



Guidance for Identifying Pesticides that have a Common Mechanism of Toxicity for Human Health Risk Assessment

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Executive Summary

This document describes the approach that the Canadian Pest Management Regulatory Agency (PMRA) will use for identifying pesticides that cause common toxic effects by common mechanisms of toxicity. Specifically, this document describes: the steps that will be taken for identifying mechanisms of toxicity of pesticides that cause a common toxic effect; the types of data needed and their sources; how these data are to be used in reaching conclusions regarding commonality of mechanisms of toxicity; and criteria the PMRA will use for categorizing pesticides for the purpose of cumulative risk assessments. Details on the other aspects of the cumulative risk assessment process will be discussed in a separate document.

The *Food Quality Protection Act* (FQPA) of 1996 requires the United States Environmental Protection Agency (EPA) to assess the cumulative risks to human health that can result from exposure to pesticides and other substances that are toxic by a common mechanism. In consultation with both the public and a Science Advisory Panel, the EPA is currently developing a process for performing cumulative risk assessments of this type. Such assessments will play an increasingly important role in the evaluation of risks posed by pesticides, and will improve the regulator's ability to make decisions that fully protect public health and sensitive subpopulations. The identification of pesticides and other substances that cause a common toxic effect by a common mechanism is the first step of the cumulative risk assessment process, and the EPA has recently issued their *Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity*, published January 29, 1999. The PMRA is proposing to harmonize with this EPA policy, and the document that follows has been adapted from the EPA guidance document.

1.0 Introduction

The passage of the United States (U.S.) *Food Quality Protection Act* (FQPA) of 1996 requires, among other things, that when determining the safety of a pesticide, the U.S. Environmental Protection Agency (EPA) shall include available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity in the assessment of risk posed by a pesticide. This is due to the possibility that low-level exposures to multiple substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the chemicals individually.

In response to scientific developments in the regulatory environment, it is necessary for the Pest Management Regulatory Agency (PMRA) to implement and articulate changes to Canadian policies that are influenced by the implementation of the FQPA in the U.S. Furthermore, the expression of the Canadian policy on this matter will assist in matters of harmonization under the North America Free Trade Agreement. Hence, in assessing the risks posed by a given pesticide chemical, the PMRA will need to assess the cumulative risks to human health that can result from exposure to combinations of pesticides that are toxic by a common mechanism. To assess these cumulative toxic effects, the PMRA needs to first identify and categorize those pesticides that cause similar toxic effects by a common mechanism. The purpose of this document is to describe the approach that the PMRA will use to accomplish this first step. This document does not address how the PMRA will assess cumulative toxicity when making determinations of safety. That issue will be discussed in a forthcoming science policy document.

2.0 Background

Common mechanism of toxicity pertains to two or more substances that share a common toxic effect to human health by the same, or essentially the same, sequence of major biochemical events. Care must be taken not to confuse “mechanism of toxicity” with “site of toxic action,” or “site of toxic action” with “toxic effect” or “site of toxic effect.” (See the glossary at the end of this document.) With many substances, the site of a toxic effect is the same as the site of toxic action. It is also true, however, that with many other substances the site of a toxic effect may be different than the site of toxic action. For example, a substance inhibits the catalytic activity of the peroxidase enzyme within the thyroid gland. Inhibition of this enzyme prevents the synthesis of thyroxine and triiodothyronine, and ultimately leads to hypothyroidism, the toxic effect. In this case, the site of the toxic effect is the same as the site of toxic action: the thyroid gland. Another substance known to cause hypothyroidism does so by preventing the synthesis of thyroid-stimulating hormone within the anterior pituitary gland. Here, the site of the toxic effect is the thyroid gland, but the site of toxic action is the anterior pituitary gland. Although these two substances cause a common toxic effect, they would not be considered for cumulative risk assessment because they have different mechanisms of toxicity.

Many substances can cause more than one toxic effect, depending upon the level of exposure, and do so by different mechanisms of toxicity that take place at different sites of toxic action. However, a chemical may also cause multiple toxic effects at multiple sites from a single mechanism of toxicity taking place at a single site of toxic action, provided that the function initially altered at the site of toxic action normally controls other functions at distant sites. For example, a substance that prevents the conversion of cholesterol to corticosteroid hormones in the adrenal cortex would ultimately cause many effects throughout the body that would differ in site and nature.

