Office of Pesticide Programs

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)

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I. Introduction

The Office of Pesticide Programs (OPP), US EPA, has previously issued memoranda and other written documents describing criteria that can be cited by registrants to bridge data for or support a waiver of the requirement for mammalian acute toxicity data for pesticide technical active ingredients and pesticide end use formulations. These documents and explanations of criteria to support waiver and bridging requests have appeared in several Agency publications over the years, which can lead to confusion for registrants seeking accurate and updated guidance. This paper integrates information from various Agency documents and other memoranda, as relevant, into one document that can be used as a single reference source for acute toxicity waiver guidance as well as criteria for bridging of acute toxicity data.

Criteria for waiving or bridging acute toxicity data appear in:

- Memoranda from OPP's Registration Division (US EPA, 1992) and Health Effects Division (U.S. EPA, 1993); these memoranda describe considerations that will generally support a waiver request for each type of mammalian acute toxicity test.
- 40 CFR 158.500, 40 CFR 161.340, 40 CFR 158.2050, and 40 CFR 158.2083, which contain footnotes to the acute toxicity testing data requirements that describe when acute toxicity tests are not required for conventional, antimicrobial, biochemical, and microbial pesticides, respectively.
- Office of Chemical Safety and Pollution Prevention (OSCPP) guidance (harmonized guideline 870.1000), which contains several Agency recommendations for reducing the number of animals used in acute toxicity testing. One significant recommendation made in this document is the concept of bridging toxicity data from one chemical or product formulation to another instead of conducting additional tests.
- Pesticide Registration Notice 2001-02, which discusses acute toxicity data requirements for granular pesticide products, and includes criteria that would support a waiver for acute toxicity testing of granular pesticide products.
- Chapter 2 of the OCSPP Pesticide Registration Manual (http://www.epa.gov/opprd001/registrationmanual/chapter2.html), which discusses bridging of toxicologically similar products.

The purpose of this document is to consolidate information from these sources and provide a single source for consultation on the use of waiver and bridging criteria for acute toxicity testing. This current document supersedes all existing OPP guidance documents on waiver and bridging criteria for mammalian acute toxicity tests. While every effort has been made to make this guidance document as comprehensive and updated 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 that will require separate review and/or consultation with the Agency. Note that as the 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.

II. Waiver Criteria

Generally, waivers are considered when a data endpoint is not relevant to the chemical, such as not requiring an acute oral toxicity study when the chemical exists as a vapor or gas. Specific waiver criteria for each type of acute toxicity study are discussed below. Note that in accordance with 40 CFR 158.45, all waiver requests must be submitted to the Agency in writing for consideration. In addition, requests for waiver of any acute toxicity data requirement or justification for bridging to an existing product should be prepared in accordance with the formatting requirements of PR 2011-3 and should include sufficient explanation and documentation to support the request.

A. ACUTE ORAL TOXICITY

An acute oral toxicity study for conventional, antimicrobial, and biochemical pesticides may not be required if any of the following criteria are met:

- The test material is a gas or is highly volatile (40 CFR 158.500(e)(1); 40 CFR 158.2050(e)(1); 40 CFR 158. 2083(e)(1); 40 CFR 161.340(b)(1))

- The test material is a non-friable material and is too large to be ingested; or the product design prevents oral exposure. Products such as pet collars, plastic ear tags and tamper-resistant roach traps and bait boxes often meet these criteria.

- Even though some products may be too large to be ingested, there is some concern when these products are 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 one of the large units.

For microbial pesticides (40 CFR 158.2140 (d)(5), "waivers…may be granted when the applicant can demonstrate that the combination of inert ingredients is not likely to pose any significant human health risks."

B. ACUTE DERMAL TOXICITY

A dermal toxicity study for conventional, antimicrobial, and biochemical pesticides may be waived if any of the following criteria are met:

- The test material has been placed in Toxicity Category I for primary dermal irritation. Such products will be placed in dermal Toxicity Category I on the basis of potential dermal effects.

- The test material is corrosive to skin, or has a pH less than 2 or greater than 11.5. (40 CFR 158.500(e)(3); 40 CFR 158.2050(e)(2); 40 CFR 158. 2083(e)(2); 40 CFR 161.340(b)(2)). Such products will be placed in dermal toxicity category I on the basis of potential dermal effects.

- The product design prevents dermal exposure. Products such as tamper-proof roach traps and bait boxes often meet these criteria.

