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Cumulative Health Risk Assessment Framework

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1.0 Executive Summary

This document describes the framework and methodology that Health Canada's Pest Management Regulatory Agency (PMRA) will use for assessing the cumulative health effects of pesticides that have a common mechanism of toxicity. It supersedes Health Canada's 2001 Science Policy Note (SPN2001-01) on Guidance for Identifying Pesticides that have a Common Mechanism of Toxicity for Human Health Risk Assessment. The document also builds upon Health Canada's response to the Commissioner of the Environment and Sustainable Development 2015 audit on pesticide safety, whereby the PMRA indicated its intention to have methodology for cumulative health assessment in place in the 2017-2018 fiscal year.[1] The framework takes into account approaches taken by other chemical regulators and outlines methods for assessing cumulative health risks. A step-wise approach for identifying pesticides that belong to a common mechanism group is presented, including criteria for initial grouping and considerations for refining a common mechanism group. A flexible, tiered framework for assessing the hazard and exposure components of an assessment is presented in order to facilitate further refinement of parameters in a cumulative risk assessment to the extent needed. While the document summarizes elements of cumulative health risk characterization, some of the uncertainties and challenges with respect to cumulative methodology in general are also presented.

In March 2017, the PMRA published a Regulatory Proposal (PRO2017-01) on a Cumulative Risk Assessment Framework for pesticides. A number of comments were received during the consultation period; responses to these comments are summarized in Appendix II of this document. In response to the comments received, modifications were also made to the regulatory proposal, which now serves as the basis for this science policy note.

2.0 Introduction

For the purpose of this policy, cumulative assessment is aimed at identifying the human health risks associated with co-exposures to two or more pesticides[2] that cause a common toxic effect(s) by the same, or essentially the same, sequence of major biochemical events (that is, a common mechanism of toxicity). Concurrent exposure routes (oral, dermal, inhalation) and pathways (for example, diet, drinking water, residential use) to pesticides that share a common mechanism of toxicity are assessed to determine the potential for cumulative effects, based on the likelihood that people may be exposed to more than one of these pesticides at the same time. Cumulative assessment is undertaken to explore the possibility of whether low-level exposures to multiple pesticides 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 pesticides individually.

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1 http://www.hc-sc.gc.ca/cps-spc/pest/part/protect-proteger/pesticide-safety-securite-pesticide/index-eng.php

2 In the context of this document, the term "pesticides" can refer to conventional and non-conventional chemicals and microbials, including their metabolic derivatives. The term "chemical" has been used in sections of this document that are more generic in nature.

The consideration of the cumulative effects of pesticides was mandated in the modernization of Canadian pesticide legislation and reflects the application of modern science. Specifically, sections 7, 11 and 19 of the *Pest Control Products Act* (PCPA, 2006) require the consideration of "available information on…cumulative effects of the pest control product and other pest control products that have a common mechanism of toxicity" in evaluating the health risks of a pesticide. According to this legislation, cumulative assessments must be undertaken in the context of new evaluations, re-evaluations, and in the establishment of Maximum Residue Limits (MRLs). These assessments may consist of a qualitative or quantitative cumulative risk assessment, or result in a determination that a cumulative risk assessment is not required. For example, situations in which no common mechanism of toxicity exists or that do not involve co-exposures, would not require a cumulative risk assessment. In some scientific circles, exposure to multiple chemicals by multiple routes and pathways is referred to as combined exposure to multiple chemicals rather than cumulative exposure; however, the terminology used throughout this document reflects that used in the *Pest Control Products Act* for the assessment of pesticides. The scope of this policy does not extend to the consideration of mixtures of pesticides that may result in cumulative effects through disparate mechanisms of toxicity; however, it is worth noting that this is an area of interest in the international regulatory community that is being closely monitored by the PMRA.

Assessing the cumulative effects of pesticides to human health differs from aggregate assessment, where the latter considers the risk from exposure (non-occupational) to a single pesticide via all relevant routes and exposure pathways. Aggregate risk assessments have been fully implemented in the review of both new and re-evaluated pesticides and are supported by policy (Health Canada, 2003). Similar to aggregate assessment, cumulative assessment is focussed on non-occupational sources of exposure; however, cumulative assessment considers exposure from multiple pesticides.

It is essential that toxicological and exposure assessments of individual pesticides are up-to-date prior to undertaking the complex task of assessing cumulative health effects. Consequently, cumulative assessments are performed when both toxicity and exposure assessments are available for all pesticides within a common mechanism group. This could occur following the review of new active ingredients or a major new use of a previously registered active ingredient, or following the completion of a re-evaluation. To date, cumulative assessments have been completed primarily through the PMRA's re-evaluation program. Although this document is focussed on science methodology, some comments received on PRO2017-01 also related to process considerations. To that end, a process map has been included in Appendix III of this document and is further described in the Response to Comments section. The process map identifies the potential paths of evaluation for a cumulative assessment, the decision points for determining the need for a cumulative risk assessment, as well as the opportunities for consultation on proposed cumulative assessment decisions.

This document sets out a framework to facilitate the assessment of cumulative health risks of pesticides that share a common mechanism of toxicity. The framework is not intended to be prescriptive, but rather is intended to function as a guide to those conducting cumulative health risk assessments, as well as a tool to communicate current practices to stakeholders. The

document outlines general methods for cumulative risk assessment, considerations for identifying pesticides that belong to a common mechanism group, a tiered framework consisting of increasing levels of hazard and exposure refinement, elements of risk characterization and a discussion of uncertainties and challenges. The framework contained herein draws from efforts undertaken by other Health Canada programs, North American Free Trade Agreement (NAFTA) partners such as the United States Environmental Protection Agency (USEPA) and by international regulatory and scientific communities.

The PMRA continuously monitors method development as well as specific cumulative assessments at the international level to determine their relevancy to the Canadian context. It is anticipated that by closely aligning the framework and methodology with that of other regulators, the PMRA can make use of cumulative assessments undertaken by those regulators, in whole or in part, provided that the assessments are relevant to the Canadian context.

3.0 Cumulative Risk Assessment Methods

In assessing the risks of pesticides with a common mechanism of toxicity, it is not necessary to have a full understanding of the entire molecular sequence of events required to produce a specific biological outcome. Rather, a more important aspect is having an understanding of the key cytological and biochemical events following chemical interaction. In this sense, the concept of mode of action, often used in cancer risk assessment, and generally considered to require less detail in the description of events than at the molecular level, is applicable. More recently, the term adverse outcome pathway has been employed to link the molecular initiating event(s) to progressive levels of biological organization at the individual or population level. Mechanism of toxicity, mode of action and adverse outcome pathway are all conceptually similar constructs for establishing the key events that define a common mechanism group.

Fundamentally, exposure to more than one chemical at a time is required for there to be a cumulative effect. When combined, chemicals can act jointly, resulting in three distinct types of action: independent, as an interaction or in an additive manner. Chemicals that act independently typically do so through different modes of action and are referred to as complex mixtures. Independently-acting chemicals, by definition, are not addressed by cumulative assessment as mandated under current pesticide legislation.

Interactions refer to synergistic or antagonistic actions between or among chemicals. From a public health perspective, synergistic interactions are of concern, as default assumptions of additivity could lead to an under-prediction of risk; however, synergistic interactions are quite rare. Data analysis suggests that when present, the magnitude of the under-prediction is relatively small (EC, 2009; EC, 2012).