3.0 Process for Identifying Pesticides that have a Common Mechanism of Toxicity

The conceptual framework of the process that the PMRA will use to identify pesticides that cause a common toxic effect by a common mechanism is illustrated in Appendix I. The framework will be gradually extended for the consideration of formulants, products of environmental degradation, and plant metabolites that also share common mechanisms of action. This process is designed to enable the PMRA to make accurate identification and categorization of substances that are toxic by a common mechanism, in both a timely and a resource-effective manner and will involve the following:

- A thorough identification and analysis of all relevant information for each pesticide under consideration. This will provide the basis for identifying underlying mechanisms of toxicity.
- A “weight-of-evidence” approach to support the development of hypotheses pertaining to mechanisms of toxicity. Generally, no single piece of information will suffice to support the characterization of a specific or common mechanism of toxicity; this finding will be supported by the analysis and interrelationships of available pieces of information.

Step 1. Identify a Candidate Set of Substances that might Cause a Common Toxic Effect by a Common Mechanism of Toxicity. The process of identifying pesticides that have a common mechanism of toxicity begins with a *preliminary* grouping of chemicals that might cause a common toxic effect by a common mechanism of toxicity (step 1, Appendix I). This preliminary grouping of substances will be based upon at least one of the following criteria.

- **Structural similarity**
It is assumed that substances that are structurally analogous could contain a common toxophore (or may yield a common toxophore upon metabolism) and may interact analogously with cellular biomolecular sites to cause a common toxic effect. This would also include any substances that are biotransformed by mammals to the same or analogous toxic metabolites.

- Similarity of mechanism of action
 - (a) General mechanism of toxicity in pests; the mechanisms by which some pesticides are toxic to humans can be fundamentally similar or, in some cases, identical to their mechanisms of intended toxicity to pests.
 - (b) General mechanism of mammalian toxicity; this is based on the possibility that substances that share a general mechanism of toxicity may cause a common toxic effect. A general mechanism of toxicity may include, for example, substances that uncouple oxidative phosphorylation.
- Similarity of toxic effect

It is possible that a particular toxic effect known to occur in experimental animals or humans could be common (i.e., concordant in both site and nature) to many substances, and that this commonality in toxicity could be due to a common mechanism. Since this type of grouping is functionally based, not structurally based, it enables the identification of structurally unrelated substances that cause a common toxic effect from a common mechanism that otherwise might not be identifiable from groupings based on structural similarity or mode of pesticidal action alone.

Not all toxic effects can be used as a preliminary basis for grouping substances. Toxic effects that have many possible unrelated causes, or that could be defined as nonspecific in origin, are not appropriate as the primary basis for the initial grouping of chemicals. These effects, such as body weight changes or death, can result from many unrelated factors and are usually of limited value in understanding the mechanism of toxicity. Such generalized effects that could have many different causes, therefore, ordinarily will not be used as a basis for an initial grouping of pesticide effect. The PMRA will group substances that cause multiple toxic effects by a common mechanism from a common site of toxic action for purposes of the preliminary grouping, provided at least one of the toxic effects is common among the substances.

It is important to emphasize and to make clear that the purpose of step 1 is for *preliminary grouping only*, and that substances (including any metabolic precursors) identified under this step will not be included in a cumulative risk assessment if, upon further analysis, it is determined that they do not cause a common toxic effect resulting from a common mechanism of action. In these instances, the policy of the PMRA is not to group such substances for cumulative risk assessment purposes.

