



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

OFFICE OF  
PREVENTION, PESTICIDES  
AND TOXIC SUBSTANCES

**MEMORANDUM**

**Date:** August 15, 2002

**Subject:** **Guidance: Waiver Criteria for Multiple-Exposure Inhalation Toxicity Studies.**

**From:** Margaret J. Stasikowski, Director  
Health Effects Division (7509C)

**To:** Health Effects Division Staff

Attached is SOP 2002.01 - "HED Standard Operating Procedure: "Guidance: Waiver Criteria for Multiple-Exposure Inhalation Toxicity Studies".

SOP provides guidance to HED staff members for determining when to grant waivers for multiple exposure inhalation toxicity studies.

If you have any questions, please contact John Whalan (305-6511) or Jess Rowland (308-2719).

A. BACKGROUND

The only reliable way to characterize inhalation toxicity and to quantify inhalation risk is through the use of inhalation toxicity studies. Chemicals tend to be more toxic by the inhalation

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route than by the oral route due to rapid absorption and distribution, bypassing of the liver's metabolic protection (portal circulation), and potentially serious portal-of-entry effects, such as irritation, edema, cellular transformation, degeneration, and necrosis. An inhalation risk assessment that is based on oral data generally underestimates the inhalation risk because it cannot account for these factors.

There are occasions when the requirement for inhalation toxicity studies should be waived for ethical or scientific reasons. The purpose of this document is to provide guidance for waiving inhalation toxicity studies when a pesticide active ingredient has a very low potential for human inhalation hazard during handling or application. This guidance is based upon the following three waiver guidance documents, but has been updated to reflect current regulatory concerns:

2. Penelope A. Fenner-Crisp. *Policy on Acute Inhalation Toxicity Data Waivers*. Health Effects Division Memorandum to Anne E. Lindsay. December 8, 1991.
3. Thomas C. Ellwanger. *Acute Toxicity Waiver Guidance Document*. Registration Division Memorandum. August 24, 1993.
4. John Whalan, Donald Cooper, Dennis Gibbons, John Ross, James Sanborn. *Inhalation Exposure Waivers for Pesticides (A Guidance Document for Pesticide Registrants)*. Draft Joint NAFTA document. 1998.

The following scientists from the various Divisions of the Office of Pesticide Program contributed to the preparation of this guidance. Ayaad Assaad, Edwin Budd, William Burnam, Jeff Evans, Timothy Leighton, Jess Rowland, Steven Weiss, John Whalan, Karen Whibty (HED), Karen Hicks (AD), Roger Gardner (BPPD), John Redden (RD), Mark Perry (SRRD)

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**B. INTRODUCTION**

This document provides guidance for determining when to grant waivers for multiple exposure inhalation toxicity studies. All waiver requests are considered on a case-by-case basis, and the burden of proof lies entirely with the registrant. The process for granting waivers will include consideration by a toxicologist, an exposure specialist, and the Exposure Science Advisory Council for Exposure (ExpoSAC). If no significant inhalation hazard is identified during risk characterization and risk assessment, HED may also initiate a waiver. The following four criteria may be used to justify a waiver:

- Severe irritation and corrosivity
- Low volatility
- Large particle size
- Inhalation Toxicity Category IV and an extrapolated Margin-of-Exposure (MOE)

Engineering solutions, such as closed systems and enclosed cabs are not included in this guidance because it is difficult to verify the accuracy of claims. Any waiver request based on an engineering solution must be definitively substantiated.

Waiver Criteria 1 and 3 (below) must be applied on a chemical-by-chemical basis. Any significant change in application methodology, including recommended equipment, will require additional waiver requests and data submission.

**C. WAIVER CRITERIA****Criteria 1 - Severe Irritation and Corrosivity**

An active ingredient which causes severe irritation or corrosion of the skin or eye will also damage the sensitive respiratory mucosa if inhaled. Waivers should be granted for active ingredients which are corrosive (pH <2 or >11.5) or severely irritating.

Waivers should not be granted for active ingredients which are slight to moderate irritants. Inhalation toxicity studies of irritants can quantify the sensitivity of this route and characterize portal-of-entry effects. This information is essential in an inhalation risk assessment.

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**Criteria 2 - Low Volatility**

Waivers will be considered for non-volatile active ingredients which are not aerosolized (i.e. generated as mists, fogs, dust, smoke, fumes), heated, evaporated, or otherwise made inhalable as a gas or vapor. Non-volatile active ingredients are defined as having vapor pressures  $<1 \times 10^{-5}$  kPa ( $7.5 \times 10^{-5}$  mmHg) for indoor uses, and  $<1 \times 10^{-4}$  kPa ( $7.5 \times 10^{-4}$  mmHg) for outdoor uses at 20-30°C. Waiver candidates based on volatility may include, but are not limited to: Viscous liquids (under conditions of use), waxes, resins, lotions, and caulks. Waivers for formulated products such as animal dips, shampoos, pour-ons, slow release collars, ear tags, and tree injections will be considered by the appropriate division.

**Criteria 3 - Large Aerosol Particle Size**

An **inhalable particle** is capable of entering the respiratory tract via the nose and/or mouth. A **respirable particle** evades capture in the upper respiratory tract and reaches the lungs. The larger the particle, the less likely it is to be inhalable or respirable. Waivers will be considered for active ingredients that do not pose a significant inhalation hazard because the particles are too large to be inhaled.