For microbial pesticides, (40 CFR 158.2140 (d)(5), "waivers…may be granted when the applicant can demonstrate that the combination of inert ingredients is not likely to pose any significant human health risks."

C. ACUTE INHALATION TOXICITY

An acute inhalation toxicity study for conventional, antimicrobial, and biochemical pesticides may not be required if any of the following criteria are met:

- Inability to Generate a Toxic Concentration:

  - If a pesticidal product cannot be generated as a gas, vapor, or aerosol in sufficient concentration to elicit animal toxicity in the optimal conditions of an inhalation chamber, then it cannot pose a "real world" human health inhalation hazard. A waiver for an acute inhalation toxicity study may be considered provided a reasonable effort has been made to generate the product. Extraordinary measures are not required. The waiver request should include a clear description of the methods and equipment used to generate 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 labeling for the paint product may be justified on the basis of testing of the active ingredient.

- Low Volatility:

  - 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 vapor under conditions of use, storage, handling, or transport. 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). The registrant must provide the vapor pressure for the active ingredient and the formulated product.

  - If an inhalation toxicity study is needed for a highly toxic product with low volatility, it may be necessary to generate an aerosol. Further guidance can be found in OECD Guidance Document 39 (OECD, 2009).

- Pesticidal products 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 provided the registrant demonstrates there is no substantial human exposure via inhalation due to off-gassing.

- Non-inhalable Aerosol Particle Size:

  - Solid aerosol particles can be generated as dusts, fumes, smoke, and granules. Liquid aerosols can be generated as mists and fogs by spraying, nebulization, and by the pouring of liquids. 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.

  - Inhalable liquid and solid particles are capable of entering the 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.

  - 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). Consideration should be made for the likelihood that liquid particles may shrink due to evaporation and therefore may become inhalable. A waiver may not be appropriate for products that may have a highly toxic potential by the inhalation route.

  - 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 (an MMAD of 1-4 μm in an acute study or 1-3 μm in a repeated exposure study). When a registrant 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. The latest version at this writing is E2316-03 (reapproved 2009). This test method can be purchased at a nominal cost from ASTM (100 Barr Harbor Drive, West Conshohocken, Pennsylvania, USA 19428-2959; or http://www.astm.org/).

  - Registrants occasionally request waivers for products sprayed from a medium or coarse nozzle. The rationale supplied for the waiver is that the large droplets (100-500 μm diameter) generated when the product is sprayed from aircraft or ground

equipment have no relevance to the small particle size (MMAD 1-4 µm) used in rodent studies. This logic is flawed and must not be used to justify a waiver. For the following reasons, waivers must not be granted for liquid aerosols on the basis of large particle size unless the registrant can demonstrate that large droplets do not shrink to an inhalable size (i.e., < 100 µm):

- Most sprayed pesticides are mixed with water before spraying. When the aqueous mix is sprayed, large droplets rapidly shrink due to water evaporation. The extent of shrinkage depends on particle size, temperature, relative humidity, and the length of time that droplets are suspended in air. Within seconds of leaving a nozzle, large droplets can rapidly shrink to a size that is inhalable and often respirable (Matthews, 2008).

- In order to derive robust inhalation toxicity data, rodents must be exposed to aerosol particles in the MMAD range of 1-4 µm to facilitate exposure to the entire respiratory tract. Rodents have tortuous nasal turbinates that are extremely efficient at removing particles larger than 1-2 µm from inhaled air. When rodents are exposed to particles larger than 4 µm, their lungs are virtually unexposed (Fund. Appl. Toxicol., 1992). For example, it would be pointless to expose rodents to 200 µm particles because there would be no inhalation exposure and thus no pulmonary toxicity.

- Because human noses are less efficient than rodent noses at removing fine particles, humans can sustain greater penetration into the respiratory tract.

- Rodents are obligate nose breathers but humans are not. When humans breathe through the mouth, such as during vigorous activity, the filtering protection of the nose is bypassed.

For biochemical pesticides (40 CFR 158.2050; 40 CFR 158.2083), an inhalation toxicity study is not required if the biochemical pesticide is a straight chain lepidopteran pheromone.

For microbial pesticides, (40 CFR 158.2140 (d)(5), "waivers…may be granted when the applicant can demonstrate that the combination of inert ingredients is not likely to pose any significant human health risks."

