by the PMRA. The guidance is applicable to conventional chemical pesticides as well as antimicrobials and biochemical/nonconventional pesticides (excluding straight chain lepidopteran pheromones). Acute toxicity data are not required for straight chain lepidopteran pheromones. This document is not applicable to microbial pesticides due to their unique nature; data requirements for microbials are addressed in DIR2001-02.

While every effort has been made to make this guidance document as comprehensive and up to date as possible, it is expected that there will also be cases where requests for waivers or bridging will fall outside the scope of this document and will require separate review and/or consultation with the Agency (e.g., products containing particles in the nanoscale). Note that as science advances, new and/or alternative approaches to waiver and/or bridging requests may be developed, and this guidance will be updated to reflect these approaches.

2.0 Waiver Criteria

Generally, waivers are considered when a data endpoint is not relevant to the pesticide (technical grade active ingredient or end-use product), such as not requiring an acute oral toxicity study when the pesticide exists as a vapour or gas. Specific waiver criteria for each type of acute toxicity study are discussed below. Note that in accordance with Regulatory Directive 2003-01: Organizing and Formatting a Complete Submission for Pest Control Products, all waiver requests must be submitted to the Agency in writing for consideration. In addition, requests for a waiver of any acute toxicity data requirement or justification for bridging to an existing product should be prepared in accordance with Agency formatting requirements and should include a valid scientific rationale and documentation to support the request.

When a waiver is granted for an acute toxicity study, this will be noted in the toxicity study profile for the product in order to acknowledge that there is not a data gap for this study.

Labelling language for acute hazard will be reflective of the basis of the granted waiver. For example, the lack of acute inhalation hazard would be reflected through no requirement for label language regarding acute inhalation hazard. By contrast, if an acute inhalation toxicity waiver is granted on the basis of the product being corrosive, the label would need to reflect the potential for corrosivity of the product by the inhalation route, as conduct of an actual inhalation study would not be humane.

2.1 Acute Oral Toxicity

An acute oral toxicity study may not be required if any of the following criteria are met:

- The test material is a gas or is highly volatile;
- The test material is a non-friable material and is too large to be ingested; or the product design prevents oral exposure. End-use products such as pet collars, plastic ear tags and tamper resistant roach traps and bait boxes often meet these criteria.
- Even though some end-use products may be too large to be ingested, there is some concern when these products are to be used in and around the home due to children's chewing, licking and sucking behavior. In some cases a waiver may be appropriate based upon the oral toxicity of the individual components of the pesticide product and the quantity of each component contained in the product. In this case, precautionary labelling (i.e., hazard symbol and signal words) should reflect the hazard potential of the technical grade active ingredient or individual formulants.

2.2 Acute Dermal Toxicity

A dermal toxicity study may be waived if any of the following criteria are met:

- The test material is corrosive to skin, or has a pH less than 2 or greater than 11.5 (OECD, 2002); or
- The product design prevents dermal exposure. Products such as tamper-proof roach traps and bait boxes often meet these criteria.

2.3 Acute Inhalation Toxicity

An acute inhalation toxicity study may not be required if any of the following criteria are met:

- **Low Volatility:** Low-volatility products are defined as having vapor pressures <1 x 10-5 kPa (7.5 x 10-5 mmHg) for indoor uses, and <1 x 10-4 kPa (7.5 x 10-4 mmHg) for outdoor uses at 20-30º C (Whalan et al., 1998).
    - Waivers for acute inhalation toxicity studies may be considered for low-volatility pesticide products that are not aerosolized (i.e., generated as a mist, fog, spray, dust, smoke, or fume), heated, evaporated, or otherwise made inhalable as a gas or vapour under conditions of use, storage, handling, or transport. The applicant must provide the vapor pressure for the active ingredient and the formulated product.
    - If an inhalation toxicity study is needed for a product with low volatility, it may be necessary to generate an aerosol. Further guidance can be found in OECD Guidance Document 39 (OECD, 2009).

- Technical grade active ingredients that have a high vapor pressure may not pose an inhalation hazard if they are contained in viscous liquids, waxes, resins, lotions, and caulks. Such uses may be considered for registration in the absence of inhalation toxicity data on the end-use product provided the applicant demonstrates there is no substantial human exposure via inhalation due to off-gassing.