Chemicals that act via the same mode of action, referred to as simple mixtures when combined, can be characterized as behaving in an additive manner. The concept of dose or concentration addition assumes no chemical interactions, but acknowledges that the combination of effects will be greater than that of each individual chemical. For the purpose of cumulative assessment, as described herein, an additive action is the default assumption used by most regulatory authorities (USEPA, 2002; EFSA, 2008).

The most common dose/concentration addition approaches are the hazard index method, margin of exposure method or relative potency factor method. These methods are described herein in further detail. The choice of method used by the PMRA in a cumulative risk assessment will be influenced primarily by the context of the assessment, the available data and the level of refinement required in the assessment. The use of an alternate approach is not precluded, but it is paramount that any alternate approach is scientifically defensible, well-documented and communicated in a transparent manner. The maximum cumulative ratio is also described herein as a tool for identifying the relative significance of cumulative toxicity compared to the toxicity of an individual chemical in the common mechanism group.

3.1 Hazard Index Method

The hazard index (HI) method is a simple and flexible approach that sums the individual hazard quotients (HQ) of individual chemicals in a cumulative assessment group. The HQ is the ratio of an individual chemical's exposure to its reference value. The reference value is the point of departure, (that is, the No Observed Adverse Effect level [NOAEL], Lowest Observed Adverse Effect level [LOAEL], or lower confidence limit on the benchmark dose [BMDL]), divided by the composite assessment factor (that is, the product of the uncertainty factors and the *Pest Control Products Act* factor (PCPA factor)). The PCPA factor is a legally-mandated margin of safety intended to afford particular protection of infants and children (Health Canada, 2008). A HI greater than one would indicate a potential health risk concern. It is worth emphasizing that the points of departure used in a cumulative risk assessment, using any method, may be different from those used in the risk assessment of an individual chemical given the focus on common effect.

$$HQ = \frac{\text{Exposure}}{\text{Reference Value}} \qquad \text{Reference Value} = \frac{\text{Point of Departure}}{\text{Composite Assessment Factor}}$$

$$HI = \frac{\text{Exposure}_1}{\text{Reference Value}_1} + \frac{\text{Exposure}_2}{\text{Reference Value}_2} \ldots + \ldots \frac{\text{Exposure}_n}{\text{Reference Value}_n}$$

The approach allows for the application of chemical-specific uncertainty factors; however, the application of these uncertainty factors can mask the relative potency of the chemicals in a common mechanism group and thus, can inflate the overall uncertainty in the group.

3.2 Margin of Exposure (MOE) Method

The margin of exposure of a chemical is the ratio of its point of departure to its exposure. The adequacy of the MOE is determined by comparing it to a target MOE, the latter being the product of the uncertainty factors and the PCPA factor associated with that chemical. The margin of exposure method (MOE_{Total}) calculates the reciprocal of the sum of the reciprocals of the MOEs of individual chemicals in a cumulative assessment group (see equation below). This method does not include consideration of the uncertainty and PCPA factors associated with each individual assessment. The uncertainty and PCPA factors associated with the common mechanism group at large are taken into account in determining the target MOE for the group.

A potential health concern would be flagged if the MOE_{Total} is less than the target MOE or composite assessment factor (that is, the product of the uncertainty factors and the PCPA factor) for the group of chemicals.

$$MOE = \frac{\text{Point of Departure}}{\text{Exposure}}$$

$$MOE_{Total} = \frac{1}{\frac{1}{MOE_1} + \frac{1}{MOE_2} \ldots + \ldots \frac{1}{MOE_n}}$$

This method is currently used by the PMRA in conducting aggregate assessments of individual pesticides. Although, as previously noted, the uncertainty and PCPA factors for each chemical in the assessment group are not quantified in this approach, it remains a simple and flexible method to assess cumulative risk.

When the target MOEs are different for the individual chemicals in a cumulative assessment group, the aggregate risk index method (ARI) can be used to assess risk. The MOEs are calculated separately and then combined using the equation below. This method accounts for the uncertainty and PCPA factors for each individual chemical in the assessment group. A potential health concern would be flagged if the ARI is less than one for the group of chemicals.

$$ARI = \frac{\text{Target } MOE_1}{MOE_1} + \frac{\text{Target } MOE_2}{MOE_2} \ldots + \ldots \frac{\text{Target } MOE_n}{MOE_n}$$

3.3 Relative Potency Factor Method

The relative potency factor method is a more complex approach that capitalizes on the occurrence of similar effects seen in chemicals with a common mechanism of action. This approach relies upon the selection of an index chemical within a cumulative assessment group, against which the other members of the group are compared. The index chemical should have a robust database and be representative of the chemicals in the assessment group. The relative potency factor (RPF), or scaling factor, for each chemical is derived by dividing the point of departure for a common measure of effect for the index chemical, termed the effective dose (ED), by the point of departure for the same measure of effect for the individual chemical. For example, the effective dose of the index chemical that results in a 10% response is compared to the effective dose of each test chemical in the assessment group that also results in a 10% response.

$$RPF_1 = \frac{ED_{index}}{ED_1}$$

In cases where the magnitude of the uncertainty and PCPA factors is the same for each chemical of the assessment group, this magnitude would be reflected as the target MOE for the combined exposures (see Table 1, Example 1). In situations where the uncertainty and PCPA factors vary among the chemicals, the relative potency factor for each chemical can be multiplied by the respective factor to yield an adjusted RPF (see Table 1, Example 2). Any factor used to adjust the RPF should not be double-counted in the target MOE for the combined exposures. For example, as illustrated in Table 1, Example 2, the uncertainty factor for interspecies extrapolation and the PCPA factors differ among the three chemicals. Therefore, the adjusted RPF for each chemical is calculated by multiplying the RPF by the chemical-specific uncertainty factor for interspecies extrapolation and PCPA factor. As the uncertainty factor for intraspecies variability for all three chemicals is the same (that is, 10-fold), and was not used to calculate the adjusted RPF, it forms the basis of the target MOE for the combined exposures.

Once the relative potency factor (adjusted or not) for each individual chemical has been derived, exposures of these chemicals can be converted to an index chemical equivalent exposure (by multiplying the chemical-specific exposure estimates by their respective RPF) and compared to the point of departure for the index chemical and the target MOE for the combined exposures.

Table 1 Examples of Uncertainty Factor Incorporation in RPF Methodology.

Chemical	RPF	UF_A	UF_H	PCPA Factor	Adjusted RPF	Target MOE
Example 1						
Index Chemical A	1	10	10	1	-	100 ($UF_A \times UF_H \times$ PCPA)
Chemical B	2.5	10	10	1	-	
Chemical C	0.4	10	10	1	-	
Example 2						
Index Chemical X	1	10	10	1	10	10 (UF_H)
Chemical Y	3	3	10	1	9	
Chemical Z	0.01	10	10	3	0.3	

UF_A – uncertainty factor for interspecies extrapolation (that is, animal to human extrapolation)
UF_H – uncertainty factor for intraspecies variability (that is, within human variability)
PCPA factor - legally-mandated margin of safety intended to afford particular protection of infants and children (Health Canada, 2008)

The RPF approach provides a more refined method for standardizing the dose metrics for chemicals in an assessment group, but is heavily reliant on the quality and availability of appropriate toxicology data. Although it allows for the consideration of potency and uncertainties of individual chemicals, a limitation of the approach is the assumption of similarly shaped dose-response curves. This approach has been utilized by the USEPA in their cumulative assessment of various pesticide classes such as the organophosphates and N-methyl carbamates.