When a waiver is granted for an acute inhalation toxicity study, this will be noted in the toxicity study profile for the chemical in order to acknowledge that there is not a data gap for this study. Labeling language for acute inhalation hazard based on granting of a waiver will be reflective of the basis of the waiver. That is, the lack of acute inhalation hazard would be reflected on the label as Toxicity Category IV and no label language regarding acute inhalation hazard would be needed. By contrast, if an acute inhalation toxicity waiver is granted on the basis of the chemical being corrosive, the label would need to reflect Toxicity Category I label language to acknowledge the corrosivity of the chemical by the inhalation route, as conduct of an actual inhalation study would not be humane.

D. PRIMARY EYE IRRITATION

A primary eye irritation study for conventional, antimicrobial, and biochemical pesticides 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. (40 CFR 158.500(e)(3); 40 CFR 158.2050(e)(2); 40 CFR 158. 2083(e)(2); 40 CFR 161.340(b)(2)). Such products will be placed in Toxicity Category I.

- The test material has been placed in Toxicity Category I for primary dermal irritation. Such products will be placed in eye irritation Toxicity Category I on the basis of potential eye effects;

- The test material has been placed in Toxicity Category I for acute dermal toxicity. Such products will be placed in eye irritation Toxicity Category I 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.

For microbial pesticides, (40 CFR 158.2140 (d)(5), "waivers…may be granted when the applicant can demonstrate that the combination of inert ingredients is not likely to pose any significant human health risks."

E. PRIMARY DERMAL IRRITATION

A primary dermal irritation study for conventional, antimicrobial, and biochemical pesticides 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. (40 CFR 158.500(e)(3); 40 CFR 158.2050(e)(2); 40 CFR 158. 2083(e)(2); 40 CFR 161.340(b)(2)). Such products will be placed in Toxicity Category I.

- The test material has been placed in Toxicity Category I for acute dermal toxicity. Such products will be placed in dermal irritation Toxicity Category I 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 of strong dyes or pigments, which may complicate interpretation of the result. In such situations the registrant should conduct a preliminary dermal exposure assessment of the material to the skin of an appropriate test animals (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.

For microbial pesticides, (40 CFR 158.2140 (d)(5), "waivers…may be granted when the applicant can demonstrate that the combination of inert ingredients is not likely to pose any significant human health risks."

F. DERMAL SENSITIZATION

A dermal sensitization study for conventional, biochemical, and antimicrobial pesticides 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. (40 CFR 158.500(e)(3); 40 CFR 158.2050(e)(2); 40 CFR 158. 2083(e)(2); 40 CFR 161.340(b)(2)).

- The product does not result in repeated dermal exposure under conditions of use. Since the possibility of repeated exposure is very high for pesticide products, such waiver claims should be supported by ample information and address the likelihood of occupational use and repeated, yet infrequent, exposure over long periods of time;

- The test material is a pesticidal paint which will not allow dermal evaluation because of strong dyes or pigments, which may complicate interpretation of the result. In this situation, the registrant should conduct a preliminary dermal exposure assessment of the material to guinea pig skin 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;

- The product design prevents dermal exposure. Products such as tamper-proof roach traps and bait boxes often meet this criterion;

- The product is corrosive to skin, or has a pH less than 2 or greater than 11.5 at the most dilute use concentration recommended on the product label, or

- The technical active ingredient(s) is a known sensitizer.

For biochemical and microbial pesticides (40 CFR 158.2050; 40 CFR 158. 2140), hypersensitivity incidents must be reported by the registrant. If no incidents have occurred to date, the registrant must so state. Incidents occurring after the initial statement must be reported as adverse data under FIFRA Sec. 6(a)(2).

G. **Granular Pesticides**

1) GRANULAR PESTICIDE PRODUCTS

Acute toxicity data requirements for granular pesticide products including when data may be waived were presented in the Agency's PR Notice 2001-2 and are summarized below.

For the purposes of this guidance, the Agency considers granular pesticide products to include those products composed of a high percentage (generally greater than 90%) of granular inert carrier(s) (corn cobs, clay, limestone, sand, food; 40CFR 180.910 and 180.950) and a minimal amount of sticker/binder (generally 5% or less of the formulation).

The PR notice for granular pesticide products only applies to granular pesticide products and granular fertilizer pesticide products. The Agency will not extrapolate for other products, because; 1) the LD50 is imprecise (dilution does not always equal reduced toxicity); 2) a complete dose response curve, required at a minimum, is rarely available; and 3) the Agency does not have a database that indicates that dilution always means reduced toxicity.