Step 2. Definitively Identify Those Substances from Step 1 That Cause a Common Effect. The primary purpose of step 2 is to further refine the preliminary grouping created at step 1 by eliminating substances that upon further examination do not cause a *common toxic effect*. Following the preliminary grouping of substances (step 1, Appendix I) a detailed evaluation of available toxicology data for each substance will be undertaken to identify and characterize the toxic effects caused by each substance, and to determine which of the substances cause toxic effects that are common with other substances (i.e., toxic effects that are concordant in both site and nature). A primary data set to be used by

the PMRA will be toxicity data generated in support of regulatory activities. The PMRA may also use toxicity data obtained from other studies, such as those described in regulatory reports, or the published literature. The evaluation of toxicology data for the purpose of identifying and characterizing toxic effects will be conducted in a manner similar to that used by the PMRA in its pesticide registration and reregistration programs.

Most substances, depending upon level of exposure, can elicit more than one toxic effect (albeit one toxic effect is generally more readily elicited than the others). All systemic toxic effects caused by each substance, regardless of the exposure levels required to induce the effects, will be evaluated and compared with the toxic effects caused by the other substances. Only those substances that cause a common toxic effect will remain grouped. Thus, for those substances initially grouped using the “similarity of toxic effect” criterion (step 1), a determination will need to be made as to which substances indeed have a common toxic effect. The toxicity data for substances initially grouped using any of the other criteria in step 1 will also be evaluated to determine which of these substances cause a common toxic effect. Substances may be placed in more than one group in instances where substances cause more than one common toxic effect.

The PMRA does not regard information that shows that substances meet the criteria for steps 1 and 2 for grouping as reliable by itself to conclude that such substances have a common mechanism of toxicity. Hence, only those substances that cause a common toxic effect by a common mechanism (through the in-depth review described below) will be considered by the PMRA for cumulative risk assessment.

Step 3. Determine the Toxic Mechanism(s) by which Each Substance Causes a Common Toxic Effect. The next phase of the review process (step 3, Appendix I) is to determine the mechanisms by which the substances cause the common toxic effect(s) identified under step 2 (Appendix I). Generally, the more that is understood about the various biochemical events that lead to a toxic effect, the more apparent and scientifically plausible is the mechanism of toxicity. While desirable, all of the specific biochemical events involving a substance in the causation of its toxicity do not need to be known or completely characterized to describe its mechanism of toxicity. What is needed, as a minimum, is an understanding of those biochemical events that are most crucial in causing the toxicity. Once the critical biochemical events pertaining to toxicity are understood for each substance, they can be compared and the identification of those substances that are toxic from a common mechanism can be made. Hence, the goal of step 3 is to determine, to the extent possible for each substance identified under step 2 as causing a common toxic effect, those biochemical events that are most critical in causing the effect.

Rather than reexamining *de novo* all of the relevant data, the PMRA will assume that a substance is toxic by the mechanism that has been previously determined (from the literature, databases, registrants, the EPA, or other regulatory authorities) provided that the mechanism is consistent with current toxicological theory and knowledge and deemed scientifically plausible by the PMRA for these purposes.

For those substances whose toxic mechanisms are not known or not well understood, or for which there is an absence of direct mechanistic data the PMRA will analyze available structural data, pharmacokinetic data, and toxicity data from the pesticide, its toxophore, and its analogs. It will then use a weight-of-evidence approach to attempt to determine the major biochemical events involving a pesticide that are most critical in causing its toxicity (step 3b). A primary source of these data and information will be studies that have been submitted to the PMRA in support of registration and reregistration decisions. Other sources of data will include peer-reviewed journals, text books, and other regulatory reports.

Steps 4 and 5. Comparison of Mechanisms of Toxicity (Step 4) and Refined Grouping of Substances (Step 5). Once the mechanism of toxicity of each substance has been identified, comparisons of mechanisms will be made to determine which substances identified under step 2 as causing a given common toxic effect do so by a common mechanism. Determinations that two or more substances are toxic by a common mechanism will be based on similarities in both the nature and the sequence of the major biochemical events that cause toxicity. Mechanistic similarities that would support a finding of a common toxic mechanism include, for example, analogous interactions of the pesticides or other substances with identical or similar biological targets, and the occurrence of similar metabolic transformations that yield common or structurally analogous metabolites that interact with similar biological targets, or that are otherwise involved in causing toxicity. Substances that cause a common toxic effect by different mechanisms will be excluded from the refined grouping (step 5).