3.4 Maximum Cumulative Ratio (MCR)

The MCR is a tool that can be used in cumulative assessment to identify chemicals that may drive the risk assessment (Price et al 2012). The MCR is the ratio of the hazard index (HI) of a group of chemicals (that is, the sum of the hazard quotients (HQ) of each chemical in that group) to the maximum hazard quotient within that group, where the hazard index is used to normalize exposures across chemicals.

$$MCR = \frac{HI}{\text{Maximum HQ}}$$

MCR values range from one to the number of chemicals in the common mechanism group. Values close to one indicate that one chemical dominates the toxicity of the group, whereas values that approximate the number of chemicals in the group indicate an equitoxic hazard among those chemicals. As the MCR is hazard-focussed, it is less useful for identifying exposure scenarios that influence the risk assessment.

4.0 Selection Considerations for Common Mechanism Groups

A common mechanism of toxicity pertains to two or more chemicals that share a common toxic effect that results from 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. Likewise, for some chemicals, the site of toxic effect may be different than the site of toxic action. For instance, the anterior pituitary gland would be the site of toxic action for a chemical inhibiting the thyroid stimulating hormone (mechanism of toxicity) whereas the thyroid would be the site of toxic effect for the ensuing hypothyroidism. Another chemical could share the common toxic effect of hypothyroidism but have a different mechanism of toxicity such as the inhibition of thyroxine and triiodothyronine; in this case, the site of toxic effect and site of toxic action would be the same.

Many chemicals can cause more than one toxic effect, depending on the level of exposure, and do so by different mechanisms of toxicity 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. An example of the latter would be the downstream effects occurring from inhibiting the conversion of cholesterol to corticosteroid hormones in the adrenal cortex.

The PMRA follows a “weight-of-evidence” approach to support the development of hypotheses pertaining to mechanisms of toxicity. Generally, a single piece of information is insufficient on its own to support the characterization of a specific or common mechanism of toxicity; this finding will require support by the analysis and interrelationships of multiple pieces of information. Toxicity data generated in support of regulatory submissions will be the primary source of information used by the PMRA. Toxicity data obtained from other studies, such as those described in reports from other regulatory authorities, or the published scientific literature will also be used. Available epidemiological and mechanistic studies are also considered.

The totality of the evidence is assessed to ensure that the mechanism is consistent with current toxicological theory and knowledge and deemed scientifically plausible by the PMRA for these purposes.

In dealing with uncertainties that arise during the process of integrating multiple lines of evidence, the PMRA employs a precautionary approach from both a hazard and exposure perspective, as described in other regulatory documents (refer to SPN series: SPN2000-01 through SPN2008-01).

4.1 Preliminary Grouping

Identification of a preliminary grouping of pesticides that might cause a common toxic effect by a common mechanism of toxicity is undertaken early in the process of cumulative assessment. This preliminary grouping of pesticides is based upon at least one of the following criteria, considered within a weight-of-evidence context.

Structural similarity

It is assumed that pesticides that are structurally analogous could contain a common toxophore and may interact analogously with cellular molecular sites to cause a common toxic effect. This would also include any pesticides that are biotransformed by mammals to yield a common toxophore upon metabolism. Data on structure-activity relationships, quantitative structure-activity relationship modelling and structural alerts can contribute to the identification of structural analogs.

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 pesticides that share a known general mechanism of toxicity may cause a common toxic effect. A general mechanism of toxicity may include, for example, pesticides 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 (that is, concordant in both site and nature) to many pesticides, 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 pesticides 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 pesticides. 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 pesticides. 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, therefore, will not typically be used as a basis for an initial grouping. The PMRA groups pesticides 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 pesticides.

Following the initial grouping of pesticides, a detailed evaluation of available toxicology data for each pesticide within the group will be undertaken to identify and characterize the toxic effects caused by each, and to determine which of the pesticides cause toxic effects that are common with other pesticides (that is, toxic effects that are concordant in both site and nature). Pesticides may be placed in more than one group in instances where they cause more than one common toxic effect.

The PMRA does not make a determination of common mechanism of toxicity solely on the basis of the preliminary grouping; rather, it is important that a preliminary group proceed through the refined grouping phase to confirm or narrow the list of pesticides that belong to a common mechanism group. Hence, only those pesticides 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.

4.2 Refined Grouping

The next phase of the review process is to determine the mechanisms by which the pesticides of the preliminary group cause the common toxic effect(s). Once the critical biochemical/molecular events pertaining to toxicity are understood for each pesticide in the preliminary group, they can be compared and those pesticides that cause toxicity through a common mechanism can be identified.

For those pesticides 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 for the pesticide, its toxophore, and its analogs. A weight-of-evidence approach will be undertaken to determine the major biochemical events that are most critical in causing toxicity. Mechanistic similarities that would support a finding of a common toxic mechanism include, for example, analogous interactions of the pesticide 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. Pesticides that cause a common toxic effect by different mechanisms will be excluded from the refined grouping.

5.0 Considerations for Determination of Cumulative Exposure

The challenges posed by complex exposure scenarios require approaches that allow the assessment of the health effects of multiple pesticides via multiple routes and exposure pathways, and over multiple time frames. Risk assessments should consider all non-occupational sources, pathways, and routes of exposure that could contribute materially to a person's total exposure. It is appropriate to integrate only those exposures that are likely to occur within the critical time window for the common toxicological effect. Toxicokinetic and toxicodynamic data can inform whether consecutive, separate or partially-overlapping exposures need to be considered in a cumulative assessment.

Exposures may originate from a single route (for example, oral exposure from a dietary pathway) or they may originate from multiple routes (oral, dermal and inhalation), all of which may vary over time and space. Determination of the combination of exposures and routes is an important step for cumulative risk assessments. Identification of use patterns of active ingredients will inform the exposure scenarios for assessment, data collection, or modelling strategies. Co-exposures will be identified on the basis of data that support temporality of exposure.

The consideration of co-exposures will be an iterative process. At the earliest stages of the cumulative assessment, it will be determined whether there is dietary or residential exposure or whether exposure is limited to occupational scenarios. As the review progresses, principles for inclusion or exclusion of exposure scenarios, similar to those used in aggregate risk assessments (SPN2003-04), will be applied to the cumulative risk assessments.

6.0 Cumulative Health Risk Assessment Framework

The PMRA supports the use of the WHO/IPCS framework to maximize efficiency in performing cumulative health risk assessment (Meek et al, 2011). The framework involves a tiered approach to the assessment of exposure and hazard, with each tier being more refined (that is, less conservative and uncertain) than the previous tier. As the tiers of assessment increase, the effort to perform the assessment generally increases, as do the data required to support the refinements. The WHO/IPCS framework has also been employed by regulators responsible for Canada's Chemical Management Plan (Health Canada, Environment Canada, 2015). This iterative process is also similar to the screening analysis framework put forth by the USEPA (USEPA, 2015).

A conceptual representation of the framework, as constructed by WHO/IPCS, is presented in Appendix I and forms the foundation of the PMRA's approach. The elements of the framework are not fixed and will vary depending on the available data. It is not necessary for the hazard and exposure components to be assessed at similar tiers of refinement; rather, the available data will dictate the extent to which either component can be refined. The risk assessor needs only to progress through the tiers to the point where risk does not exceed the level of concern. This process may include consideration of viable mitigation measures. If unacceptable risk is still present with the maximal level of refinement, then further regulatory action is warranted.