For purposes of a waiver, if the acute toxicity profile of the registered source product(s) proposed for use in a granular pesticide is in Toxicity Category III or IV for all endpoints, then this acute toxicity profile may generally be used for the proposed granular pesticide product.

In addition, where the systemic toxicity (i.e. acute oral, dermal and inhalation) endpoints for the registered product used in a granular pesticide fall into Toxicity Category III, the granular pesticide product can generally be treated as falling in Category IV. This extrapolation for acute systemic toxicity is based on dilution. The assumption is that the innocuous inert does not contribute to the toxicity, and thus acts as a diluent.

EXAMPLE 1:

Source Product Study	Toxicity Category	Toxicity Category for Granular Product
Acute oral LD50	III	IV
Acute dermal LD50	III	IV
Acute inhalation LD50	III	IV
Primary Eye Irritation	III	III
Primary Skin Irritation	III	III
Skin Sensitization	Non-sensitizer	Non-sensitizer

If the acute LD50, dermal LD50, Inhalation LD50, primary dermal and/or eye irritation effects for the registered product(s) are classified in Category I and/or II, then the Agency generally will not accept calculations that bridge down from these categories, and additional data would

generally be required for the proposed pesticide product. Either these studies would need to be submitted, or the registrant would need to cite data on a substantially similar product.

EXAMPLE 2:

Source Product Study	Toxicity Category	Toxicity Category for Granular Product
Acute oral LD50	II	II
Acute dermal LD50	II	II
Acute inhalation LD50	I	I
Primary Eye Irritation	III	III
Primary Skin Irritation	III	III
Skin Sensitization	Non-sensitizer	Non-sensitizer

Granular pesticides and dermal sensitization: If a granular product contains any ingredient that is a known sensitizer, the formulated product generally would be labeled as a sensitizer. If the product is not a dermal sensitizer, and there are no known dermal sensitizers in the product, a dermal sensitization study may be waived and the product will not require sensitization labeling. 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 registrant on an inert (e.g., Material Safety Data Sheet - MSDS). If the registrant knows there is a dermally sensitizing component in the granular pesticide product, the Agency will label the product as a dermal sensitizer and will waive sensitization testing.

Other considerations for granular pesticides: If the primary eye and dermal irritation effects are classified in Category III and/or IV, the 3 categories of the source registered product may be used for the proposed pesticide product and the toxicity profile will be complete.

2) GRANULAR FERTILIZER PESTICIDE PRODUCTS

For purposes of this guidance, EPA considers granular fertilizer pesticide products as products composed of a high percentage (generally 90% or greater) of granular fertilizer components plus clearly recognized innocuous (List 4) inert carrier(s), and a minimal amount of sticker/binder (5% or less of the formulation).

The fertilizer components of these products are generally considered analogous to the innocuous inert ingredients described above, with the exception of eye irritation. In some cases, fertilizer products are more irritating to the eye than comparable non-fertilizer granular products. A separate eye irritation study is expected to be performed with the pesticide/fertilizer formulation containing the highest free level of nitrogen. If, at some point, the nitrogen content of the fertilizer component in the product is increased above the level tested, a new primary eye irritation study will be required.

3) RODENTICIDE BAITS

As noted in Pesticide Registration (PR) Notice 2001-2, rodenticide baits are not included in the policy for granular pesticides or granular fertilizer pesticide products. The section in PR notice 2001-2 regarding rodenticide baits states that "In the Agency's experience, rodenticide baits are often more toxic than would be predicted using the bridging methods outlined above." That is, the assumption that dilution equals reduced toxicity is not the case with respect to acute toxicity of rodenticide baits. Therefore, in general, the Agency will continue to allow similar baits to use one set of data for purposes of precautionary labeling.

III. Use Dilutions

The following guidance is taken from the Label Review Manual and addresses use dilutions of aqueous pesticide solutions.

Statements which correspond with the toxicity categories associated with a product's use dilution may be allowed on product labels provided the conditions below are satisfactorily addressed. Following is guidance for the submission and review of such data and for the content and placement of associated labeling.

A. DATA REQUIREMENTS

All data and draft labeling for use dilution statements should be sent to the appropriate Product Manager with a request for pesticide amendment. In some cases, use dilution labeling statements triggered by systemic toxicity (acute oral, dermal or inhalation toxicity) may be supported by extrapolation from the LD50/LC50 for the concentrate. At a minimum the following is required to even consider extrapolating toxicity categories. This information must be submitted by the Registrant with the extrapolation request.