4.0 Assessing the Cumulative Toxicity Posed by Two or More Substances that are Toxic by a Common Mechanism

The goal of the cumulative risk assessment process is to characterize the potential for a cumulative toxic effect and the magnitude of the effect in individuals following known or anticipated exposures to multiple substances that cause the effect by a common mechanism. Pesticides within a refined common mechanism grouping (step 5, Appendix I) will undergo consideration for cumulative risk assessment to determine the potential cumulative toxicity posed by exposures to such substances. The cumulative risk assessment process that the PMRA will use will be described in a forthcoming PMRA science policy guidance document once appropriate methods are developed.

Glossary

Analog(s). Analog is a generic term used to describe substances that are chemically closely related. Structural analogs are substances that have similar or nearly identical molecular structures. Structural analogs may or may not have similar or identical biological properties.

Common Mechanism of Toxicity. Common mechanism of toxicity pertains to two or more substances that cause a common toxic effect to human health by the same, or essentially the same, sequence of major biochemical events. Hence, the underlying basis of the toxicity is the same, or essentially the same, for each chemical.

Common Toxic Effect. Two or more substances that are known to cause the same toxic effect in or at the same anatomical or physiological site or location (e.g., same organ or tissue) are said to cause a common toxic effect. Thus, a toxic effect observed in studies involving animals or humans exposed to a pesticide is considered common with a toxic effect caused by another chemical if there is concordance with both site and nature of the effect.

Cumulative Toxic Effect. A cumulative toxic effect is the net change in magnitude of a common toxic effect resulting from the exposure to two or more substances that cause this common toxic effect by a common mechanism, relative to the magnitude of the common toxic effect caused by exposure to any of the substances individually.

Mechanism of Toxicity. Mechanism of toxicity is defined as the major steps leading to a toxic effect following interaction of a pesticide with biological targets. All steps leading to an effect do not need to be specifically understood. Rather, it is the identification of the crucial events following chemical interaction that are required to describe a mechanism of toxicity. In the context of this document, mechanism of toxicity refers to the mechanism by which a pesticide is toxic to humans or experimental animals, and not the mechanism by which it is toxic to target or intended species (i.e., its mechanism of pesticidal action). With some pesticides, however, the mechanism responsible for causing toxicity to humans or experimental animals is similar to the mechanism of pesticidal action.

Site of Toxic Action. The site of toxic action of a given substance is the anatomical or physiological site(s) or locations (locus or loci) at which the interaction of the substance with its biological targets occurs that leads to a toxic effect.

Site of a Toxic Effect. The site of a toxic effect is the specific anatomical or physiological site or location (e.g., organ or tissue) at which the effect occurs.