As part of the approach to conserving resources in assessment and focussing on critical areas, the PMRA will leverage assessments (or parts of assessments) from other jurisdictions that have undertaken a cumulative health assessment. In these cases, the assessments must be applicable to the Canadian context and consistent with current policy.

A narrative is provided below to illustrate levels of refinement in both the hazard and exposure components of an assessment. The content of each tier is not meant to be prescriptive or fixed, but is intended to show the progressive steps that could be undertaken in a cumulative health risk assessment.

6.1 Hazard Assessment

At the least refined level (Tier 0), it is assumed that all pesticides in a common mechanism group have the same potency and the point of departure of the most potent member of the group is used in the assessment. This assumption, while conservative, can be used as an initial screening method to determine if further refinement is necessary and if so, to what degree. Similarly, selecting the lowest point of departure for a pesticide, rather than the most relevant point of departure, can be used at an early screening stage.

At the next level of refinement (Tier 1), information on each of the pesticides in the common mechanism group can be integrated into the assessment to provide relative measures of potency. Points of departure such as the NOAELs or LOAELS for the apical effect of the individual pesticides can be used.

At a higher tier of refinement (Tier 2), additional refinements can be made by incorporating information on mode of action where available. The use of benchmark dosing can allow for a more refined comparison of potencies in that it can determine the dose associated with a defined response level (for example, a 10% change in the parameter of interest) for each pesticide of the common mechanism group. This facilitates the comparison of potency of each pesticide against an index pesticide in the common mechanism group, which is then expressed as an equivalent of the index pesticide or relative potency factor.

At the highest level of refinement (Tier 3), analyses can be quite sophisticated and include further consideration of mode of action data, toxicokinetics and toxicodynamics. Data modelling and probabilistic techniques can be employed, although the extent of these advanced analyses will depend on the data availability, quality, strength and reliability.

6.2 Exposure Assessment

At the least refined level (Tier 0), it is assumed that exposure is based on simple semi-quantitative estimates of exposure. Semi-quantitative estimates are based on limited data and a few very simple assumptions to determine a worst-case scenario. Similarly, determining a best-case scenario can be used at an early screening stage.

At the next level of refinement (Tier 1), generic exposure scenarios are assessed using conservative point estimates. These are developed based on assumptions and modelled data, rather than measured data. These assumptions provide a conservative risk assessment in the absence of more specific, reliable exposure data, addressing a range of similar uses with limited numbers of parameters being included. However, if the risk estimates from these conservative assumptions are considered acceptable, no further evaluation is necessary.

At the next level of refinement (Tier 2), pesticide-specific and more detailed and reliable data for key parameters, in conjunction with risk mitigation factors are incorporated to refine the exposure and risk assessment. These data may include biomonitoring data from the Canadian Health Measures Survey (CHMS), food residue data from the Canadian Food Inspection Agency (CFIA) and the United States Department of Agriculture's Pesticide Data Program (USDA PDP), and water monitoring data. Additional data for refinement may be drawn from the Residential Joint Venture (REJV) homeowner survey data and use data from the Canadian Pest Management Association (CPMA). Trade data, for imported food commodities and for common mechanism group active ingredients not registered in Canada, can also be utilized. Although still conservative, this results in more realistic exposure estimates.

At the highest level of refinement (Tier 3), probabilistic techniques and more sophisticated data modelling can be employed. This approach requires representative information on exposure for the scenarios of interest, and for the relevant populations and different uses across populations. At this tier, more defined and tailored exposure estimates are developed using fewer assumptions. More emphasis is placed on measured data and modelling software such as Calendex, CARES NG (Cumulative and Aggregate Risk Evaluation System Next Generation), SHEDs (Stochastic Human Exposure and Dose Simulation), and purpose built algorithms, if available. The extent of these advanced analyses will depend on the data availability, quality, strength and reliability.

6.3 Risk Characterization

In case studies undertaken by the WHO/IPCS, it has been demonstrated that refinements in the exposure assessment lead to the largest gains in characterizing risk (Meek, 2013). There is likely to be a greater difference between the lower and upper tiers of exposure assessment than there is for the tiers of hazard assessment, due to the higher reliance on assumptions in the exposure assessment. Hazard refinement, particularly at the uppermost tier, is more constrained by the absence of data on mode of action or toxicokinetics and toxicodynamics.

Given the complexity of cumulative risk assessment, the characterization of risk is of utmost importance. Each assessment must clearly identify the pesticides and exposure scenarios addressed, the types and quality of data available, and the methods of estimation. It is critical that the strengths and limitations associated with the data and analyses be discussed together with the uncertainties and assumptions. The overall level of risk can be expressed in different ways, depending on whether deterministic or probabilistic methods were used, and can reflect a series or range of estimates in light of the numerous input parameters in the assessment. These risk estimates can be specific to different age groups, durations of exposure and/or geographic regions where data permit. The target against which the cumulative health risk estimates are

compared should incorporate uncertainty factors that represent the cumulative assessment group as a whole (such as the factors for interspecies extrapolation and intraspecies variability), as well as the PCPA factor.

Acceptability of cumulative health risk estimates must also take into account direction and magnitude of bias in the data and confidence in the data. Sensitivity analyses can assist in determining the impact of various parameters in the assessment and can contribute to the development of risk mitigation options by identifying drivers of risk. As with individual pesticide risk assessments, the finding of unacceptable risk in a cumulative health risk assessment will warrant risk mitigation. Risk mitigation can include a host of measures ranging from label amendments to cancellation of uses or products, as well as MRL amendments.

In those cases where the PMRA has leveraged a cumulative health assessment from another jurisdiction, a narrative that characterizes the risk and its acceptability in the Canadian context is vital. Regardless of the approach utilized, cumulative health assessments will be subject to consultation prior to final decisions as per established processes; accordingly, it is imperative that the assessments are transparent and clearly communicated.

7.0 Uncertainties and Challenges

Cumulative risk assessment represents a complex series of analyses; as such, varying degrees of uncertainty are unavoidable. These sources of uncertainty can be generic or pesticide-specific.

In the case of the hazard assessment, generic sources of uncertainty can include the assumptions of dose-additivity or similar-shaped dose-response curves of pesticides within a common mechanism group and the lack of data on mode of action. Pesticide-specific sources of uncertainty in hazard assessment can include the adequacy of the toxicological data to define appropriate points of departure (that is, points of departure that are temporally relevant, age relevant, etc.,) as well as lack of knowledge regarding human relevance.

Uncertainties in the cumulative exposure assessment include, but are not limited to, the following:

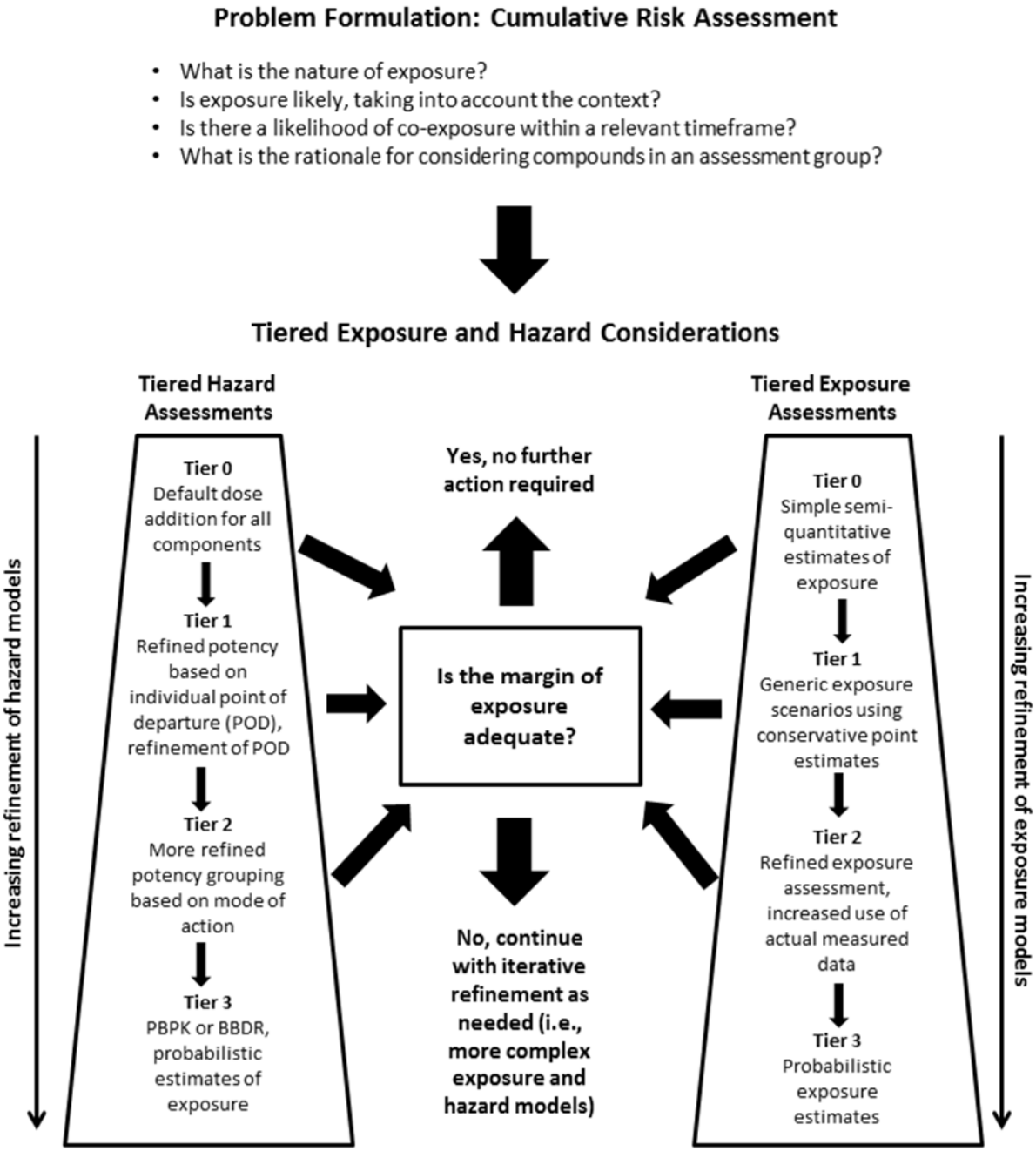
- the level of accuracy with which exposure to different pesticides can be characterised;
- the degree of understanding on the extent and profile of co-exposure to different pesticides. Different pesticides have different persistence in the environment and in the body, and therefore, duration of exposure will vary; in other words, it may be episodic for one pesticide and continuous for another; and
- the variability and uncertainty within the algorithms used to estimate exposure, which are compounded across substances in a cumulative context and may also lead to overestimates of exposure.

The legislative requirement for precaution will be applied in cumulative assessment in a manner similar to that applied for individual pesticide assessments. Accordingly, conservative assumptions and methods will be employed in the absence of data.

8.0 Conclusions

Cumulative health risk assessment methodology is a rapidly developing field as more regulatory authorities incorporate cumulative assessment into their practices. It is expected that methodology will continue to evolve with increased experience in conducting cumulative health risk assessment; hence, the current framework is considered a starting point upon which the methodology will be further developed as approaches and scientific understanding progress.

Appendix I WHO/IPCS Framework for Risk Assessment of Combined Exposure to Multiple Chemicals (modified from M.E. Meek et al., (2011) Regulatory Toxicology and Pharmacology, 60: S1-S14).



Appendix II Response to Comments

Seven sets of comments were received during the consultation period for PRO2017-01. Commenters represented a wide array of stakeholders including the pesticide industry and non-governmental organisations representing the interests of public health and the environment. All commenters were supportive of the proposed framework and methodology outlined in PRO2017-01. Additional comments were provided that were general in nature or specific to certain sections. These comments have been summarized and where relevant, grouped by theme. The summarized comments and the PMRA's responses are outlined below; where appropriate, the PMRA has modified the science policy to address these comments.

General Comments

1. Comment related to the applicability of the policy to cumulative environmental assessment

Several commenters questioned whether the policy was limited to cumulative human health risk assessment. Some commenters indicated that, over time, the PMRA should expand its framework to enable the assessment of cumulative environmental risks, consistent with other international regulatory bodies such as the European Union.

PMRA Response:

The legislative requirement to consider the cumulative effects of pesticides is restricted to the evaluation of health risks; accordingly, the policy is focussed on human health risk assessment. That said, the PMRA recognizes that there is scientific merit in also considering the cumulative effects of pesticides on the environment. The PMRA has previously conducted cumulative assessments for the environment on a case-by-case basis where there has been clear evidence of pesticides with the same mode of action co-occurring in environmental media. Moving forward, the PMRA will be exploring potential options for developing a more formal approach for conducting these cumulative assessments.

2. The PMRA is encouraged to work with international partners in developing the policy

One commenter encouraged the PMRA to work with NAFTA and Organization for Economic Co-operation and Development (OECD) partners to ensure consistent approaches.

PMRA Response:

The PMRA is committed to maintaining engagement with international partners on this issue. The PMRA has recently provided comments on an OECD guidance document on assessing the risks of combined exposure to multiple chemicals, and this is also a topic of ongoing dialogue with USEPA counterparts. In addition, from an intradepartmental perspective, the PMRA maintains linkages with other programs interested in cumulative health assessment (for example, the Chemical Management Program [CMP]).

3. Comments related to the applicability of the cumulative health risk assessment framework to genetically modified (GM) crops/traits

One commenter suggested that the use of herbicide-tolerant crops is relevant to the proposed cumulative health risk assessment framework, and made several recommendations regarding the use of GM crops and traits, and their relationship to herbicide use.

PMRA Response:

Plants with novel traits are regulated separately by the Canadian Food Inspection Agency (CFIA), and by Health Canada under the *Food and Drugs Act*. As such, the regulation of genetically or otherwise modified crops and traits falls outside the scope of the *Pest Control Products Act*, as well as the SPN2018-02. However, the impact of the novel trait on how a pesticide may be used on the growing crop is factored into all pesticide risk assessments conducted by the PMRA.

Herbicide-tolerant traits extend the window of application for a herbicide to the growing crop. For example, transgenic crops may be tolerant to both pre- and post-emergent herbicide applications, whereas conventional crops may be tolerant to only pre-emergent treatments. The increased intensity of herbicide use is accounted for in pesticide risk assessments. Plant metabolism studies and residue data are required for both types of crops in order to identify and delineate differences in how plants metabolise the pesticide, as well as differences in the potential residue levels between transgenic and conventional crops. Use data are also factored into the assessment so as to account for the fraction of the total amount of crop treated with the specific herbicide. In situations where reliable use data are not available, a health protective estimate of 100 per cent crop treated is assumed for risk assessment purposes.