- **Non-inhalable Aerosol Particle Size:** Inhalable liquid and solid particles are capable of entering the human respiratory tract via the nose and/or mouth, and are generally defined as being smaller than 100 µm in diameter. Particles larger than 100 µm are less likely to be inhalable. Of those particles which are inhalable, respirable particles pose a particular hazard because they are small enough to reach the alveoli, the major site of absorption in the respiratory tract. It is important to note that a pesticide need not be respirable to pose a hazard. Many chemicals are well absorbed in the nasal mucosa. Waivers for studies of any duration may be considered for test articles that do not pose a significant inhalation hazard because the particles are too large to be inhaled.
  - Solid aerosol particles can be generated as dusts, fumes, smoke, and granules. When performing an inhalation toxicity study of a solid material, the test article is typically crushed in a ball mill to achieve a respirable particle size for the species being tested (a mass median aerodynamic diameter (MMAD) of 1-4 µm in an rat acute study or 1-3 µm in a rat repeated exposure study). When an applicant requests a waiver on the basis of solid particle size, they must demonstrate that their product contains large, non-inhalable particles which are resistant to attrition. This can be accomplished by using the latest version of the American Society of Testing Materials (ASTM) Test Method E728-91-Standard Test Method for Resistance to Attrition of Granular Carriers and Granular Pesticides (http://www.astm.org/).
  - Liquid aerosols can be generated as mists and fogs by spraying, nebulization, and by the pouring of liquids. An aerosol for a product formulation or application method may be considered essentially non-inhalable provided >99% of the particles by mass are >100 µm in diameter at the point where humans are exposed (Whalan et al., 1998). Waiver rationales based on the use of medium or coarse spray nozzles that result in large droplets (100 – 500 µm diameter) are generally insufficient as it has been shown that within seconds of leaving a nozzle, large droplets of an aqueous mix can rapidly shrink to a size that is inhalable and often respirable (Matthews, 2008). Consideration should be made for the likelihood that liquid particles may shrink due to evaporation and therefore may become inhalable. Waivers will not be granted for liquid aerosols on the basis of large particle size unless the applicant can demonstrate that large droplets do not shrink to an inhalable size (i.e., < 100 µm).
  - A waiver may not be appropriate for products that may have a high toxic potential by the inhalation route.

- **Other Considerations:**
  - A waiver for an acute inhalation toxicity study may be considered if an inhalable atmosphere cannot be generated with reasonable effort. Extraordinary measures are not required. The waiver request should include a clear description of the methods and equipment used to generate an inhalable concentration of the product. A product that cannot be generated as a vapor at a toxic concentration should be generated as a liquid aerosol. Further guidance can be found in OECD Guidance Document 39 (OECD, 2009).

- An example of a waiver candidate under this criterion is pesticidal paint (*e.g.*, antifouling paint) which may clog the airways of animals and which may be impractical to generate as an aerosol in an inhalation chamber. If it is not practical to test a product formulation, an acute inhalation toxicity study of the pesticidal active ingredient is recommended. Precautionary labelling for the paint product may be justified on the basis of testing of the active ingredient.
- A waiver for an acute inhalation toxicity study may be considered for products that demonstrate the highest toxicity category for acute oral or dermal toxicity according to PMRA criteria (see Appendix for further details). Such products will require the signal words DANGER POISON on the label.
- The test material is corrosive to skin, or has a pH less than 2 or greater than 11.5 (OECD, 2002).

2.4 Primary Eye Irritation

A primary eye irritation study may not be required if any of the following criteria are met:

- The test material is corrosive to skin, or has a pH less than 2 or greater than 11.5 (OECD, 2012);
- The test material has been placed in the highest toxicity category for acute dermal toxicity (i.e. warranting signal words DANGER POISON on the label). Such products will require the signal words DANGER EYE IRRITANT on the label on the basis of potential eye effects; or
- The product design prevents ocular exposure. Products such as tamper-resistant roach traps and bait boxes may meet this criterion.
    - Waivers may be appropriate for products composed of granules or pellets that are very large (unable to be retained in the eye) or non-friable (as demonstrated by an attrition study), if the material retains its physical form under application conditions (i.e., it is not dispersed in water prior to application). Size range of the granules which compose the product should be documented and submitted as part of the request.
    - Although it may not seem as though some products have ocular exposure potential, full consideration of the conditions of use are necessary prior to determining the applicability of a waiver and the resulting labelling. For instance, while treated fabric may not come into direct contact with eyes, the possibility exists that sweaty hands could transfer residues from treated clothing to the eyes. In this case, an eye irritation study may be waived for the treated fabric but it would require labelling based on the eye irritation potential of the technical grade active ingredient.