(a) A slope calculated from at least three, and preferably more, dose levels having partial responses (i.e., a well characterized dose-response);

(b) Dose groups sufficiently large (>5 per group) to allow for the calculation of confidence limits that fall within the defined Toxicity Category boundaries;

(c) Extrapolation to higher toxicity categories will only be applied to water dilutions. It should also be determined that there are no other factors affecting the toxicity of the EP (e.g., inerts that enhance the absorption of the active ingredient, promote the active ingredient's toxicity, etc.). Other types of extrapolations will be done on a case by case basis.

(d) Use dilution Hazards to Humans and Domestic Animals statements triggered by skin or eye irritation must be supported by new or cited studies. If another registered diluted product (such as a ready-to-use formulation) has acceptable data and is found similar to the concentrated product after it has been diluted, those data may also be used to support revised labeling.

B. DILUTION WITH INERTS OTHER THAN WATER

The same considerations as above could also be used in situations involving dilution with non-aqueous (but reasonably non-irritating and non-toxic) solvents such as polyethylene glycol or soybean oil, or in cases involving addition of relatively inert solid carriers, such as sand, corn cob grits, or some fertilizers. The review approach as to what constitutes a reasonably non-irritating and/or non-toxic solvent or carrier would remain based on scientific expertise and judgment. It would be to the registrant's advantage to use solvents and/or inerts whose effects are both well known and innocuous.

If the available acute toxicity data indicate that the concentration of active ingredient(s) is less than a concentration that would cause any eye irritation (toxicity category IV by the eye exposure route) but there is a significant amount of a systemically inert carrier (such as sand, silica gel, corn cob grits, vermiculite, some types of fertilizers) with abrasive potential to cause minor eye irritation, then Agency toxicologists would usually assign the proposed product to Toxicity Category III for eye exposure in the absence of an eye irritation study.

IV. Mixtures

In general, for bridging of acute toxicity data for mixtures to be considered, mixtures should have the same physical form, similar concentrations of active ingredients, and similar uses. A comparison of the Confidential Statement of Formula (CSF) for both mixtures should also show similar composition of ingredients in the mixture.

For pesticides, a new product may sometimes be formulated by mixing, in some proportion, two or more existing products. If each of the existing product components is in the same toxicity category in terms of an exposure route (for example, category III in terms of acute oral LD50 value), and there is no indication that potentiation or toxicological enhancement occurs from combining the active ingredients, then OPP may accept the argument that the resulting product falls in the same common toxicity category (here, toxicity category III in terms of the oral LD50).

V. Bridging of data for acute toxicity endpoints/labeling

Bridging refers to the use 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 is existing data on a product to address an endpoint for a proposed product so that data do not need to be generated in each case. Bridging principles are presented in the Agency's OCSPP guideline 870.1000 and have been discussed in other Agency documents as well. Specific areas where this is currently applied in OPP are discussed below.

A. BRIDGING OF END-USE PRODUCT DATA (US EPA, 1992)

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. Similarly, acute toxicity data may exist for two registered products with different percentages (one higher, one lower) of the same active ingredient(s) as the proposed product, all containing the same or similar inerts. In these cases and other situations, toxicologists may be able to determine a complete or partial acute toxicity profile for the proposed product, and would define the hazards with appropriate toxicity categories for: 1) oral LD50; 2) dermal LD50; 3) inhalation LC50; 4) primary eye irritation; 5) primary dermal irritation; and 6) dermal sensitization. Each hazard determination eliminates the need to conduct an acute toxicity study on the proposed product. The underlying logic for each determination is, in most cases, based on expert scientific judgment.

Bridging of data from a registered product(s) with a complete acute toxicity data base to a proposed product(s) can be advantageous to registrants (it eliminates or reduces expenses associated with conducting toxicity studies) and to the Agency (it can reduce review time as well as provide an adequate acute hazard profile for the proposed product while reducing animal usage). Bridging also encourages registrants claiming similarity to existing products to formulate their products with solvents that are relatively innocuous, both in terms of systemic toxicity and potential eye or dermal irritation effects.

The proposed product should cite a specific, well-defined acute toxicity profile of an existing product. The physical form of the product for which bridging is being requested should also be similar to the existing product. In addition, bridging of acute toxicity study results on a product containing a lower concentration of the active ingredient to a proposed product containing a higher concentration of the active ingredient is not recommended, as a higher concentration of the active ingredient cannot be expected to have the same toxicity categories as a lower concentration and thus may need to be tested separately.