4. Comments related to the process for conducting cumulative health risk assessments, including opportunities for consultation and timelines

Several comments were related to the process for conducting cumulative health risk assessments. These included queries regarding how the findings of a cumulative health risk assessment are integrated into the regulatory process, whether such assessments would be conducted as part of a

re-evaluation, and whether the framework would include a "gatekeeper" step as outlined in Solomon et al, 2016[3] and Moretto et al, 2017[4]. Commenters also highlighted the importance of consultation at various points in the assessment, as well as the establishment of timelines.

PMRA Response:

The PMRA has developed a process map for cumulative health assessments to address the received comments (see Appendix III). Cumulative health assessments that can be addressed within the context of the individual pesticide documentation (Proposed Registration Decision [PRD] or Proposed Re-evaluation Decision [PRVD]) will continue in this manner as per current practice. Those assessments that are more complex will be handled as stand-alone re-evaluations for a cumulative assessment group. For the latter type, the PMRA will undertake a scoping assessment to identify the available evidence relating to both the evidence for common toxicity and evidence for co-exposure. This step is an initial collection of information and is analogous to the gatekeeper step referred to in the cited publications. Based on this information, the PMRA determines whether a cumulative health risk assessment is required, and, if so, the PMRA then undertakes a problem formulation to identify the scope and depth of the necessary analysis. Upon completion of the problem formulation, the PMRA will announce the proposed cumulative assessment group, and request toxicological, exposure and use pattern information relevant to the cumulative health risk assessment. Following this information-gathering step, the PMRA will publish a project plan which will include timelines for completion of the cumulative health risk assessment and then proceed with the review. Regardless of which path an assessment follows, there will be an opportunity for interested stakeholders to comment on the proposed decision prior to the publication of the final decision.

5. Comment on completion of re-evaluations without a cumulative health assessment

One set of comments recommended that the re-evaluation of individual pesticides within the same group not be considered complete until cumulative health risks have been assessed.

PMRA Response:

As indicated in the process map (Appendix III), in some cases, cumulative health assessments will be undertaken within the scope of the re-evaluation for individual pesticides. In other cases that require a more complex assessment, the PMRA will initiate a separate re-evaluation for a

[3] Solomon KR, Wilks MF, Bachman A, Boobis A, Moretto A, Pastoor TP, Phillips R and Embry MR. (2016). Problem formulation for risk assessment of combined exposures to chemicals and other stressors in humans. Crit Rev Toxicol 46(10): 835-844.

[4] Moretto A, Bachman A, Boobis A, Solomon KR, Pastoor TP, Wilks MF and Embry MR. (2017). A framework for cumulative risk assessment in the 21st century. Crit Rev Toxicol 47(2):85-97.

cumulative assessment group, after completing the re-evaluations of the individual pesticides within that group. The latter process will ensure that there is no delay in implementing required risk mitigation measures for individual pesticides, while at the same time maintaining regulatory authority for the subsequent evaluation of cumulative health risk.

6. Comment related to updating the framework, including the consideration of a "gatekeeper" step

One commenter recommended updating the framework to reflect the processes outlined in Solomon et al., 2016[5] and Moretto et al., 2017[6]. Specifically, the commenter recommended inclusion of a gatekeeper step which involves assembling available information on toxicity and exposure to determine if sufficient evidence is available to warrant a cumulative risk assessment.

PMRA Response

There will be a scoping step in the cumulative health risk assessment process aimed at identifying the available toxicological, exposure, and use information relevant to a determination of co-exposure and common mechanisms of action. This information will be used to determine if a cumulative health risk assessment is required and if it is required, a problem formulation will define the scope and the depth of the risk assessment. A cumulative health risk assessment is deemed unnecessary if the information indicates either a lack of co-exposure or common mode of toxic action. The scoping step does not involve a complete assessment, but rather documents the initial collection and summary of the data in-hand for the cumulative assessment group.

7. Comments related to how and when cumulative health risk assessments are triggered/required

Several commenters recommended that the framework should specify the conditions that would trigger the need for a cumulative health risk assessment, and identify points in the decision-making process where the need for a cumulative health risk assessment is determined.

PMRA Response:

According to the *Pest Control Product Act*, cumulative assessments of health effects for pesticides must be undertaken for new evaluations, re-evaluations and in the establishment of MRLs. These assessments may consist of a qualitative or quantitative cumulative health risk

[5] Solomon KR, Wilks MF, Bachman A, Boobis A, Moretto A, Pastoor TP, Phillips R, Embry MR. (2016). Problem formulation for risk assessment of combined exposures to chemicals and other stressors in humans. Crit Rev Toxicol 46(10): 835-844.

[6] Moretto A, Bachman A, Boobis A, Solomon KR, Pastoor TP, Wilks MF and Embry MR. (2017). A framework for cumulative risk assessment in the 21st century. Crit Rev Toxicol 47(2):85-97.

assessment, or result in a determination that a cumulative health risk assessment is not required, as further outlined in the process map that has been developed for cumulative health assessments (see Appendix III). The process map highlights conditions under which a cumulative health risk assessment would not be required (for example, lack of a common mechanism of action, or on the basis of use pattern). It also details the process that will be followed in situations that require a more complex cumulative health risk assessment, for example, where several pesticides have been identified to belong to a cumulative assessment group, and it is anticipated that co-exposure will occur. Moving forward, the process identified in Appendix III will be undertaken for all re-evaluations, for evaluations of new pesticide active ingredients, as well as those involving major new uses of previously registered pesticide active ingredients.

8. Comment on regulatory impact

Several commenters recommended that the PMRA indicate how conclusions about cumulative health risk will influence regulatory decisions.

PMRA Response:

As with individual pesticide risk assessments, the finding of unacceptable risk in a cumulative health risk assessment will warrant risk mitigation. Risk mitigation measures can include a host of possible measures ranging from label amendments to cancellation of uses or products, as well as MRL amendments. Given the potential complexity of a cumulative health risk assessment, the need to identify risk drivers will be of paramount importance in a finding of unacceptable risk. Sensitivity analyses can help to discern whether risks are driven by one pesticide in the common mechanism group or by certain uses, pathways of exposure or other factors, such as whether risks are specific to a certain population. Regulatory actions would be tailored to address the risk of concern. The PMRA recognizes that the challenges will increase in identifying appropriate risk mitigation options with larger common mechanism groups and increased number of potential co-exposure events. For these reasons, stakeholder consultation will be vital to developing appropriate mitigation options.

9. Comments relating to the incorporation of a precautionary approach in cumulative health risk assessments

One commenter recommended describing the application of the legislative requirement for precaution in the framework document. Another commenter indicated that a precautionary approach is a more appropriate way to proceed than relying on a weight-of-evidence approach when assessing common mechanisms of action.

PMRA Response:

The legislative requirement for precaution will be applied in cumulative health risk assessments in a manner similar to that applied for individual pesticide assessments. Accordingly, conservative assumptions and methods will be employed in the absence of data, acceptability of risk will be determined and unacceptable risks will be mitigated. These features have been reflected in the SPN2018-02.

The PMRA does not consider the weight-of-evidence approach and the precautionary approach to be mutually exclusive. The weight-of-evidence approach is a qualitative process of integrating multiple lines of evidence to reach a conclusion using professional judgement. Uncertainties that result from incomplete or absent scientific data during this integration frequently require scientists to make inferences, assumptions and judgements in order to characterize risk. As noted above, the PMRA employs a precautionary approach in the absence of data through the use of conservative assumptions and methods.