2.5 Primary Dermal Irritation

A primary dermal irritation study may not be required if any of the following criteria are met:

- The test material is corrosive to skin, or has a pH less than 2 or greater than 11.5 (OECD, 2002);
- The test material has been placed in the highest toxicity category for acute dermal toxicity (i.e. warranting signal words DANGER POISON on the label). Such products will require the signal words DANGER SKIN IRRITANT on the label on the basis of potential dermal effects;

- The product design prevents dermal exposure. Products such as tamper-proof roach traps and bait boxes may meet this criterion; or
- The test material is a pesticidal paint which will not allow evaluation of dermal irritation because strong dyes or pigments may complicate interpretation of the result. In such situations the applicant should conduct a preliminary dermal exposure assessment of the material to the skin of an appropriate test species (rat or rabbit, preferably) in order to determine the degree of adherence and/or dermal staining. All observations made during this preliminary dermal exposure, as well as supporting acute toxicity data on the formulation components, should be included in the waiver request.

2.6 Dermal Sensitization

A dermal sensitization study may not be required if any of the following criteria are met:

- The test material is corrosive to skin, or has a pH less than 2 or greater than 11.5 (OECD, 2002) at the most dilute use concentration recommended on the product label;
- The product design prevents dermal exposure. Products such as tamper-proof roach traps and bait boxes often meet this criterion; or
- The technical active ingredient(s) or one of the formulants contained in the end-use product is a known sensitizer. Such products will require the signal words POTENTIAL SKIN SENSITIZER on the label.

Waivers will not be granted for pesticidal paints with rationales that dyes and pigments will interfere with interpretation of results in guinea pig sensitization models. Instead, applicants and registrants are encouraged to utilize alternate methods such as the local lymph node assay that are not compromised by the presence of dyes or pigments.

2.7 Granular End Use Products

For the purposes of this guidance, granular end use products are limited to those products composed of a high percentage (generally greater than 90%) of granular inert carrier(s) (corn cobs, clay, limestone, sand, food) and a minimal amount of sticker/binder (generally 5% or less of the formulation). Rodenticide baits are excluded from the data waiver/bridging approach outlined below.

Acute toxicity studies (acute oral, dermal or inhalation toxicity studies) can be waived for granular end-use products that comply with the description above. If the acute toxicity profile of the technical grade active ingredient(s) proposed for use in a granular pesticide requires no signal word on the label or requires the signal word CAUTION POISON, the end use product can be labelled to reflect low acute toxicity (i.e., no signal words required). This extrapolation for acute systemic toxicity is based on dilution. The assumption is that the innocuous formulant does not contribute to the toxicity, and thus acts as a diluent. If the acute toxicity profile of the active ingredient(s) requires the signal word DANGER POISON or WARNING POISON, then the Agency generally will not accept calculations that bridge downward from these categories, and hazard labelling would have to reflect that of the technical grade active ingredient; data would generally be required for reducing the toxicity category and hazard statements on labels of the proposed end use product.

Irritation studies (skin and eye) can be waived for the granular end use-products described above. Labelling for irritation potential for the end-use product would need to conform to irritation labelling used for the technical grade active ingredient(s) or reflect the known irritation of formulants contained in the end-use product. If a granular end use product contains any ingredient (technical grade active ingredient or formulant) that is a known sensitizer, the formulated product generally would be labelled as a sensitizer. If the technical grade active ingredient is not a dermal sensitizer, and there are no known dermal sensitizers in the end-use product, a dermal sensitization study may be waived for the end-use product and the product will not require sensitization labelling. If dermal sensitization data on a substantially similar product indicate no dermal sensitization, these data may be cited in support of the product. This determination will be made with data on the active ingredient or information provided by the applicant on a formulant (e.g., Material Safety Data Sheet - MSDS).