Large particles have the potential to do considerable local damage if they are absorbed because of the volume of material they contain. Table 1 demonstrates that with each 10-fold increase in particle diameter, there is a 1000-fold increase in particle volume. Compared to a 0.1 µm particle, a 100 µm particle has 1000-times the diameter and a billion-times the volume.

**Table 1. A Comparison of Aerosol Particle Diameters and Volumes**

Particle Diameter (µm)	Diameter Δ	Particle Volume (µm <sup>3</sup> ) <sup>a</sup>	Volume Δ
0.1	–	0.000524	–
1.0	10	0.524	1000
10	100	524	1,000,000
100	1000	523,599	1,000,000,000

$$^a \text{Volume of a sphere: } \frac{4}{3} \pi r^3$$

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An aerosol for a product formulation or application method can be considered essentially non-inhalable provided  $\geq 99\%$  of the particles are  $>100 \mu\text{m}$  in diameter. Although aerosols that meet this criteria are candidates for waivers, it is the responsibility of the registrant to provide data on aerosol size distribution. Waiver candidates based on large particle size include, but are not limited to:

9. Microencapsulated formulations which are not readily fractured, dissolved, time-released, leaky, or small enough to be respirable during mixing/loading or application. Evidence of capsule durability must be provided.
10. Granular products placed in or on the soil, and baits applied by hand or during seed planting. Although granular products are inherently non-inhalable, they may pose a significant inhalation hazard if attrition occurs. **Attrition** is the breaking down of a material into smaller particles as can occur during shipping, handling, pouring, and application. A product susceptible to attrition is said to be **friable**. A friable product may pose a significant inhalation hazard if it produces a measurable quantity of dust when poured or scattered.

A registrant requesting a waiver on the basis of particle size 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 35.22–Pesticide Formulations and Application Systems Method for the Determination of Inhalable Particles of Granular Products*. This test method is not available from the EPA, but can be purchased from ASTM (100 Barr Harbor Drive, West Conshohocken, Pennsylvania, USA 19428-2959; or <http://www.astm.org/>).

#### **Criteria 4 - Toxicity Category IV and An Extrapolated MOE**

Inhalation waivers are not granted for active ingredients based solely on low oral toxicity because:

- Toxicity via the inhalation route tends to be more severe than by other routes.
- Inhaled chemicals by-pass the metabolic protection of the liver (portal circulation).
- Oral data cannot be used to predict respiratory portal-of-entry effects (e.g. irritation, edema, cellular transformation, degeneration, and necrosis).
- The use of route extrapolation in a risk assessment minimizes the true inhalation risk (**see example below**).
- The application rate is usually higher for pesticides with low oral toxicity, so there is a potential for high inhalation exposure.

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Nevertheless, a waiver may be granted for an active ingredient that is Toxicity Category IV for inhalation provided an extrapolated inhalation MOE (based on an oral NOAEL) exceeds a target MOE of 1000 or greater. The target MOE may include the conventional UF of 100; an additional UF of 10-100 to account for unknown pharmacokinetic and pharmacodynamic differences between the oral and inhalation routes in animals and humans, and respiratory portal-of-entry effects; and any other additional assigned UF (e.g. for use of a LOAEL).

## Example: Route-Specific MOE v Route-Extrapolated MOE

When calculating inhalation risk, a route-extrapolated MOE will be 6-fold greater than a route-specific MOE when based on rat data. Thus, route extrapolation makes a chemical appear 600% “safer” than it really is. This is because HED’s route extrapolation method includes only one pharmacokinetic adjustment—respiratory volume—which is 6-fold greater in rats than in humans (relative to body weight). Missing from HED’s route extrapolations are adjustments for other pharmacokinetic differences between rats and humans, such as distribution, metabolism, and excretion.

**Rat:**

Inhalation NOAEL = 0.02 mg/m<sup>3</sup>/day

Extrapolated inhalation NOAEL ≈ 0.0052 mg/kg/day

**Human:**

Inhalation exposure = 0.3 mg/m<sup>3</sup>/day

Extrapolated inhalation exposure ≈ 0.013 mg/kg/day

Route-Specific MOE:

$$RS\ MOE_I = \frac{0.02\ mg/m^3/day\ (NOAEL) \times 6\ h}{0.3\ mg/m^3/day\ (Human\ Exposure) \times 6\ h \times (1)} = 0.067$$

Route-Extrapolated MOE:

$$R \rightarrow R\ MOE_I = \frac{0.0052\ mg/kg/day\ (NOAEL) \times 6\ h}{0.013\ mg/kg/day\ (Human\ Exposure) \times 6\ h \times (1)} = 0.4$$

Comparison: Route-Extrapolated MOE v Route-Specific MOE:

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$$\frac{0.4 \text{ (Route - Extrapolated MOE)}}{0.067 \text{ (Route - Specific MOE)}} = 6$$

If the extrapolated inhalation MOE had been based on an oral endpoint instead of an inhalation endpoint, the true inhalation risk would probably be under-stated by more than 600%. This is because the oral endpoint would neither reflect the impact of an inhaled chemical by-passing the metabolic protection of the liver, nor consider the extent of respiratory portal-of entry effects.