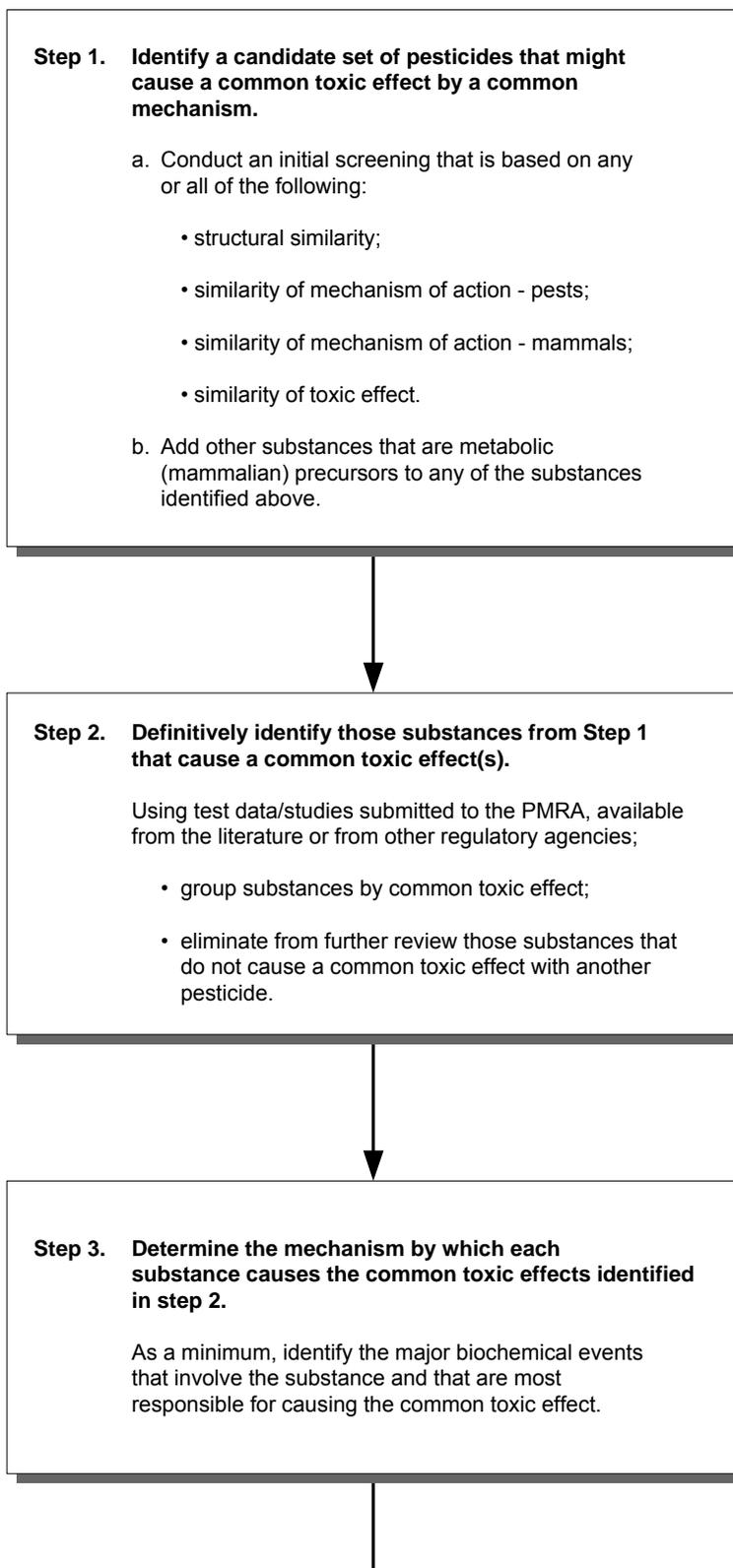
Toxic Action. Toxic action of a given substance is its interaction with biological targets that leads to a toxic effect.

Toxic Effect. A toxic effect is an effect known (or can reasonably be expected) to occur in humans that results from exposure to a chemical substance and that will or can reasonably be expected to endanger or adversely affect the quality of life. Some examples of toxic effects are acute lethality, loss of hearing, renal tubule necrosis, and cardiomyopathy, to name just a few.

Toxophore. Substances that are capable of causing a toxic effect contain a structural feature or moiety that bestows the toxic property. This structural feature or moiety is referred to generically as the toxophore, or toxophoric moiety. A toxic substance elicits its toxicity through the interaction of its toxophore with a biomolecular site (e.g., receptor) in cells of tissue or organs to cause changes or alterations in normal cellular biochemistry. These biochemical changes or alterations lead to the disruption of the physiological process(es) performed by the tissue or organs and, ultimately, to the toxic effect. The toxophoric portion of a given pesticide may interact reversibly or irreversibly with its biomolecular site, depending upon the reactive nature of the toxophore and the biomolecular site. The toxicity of many substances, however, is not due to a direct interaction with a biomolecular site. Rather, the toxicity results from the metabolism of a structural substituent to a toxophore, which then causes the toxicity. Metabolic pathways that lead to toxicity are often called *bioactivation pathways*.

Weight-of-Evidence. Weight-of-evidence refers to a qualitative scientific evaluation of a chemical substance for a specific purpose. A weight-of-evidence evaluation involves a detailed analysis of several data elements, such as data from different toxicity tests, pharmacokinetic data, and chemistry data, followed by a conclusion in which a hypothesis is developed or selected from previous hypotheses.

Appendix I Weight-of-Evidence Process for Identifying Pesticides that Cause a Common Toxic Effect by a Common Mechanism



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