EXAMPLE :

Known Active Ingredient Toxicity	Active Ingredient Labelling	Presumed Granular End Use Product Toxicity	Granular End Use Product Labelling
Oral – moderate toxicity	WARNING POISON	Oral – moderate toxicity	WARNING POISON
Dermal – slight toxicity	CAUTION POISON	Dermal – low toxicity	No signal word required
Inhalation – low toxicity	No signal word required	Inhalation – low toxicity	No signal word required
Eye Irritation – moderate irritant	WARNING EYE IRRITANT	Eye Irritation – moderate irritant	WARNING EYE IRRITANT
Skin Irritation – mild irritant	CAUTION SKIN IRRITANT	Skin Irritation – mild irritant	CAUTION SKIN IRRITANT
Skin Sensitization – positive skin sensitizer	POTENTIAL SKIN SENSITIZER	Skin Sensitization – positive skin sensitizer	POTENTIAL SKIN SENSITIZER

3.0 Bridging of Data for Acute Toxicity Endpoints and Labelling

Bridging refers to the use of an existing data set to characterize the hazard for another chemical for which there is little or no existing data. Generally, bridging can be supported when there are existing data on a product to address an endpoint for a proposed product and data protection provisions have been respected. Specific areas where this is currently applied in the PMRA are discussed below.

Many end-use products proposed for registration are similar in composition to one or more currently registered products with an existing complete acute toxicity data base. In these and certain other situations, evaluators may be able to determine a complete or partial acute toxicity profile for the proposed product, and would define some or all of the hazard classifications for acute systemic toxicity (i.e., by oral, dermal and inhalation routes, skin and eye irritation and dermal sensitization) based on the applicability of the existing data. Each route-specific hazard determination eliminates the need to conduct the associated acute toxicity study on the proposed

product. The underlying logic for each determination is, in most cases, based on expert scientific judgment.

The proposed end-use product should cite a specific, well-defined acute toxicity profile of a registered product. The physical form of the product for which bridging is being requested should also be similar to the existing product. Attempts to bridge acute toxicity study results from a product containing a lower concentration of the technical grade active ingredient to a proposed product containing a higher concentration of the technical grade active ingredient is not recommended, as a higher concentration cannot be expected to have the same toxicity categories as a lower concentration and thus may need to be tested separately. Conversely, study results on higher concentrated products may be used to support lower concentrated products containing the same technical grade active ingredient and formulants; however, precautionary labelling would reflect that of the higher concentrated product (additional explanation below).

Determining the similarity of the proposed product to the registered product involves a comparison of the product chemistry and product formulation data (including the percentage of active ingredient(s) as well as formulants). Examples of dissimilar products from a toxicological perspective include (but are not limited to): use of a formulant that is not currently contained in any other pesticide formulation; significant changes in the percentage of active ingredient; new formulation types; changes in the identity or proportion of formulants. Although toxicological similarity is usually the simplest form of bridging, the process can be complex, involving a great deal of judgment on the part of the evaluator(s) making the comparison.

Where a proposed product has been found to be toxicologically similar to a registered product, the precautionary labelling of the proposed product should reflect that of the registered product as appropriate.

In the simplest example, a registered product may be cited to support the registration of a new product that is essentially a water dilution of the registered product. Even though dilution with water may make the new product less hazardous, there would be no change in the signal words. In the absence of new acute toxicity data, the precautionary labelling for the diluted product would be the same as for the cited product.

Situations may arise where an applicant may claim that their proposed product has a reduced hazard potential by one or more exposure routes relative to the otherwise toxicologically similar cited product(s). To support this statement, an appropriate study should be submitted. For example, suppose an existing product requires the signal word WARNING –EYE IRRITANT in terms of eye irritation potential, but no other signal words for other hazards, and there is a proposal to reformulate this product in such a way that the eye irritation potential is reduced. The lowered toxicity may be a result of reducing the percentage of an active ingredient, changing formulants, or changing the pH. In these cases, the applicant should cite the existing data base for the old formulation, and submit an eye irritation study which demonstrates that the proposed reformulated product has lower eye irritation potential. The signal word and precautionary labelling can be revised accordingly.

4.0 References

G.A. Matthews. Pesticide Application Methods. Third Edition. Wiley-Blackwell. London.2008. Pages 74-102.