10. Comment related to the level of conservatism in the proposed approaches

One commenter indicated that the flexibility provided in the cumulative health risk assessment framework with regards to the proposed options for assessment methods was appreciated. However, the commenter indicated that it was important that the PMRA not default to the use of overly-conservative approaches.

PMRA Response:

The PMRA will be mindful to not introduce unnecessary conservatism into cumulative health risk assessments through the choice of assessment methods. However, the choice of methods will be largely driven by the quality and amount of data that are available, and the level of refinement that is deemed necessary. According to the proposed tiered approach outlined in the cumulative health risk assessment framework, more conservative approaches for assessing the hazard and exposure components of an assessment generally will be used in the earlier stages of the cumulative health risk assessment, with refinement of these parameters undertaken as needed, in an effort toward efficient use of resources.

11. Request to include real-life examples in the document including the determination of relevant exposure scenarios and data

One commenter indicated that it would be useful to provide real-life examples in the document including the determination of relevant exposure scenarios and data, as this information will impact the risk assessment the most.

PMRA Response:

Given the high level of interest in publishing the framework document in an expeditious manner, the PMRA has chosen to not include real-life examples at this time. However, as the PMRA will be publishing and consulting on cumulative health assessments, stakeholders will have the opportunity to provide further comments on the approach to cumulative assessment.

12. Comment on backlog of pesticides without a cumulative health risk assessment

Several commenters recommended that the PMRA establish timelines for addressing the backlog of currently registered pesticides for which cumulative health risks have not been assessed.

PMRA Response:

The PMRA acknowledges that cumulative health assessments for some pesticides in the re-evaluation program (for example, the N-methyl carbamates or organophosphates) were deferred. The reason for this deferral was to ensure that risks associated with individual pesticides within a group had been adequately characterized by way of a modern assessment and mitigated to acceptable levels. The PMRA will review past assessments for pesticides belonging to already-known common mechanism groups and will develop a strategic plan to address those with outstanding cumulative health risk assessments. New active ingredients that have been registered since the requirement for conducting cumulative health assessments, will be addressed in future re-evaluations and in the assessment of new active ingredients.

13. Suggestion to develop an evaluation strategy for the cumulative health risk assessment framework

One commenter recommended the inclusion of an evaluation strategy to determine the effectiveness of the framework and identify areas for future analysis and assessment.

PMRA Response:

Recognizing that the area of cumulative health risk assessment is an evolving science, the PMRA will update related policies as necessary. Continued involvement with international partners will ensure that the PMRA stays abreast of key developments.

14. Comment related to the maintenance of a cumulative health assessment database

One set of commenters recommended that the PMRA maintain a publicly accessible database of pesticide toxic effects and associated hypotheses about mechanisms of toxicity, including groupings of pesticides for cumulative health assessments.

PMRA Response:

The PMRA will explore mechanisms for tracking cumulative health assessments and providing public access to such records.

15. Comments related to expanding and updating the PMRA's cumulative health risk assessment approach in the future

It was recommended that a timeline be included for the development of more advanced methodologies in the future. Commenters suggested that the scope of cumulative health risk assessments should be expanded in the future to include consideration of cumulative health risks associated with pesticide formulations, mixtures of pesticides with disparate mechanisms but similar toxic effects, as well as mixtures of pesticides with other chemicals that share common toxic effects and/or mechanisms of toxicity. It was also suggested that future methods should consider synergistic effects of pesticide mixtures, regardless of their mechanisms of toxicity and individual toxic effects, as well as alternate modes of action for individual pesticides.

PMRA Response:

The PMRA's current focus remains the prompt completion and implementation of the SPN2018-02, which includes currently recognized and widely adopted methods. The PMRA acknowledges that methodology in this subject area will continue to evolve, and will continue to update cumulative health risk assessment methods accordingly. With regards to the suggestion that future methods should consider alternate modes of action for individual pesticides, it should be noted that this point is already addressed in the current framework. The SPN2018-02 indicates that pesticides may be placed in more than one group in instances where pesticides cause more than one common toxic effect.

Specific Comments

Comments on Section 2 - Introduction

16. Comment related to use of the wording "increased health risk"

One commenter asked for clarification of the term "increased health risk" in the statement "Cumulative assessment is undertaken to explore the possibility that low level exposures to specific multiple chemicals could lead to the same or increased health risk relative to a higher level of exposure to any of these chemicals individually."

PMRA Response:

The PMRA has modified the statement to clarify its meaning. The sentence now reads "Cumulative assessment is undertaken to explore the possibility of whether low-level exposures to multiple pesticides 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 pesticides individually".

Comments on Section 3 - Cumulative Risk Assessment Methods

17. Comment related to selection of the appropriate cumulative health risk assessment method

One commenter requested that the PMRA provide clarification regarding how the method of assessment would be selected for a given cumulative health risk assessment. This commenter suggested that the problem formulation methods outlined in Solomon et al (2016)[7] could be used to inform method selection.

PMRA Response:

The cited reference (Solomon et al, 2016)[8] focusses on the subject of problem formulation, rather than on method selection for cumulative risk assessments. Problem formulation has now been incorporated into the PMRA's process map for cumulative health assessment (see Appendix III). The choice of method for cumulative health risk assessment will be influenced primarily by the context of the assessment (for example, whether the assessment involves single or multiple exposure pathways), the quality and extent of the available data, and the level of refinement required in the assessment.

18. Comment related to maximum cumulative ratio approaches

One commenter requested that the PMRA consider the papers of Price et al (2011[9], 2012[10] and 2014[11]) which discuss the maximum cumulative ratio (MCR) approach and its applicability to cumulative health assessment.

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7 Solomon KR, Wilks MF, Bachman A, Boobis A, Moretto A, Pastoor TP, Phillips R, Embry MR. (2016). Problem formulation for risk assessment of combined exposures to chemicals and other stressors in humans. Crit Rev Toxicol 46(10): 835-844.

8 Ibid.

9 Price PS and Han X. (2011). Maximum Cumulative Ratio (MCR) as a Tool for Assessing the Value of Performing a Cumulative Risk Assessment. Int. J. Environ. Res. Public Health 8:2212-2225.

10 Price P, Dhein E, Hamer M, Han X, Heneweer M, Junghans M, Kunz P, Magyar C, Penning H and Rodriguez C. (2012). A decision tree for assessing effects from exposures to multiple substances. Environmental Sciences Europe 24:26.

PMRA Response

The MCR is the ratio of the hazard index of a group of chemicals (that is, the sum of the hazard quotients of each chemical in that group) to the maximum hazard quotient within that group, where the hazard index is used to normalize exposures across chemicals. The PMRA concurs that this approach provides an additional tool that can be used in the tiers of assessment to identify pesticides that may drive the risk assessment and for which refinements may be of greater importance. As the MCR is hazard-focussed, it is less useful for identifying exposure scenarios that influence the risk assessment. Additional text has been included in the SPN2018-02 referencing this method.

Comments on Section 4 – Selection Considerations for Common Mechanism Groups

19. Comments related to preliminary grouping

One commenter recommended a tiered approach to preliminary grouping. The commenter suggested that grouping should not be based on only one of the listed criteria, particularly not structural similarity. They further stated that common mechanism of toxic effect and co-exposure are the most important determinants in grouping, and should be prerequisites for conducting cumulative health risk assessments.

Another commenter suggested the following addition (in underline) "The PMRA does not regard the preliminary grouping alone <u>to be sufficient</u> to reliably conclude that such chemicals have a common mechanism of toxicity."