Bridging of end-use acute toxicity data may encompass (but is not necessarily limited to) the following situations:

1) Proposed product alleged to have reduced hazard potential

In this situation, specific acute toxicity data previously received and approved by the Agency is cited by the applicant, and the proposed product has the same toxicity profile as the product on which the cited data was submitted. The applicant claims, however, that its proposed product has a reduced hazard potential by one or more exposure routes relative to the cited product(s). To support this statement, an appropriate study should be submitted.

For example suppose an existing product is in toxicity category I or II (signal word DANGER or WARNING) in terms of eye irritation potential, but in toxicity category III or IV by all other exposure routes, 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 inert ingredients, or changing the pH. In these cases, the registrant

should cite the existing data base for the old formulation, and submit an eye irritation study which demonstrates that the proposed reformulated product would be in toxicity category III in terms of eye irritation potential. The signal word and precautionary labeling can be revised accordingly.

2) Dilution with water

In this situation, 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 word. In the absence of new acute toxicity data or addressing the criteria stated below from the Label Review Manual, the Toxicity Category and associated precautionary labeling for the diluted product would be the same as for the cited product.

B. BRIDGING OF TOXICOLOGICALLY SIMILAR PRODUCTS

Bridging may also be appropriate for toxicologically similar products. Chapter 2 of the OPP Pesticide Registration Manual (http://www.epa.gov/opprd001/registrationmanual/chapter2.html) presents details where the need may arise for this type of determination. In general, a determination of whether a proposed product is identical or substantially similar to an existing (registered) product arises when there is a request to "register a new pesticide product that is identical in its uses and formulation or substantially similar in its uses and formulation to one or more products that are currently registered and marketed in the United States or differs only in ways that would not significantly increase the risk of unreasonable adverse effects on the environment." Determining the similarity of the proposed product to the registered product involves examination of the product chemistry and product formulation data between the proposed and registered product (including the percentage of active and inert ingredient(s) as well as any other components in the formulation). Examples of what is considered an identical/substantially similar product as well as when products are not considered identical/substantially similar are presented in Chapter 2 of the Pesticide Registration Manual. In addition to the above, OPP will also need to verify that the precautionary labeling of the cited product is also appropriate for the proposed product. 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 reviewer(s) making the comparison.

VI. References

Code of Federal Regulations: 40 CFR, Parts 150 to 189. Protection of Environment. Revised as of July 1, 2010.

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

Office of Chemical Safety and Pollution Prevention: Series 870 Harmonized Test Guidelines. Found at : http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series870.htm

Office of Chemical Safety and Pollution Prevention. Pesticide Registration Manual. Found at: http://www.epa.gov/opprd001/registrationmanual/

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

U.S. EPA (1992): Bridging of Data for End-Use Product Acute Toxicity. Memorandum from Donald Stubbs, Chief, Registration Support Branch, Registration Division, to RD Branch Chiefs.

U.S. EPA (1993): Review of Revised Acute Toxicity Waiver Guidance Document – HED Comments. Memorandum from Elizabeth A. Doyle, Ph.D. and John Redden, MS through Marcia Van Gemert, Ph.D. and Karl Baetcke, Ph.D.

U.S. EPA, (1999): Policy for Determining Toxicology Data Requirements and Derivation of RFD and Q1* for Enriched Isomer Technical Chemicals. Memorandum from Mike Ioannou, HED and Bill Burnam, HED.

Pesticide Registration Notice 2001-2: Acute Toxicity Data Requirements for Granular Pesticide Products, including those with Granular Fertilizer in the Product. Found at: http://www.epa.gov/PR_Notices/pr2001-2.pdf

Pesticide Registration Notice 2011-3: Standard Format for Data Submitted Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and Certain Provisions of the Federal Food, Drug, and Cosmetic Act (FFDCA). Found at: http://www.epa.gov/PR_Notices/pr2011-3.pdf

Recommendations for the Conduct of Acute Inhalation Limit Tests. *Fund. Appl. Toxicol*. 18, 321-327 (1992).

Technical Committee of the Inhalation Specialty Section, Society of Toxicology. Recommendations for the Conduct of Acute Inhalation Limit Tests. Fundamental and Applied Toxicology. Volume 18. 1992. Pages 321-327.

U.S. EPA, 2010: Label review Manual. Found at: http://www.epa.gov/oppfead1/labeling/lrm/

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.