OECD (2002). Supplement to Test Guideline 404. A Sequential Testing Strategy for Dermal Irritation and Corrosion. doi: 10.1787/9789264070622-en

OECD (2009). Guidance Document on Acute Inhalation Toxicity Testing. Environmental Health and Safety Monograph Series on Testing and Assessment No. 39.

OECD (2012). Supplement to Test Guideline 405. A Sequential Testing Strategy for Eye Irritation and Corrosion. doi: 10.1787/9789264185333-en

PMRA (2001). Regulatory Directive (2001-02): Guidelines for the Registration of Microbial Pest Control Agents and Products. Ottawa, Canada. http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_pol-guide/dir2001-02/index-eng.php

PMRA (2003). Regulatory Directive (2003-01): Organizing and Formatting a Complete Submission for Pest Control Products. Ottawa, Canada. http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_pol-guide/dir2003-01/index-eng.php

U.S. EPA (2012). Guidance for Waiving or Bridging of Mammalian Acute Toxicity Tests for Pesticides and Pesticide Products (Acute Oral, Acute Dermal, Acute Inhalation, Primary Eye, Primary Dermal, and Dermal Sensitization). Washington, D.C. http://www.epa.gov/pesticide-registration/bridging-or-waiving-data-requirements

Whalan, J., Cooper, D., Gibbons, D., Ross, J., Sanborn, J. (1998): Inhalation Exposure Waivers for Pesticides (A Guidance Document for Pesticide Registrants**)**. Draft Joint North Atlantic Free Trade Agreement (NAFTA) document.

Appendix – Current PMRA Hazard Categories

ACUTE TOXICITY HAZARD:

LETHAL DOSE - 50%	DESCRIPTOR	PRIMARY DISPLAY PANEL LABEL SIGNAL WORDS
Oral Toxicity (mg/kg bw)		
< 500	Highly acutely toxic	DANGER POISON
500 - 1000	Moderately acutely toxic	WARNING POISON
1000 - 2000	Slightly acutely toxic	CAUTION POISON
> 2000 (commercial)	Low acute toxicity	*[no labelling required]*
> 2000 (domestic) a) *poisoning of child possible based on net contents* b) *no poisoning likely based on net contents*	Low acute toxicity	a) CAUTION POISON b) *[no labelling required]*
Dermal Toxicity (mg/kg bw)		
< 500	Highly acutely toxic	DANGER POISON
500 - 1000	Moderately acutely toxic	WARNING POISON
1000 - 2000	Slightly acutely toxic	CAUTION POISON
> 2000	Low acute toxicity	*[no labelling required]*
Inhalation Toxicity (mg/L)		
< 0.05	Highly acutely toxic	DANGER POISON
0.05 - 0.5	Moderately acutely toxic	WARNING POISON
0.5 - 2.0	Slightly acutely toxic	CAUTION POISON
> 2.0	Low acute toxicity	*[no labelling required]*

IRRITATION AND SENSITIZATION HAZARD:

QUALITATIVE DESCRIPTOR *(Draize score)*	**PRIMARY DISPLAY PANEL LABEL STATEMENT**
Primary Eye Irritation	
Extremely corrosive or irritating, irreversible within 21 days.*(MAS = 80 - 110)*	DANGER - CORROSIVE TO EYES
Severely irritating,, reversible within 21 days.(*MAS = 50 - 80)*	DANGER - EYE IRRITANT
Moderately irritating, reversible.(*MAS = 25 - 50)*	WARNING - EYE IRRITANT
Mildly irritating, reversible.(*MAS = 15 - 25)*	CAUTION - EYE IRRITANT
Minimally to non-irritating.*(MAS < 15*)	*[no labelling required]*
Primary Dermal irritation	
Extremely irritating. *(MAS = 6.6-8.0)*	DANGER SKIN IRRITANT
Severely irritating. *(MAS = 5.1-6.5*)	DANGER SKIN IRRITANT
Moderately irritating. *(MAS = 3.1-5.0)*	WARNING SKIN IRRITANT
Mildly irritating.*(MAS = 1.6-3.0)*	CAUTION SKIN IRRITANT
Slightly to non-irritating. *(MAS = 0-1.5)*	*[no labelling required]*
Skin Sensitization	
Positive skin sensitizer	POTENTIAL SKIN SENSITIZER
Negative skin sensitizer	*[no labelling required]*