PMRA Response:

A tiered approach is already outlined in the framework in that a cumulative assessment group identified during preliminary grouping undergoes further analysis at the refined grouping step to determine whether there is sufficient support for a common mechanism group. Notwithstanding this iterative approach, structural similarity is a useful criterion for screening at the preliminary grouping step, given the potential for common toxophores. As outlined in Appendix III, stakeholders will have an opportunity to provide additional information during the process regarding the proposed common mechanism groups.

[11] Price P, Zaleski R, Hollnagel H, Ketelslegers H and Han X. (2014). Assessing the safety of co-exposure to food packaging migrants in food and water using the maximum cumulative ratio and an established decision tree. Food Additives & Contaminants, Part A, 31(3):414-421.

The PMRA concurs that common mechanism of toxic effect and co-exposure are important determinants in grouping. For this reason, complex cumulative health assessments will incorporate a scoping step to elaborate on these elements prior to undertaking a full review.

Regarding the suggested text modification, the intent of the original sentence was to indicate that it was necessary to further consider a preliminary grouping, as per Section 4.2. Refined Grouping, prior to making a common mechanism determination. The insertion of the suggested text would alter the meaning of the sentence, such that it would imply that a preliminary group could never be considered sufficient to conclude that such pesticides have a common mechanism of toxicity. The PMRA has not made this modification, as it is plausible that a preliminary group could be confirmed at the refined grouping stage for a common mechanism finding. The text has been modified in the SPN2018-02 to clarify the intent.

20. Comments related to use of the precautionary approach in grouping

One set of comments recommended adoption of a precautionary approach to grouping. It was suggested that the PMRA should proceed with the cumulative health risk assessment if there is uncertainty regarding the mechanism of toxicity with the onus on the registrant to disprove hypotheses on common mechanisms.

PMRA Response:

The PMRA is exploring options to solicit information on mechanisms of action from the registrant earlier in the evaluation and re-evaluation process of individual pesticides. For complex assessments, the preliminary evidence on common toxicity and co-exposure is identified during the scoping step and a problem formulation is created. This information will be published at the information gathering step at which point there will be a request for any additional information to inform the cumulative health risk assessment and address uncertainties. If it is decided at any point in the process that a cumulative health risk assessment is not required, this proposed decision will also be published to allow for consultation.

21. Comment related to basis for grouping pesticides

One commenter recommended that grouping pesticides for cumulative health risk assessments should be based on findings on a ‘tissue level’ rather than being defined at the level of a particular biochemical reaction.

PMRA Response:

The PMRA acknowledges that there is interest in considering common findings on a tissue level when grouping pesticides for cumulative health risk assessment. As outlined in the SPN2018-02, information regarding similar toxic effects is considered during the preliminary grouping step to assess whether further investigation is warranted at the refined grouping step.

22. Comment related to grouping pesticides that have more than one mechanism of toxicity

One commenter asked the PMRA to clarify how pesticides for which more than one mechanism of toxicity has been identified would be handled under the cumulative health risk assessment framework.

PMRA Response:

The PMRA recognizes that some pesticides may exert toxic effects via more than one mechanism of action. If this is the case, and the identified mechanisms of action are shared by one or more other pesticides, then the pesticide will be included in each applicable cumulative health risk assessment, as outlined in the SPN2018-02.

23. Comment related to the types of health effects that would be considered relevant for cumulative health risk assessments, and the methods used to conduct literature-based health assessments

One commenter asked whether the cumulative health risk assessment framework will be applicable to adverse health outcomes such as endocrine disruption, neurodevelopmental effects and cancer. The commenter recommended that a weight-of-evidence approach that considers epidemiologic data, in addition to in vivo animal studies, in vitro genotoxicity assays, and mechanistic studies be used to assess the potential for such health effects, and to elucidate their mechanisms of action. It was further recommended that systematic review methods and reporting, such as described by Rooney et al (2014),[12] be used in such weight-of-evidence approaches to ensure transparency, rigour and confidence.

PMRA Response:

The cumulative health risk assessment framework is applicable to any toxicity endpoints that are the result of a common mechanism of toxicity, except those that are non-specific in origin or those that could have many possible unrelated causes. The PMRA currently considers, and

[12] Rooney AA, Boyles AL, Wolfe MS, Bucher JR, Thayer KA. (2014). Systematic review and evidence integration for literature-based environmental health science assessments. Environ Health Perspect 122 (7): 711-18.

utilizes as appropriate, all of the types of data suggested by the commenter in a weight-of-evidence approach when evaluating health effects associated with individual pesticides, and will continue to use this approach in the context of cumulative health risk assessments, as further described in the SPN2018-02.

The PMRA acknowledges the benefits and sound principles of the systematic review methods described in the cited reference (Rooney et al, 2014). In general, the principles will be followed to the extent possible for cumulative health risk assessments, using a 'fit for purpose' approach. Some of the principles, although not formally documented, are routinely taken into consideration during the PMRA's health assessment of individual pesticides, including many of the factors described for determining the level of confidence in the available data.

Comments on Section 5 – Cumulative Risk Assessment Framework

24. Comment related to providing more detail on types of data or models used to estimate exposure at each tier and how the proposed models will accommodate new active ingredients

Commenters requested that the PMRA provide more detail on the types of data or models used to estimate exposure at each tier and include a discussion on the use of the Residential Joint Venture (REJV) homeowner survey data. There was also a concern expressed regarding the ability to refine exposure estimates for new active ingredients due to the lack of information on use patterns and market share.

PMRA Response:

The typical data and assumptions used to conduct risk assessments for individual pesticides will, to a large extent, also be used to determine exposure estimates for cumulative health risk assessments. This approach will apply to cumulative health assessments for new active ingredients, as well as those assessed through the re-evaluation process. Exposure information generally will be derived from the submitted regulatory data package and assessed in accordance with SPN2014-01 General Exposure Factor Inputs for Dietary, Occupational and Residential Exposure Assessments. These data include registrant field trial data, drinking water residue estimates derived from modelling, demographic and food intake data from the National Health and Nutrition Examination Survey (NHANES), and generic exposure algorithms from the USEPA Residential Standard Operating Procedures.

The derivation of exposure estimates can progress from the use of deterministic methods at lower tiers, to more complex probabilistic assessments at higher tiers. This has been described more fully in the SPN2018-02. Notwithstanding the lack of information regarding the extent of use and market share data on new pesticides, much of the data cited in the SPN2018-02 are used as generic and/or surrogate data to refine risk assessments for all pesticides.

25. Comments related to how the proposed models would accommodate multi-route exposure scenarios

Commenters suggested that clear examples of multi-route exposure analyses with recommendations be provided and also noted the USEPA's Aggregate Risk Index (ARI) as an additional method that can be used when uncertainty factors differ by route.

PMRA Response:

As described in the SPN2018-02, exposures may originate from a single route (for example, oral exposure from a dietary pathway) or multiple routes (oral, dermal and inhalation), all of which may vary over time and space. Determination of the combination of exposures and routes is an important step for cumulative health risk assessments. Identification of use patterns of active ingredients is required to develop exposure scenarios for assessment (including route, duration, and frequency of exposure), data collection, or modelling strategies. The problem formulation will address questions regarding the route, duration, and frequency of exposure to the exposed target populations being considered and the probability of co-occurrence of exposures within a relevant timeframe. If information is not available to make this determination, it will be requested by the PMRA during the information gathering stage. When combining the different routes of exposure for multiple pesticides, methods similar to those used for combining multi-route exposures for individual pesticide risk assessments will be employed. These methods include the combined MOE and the ARI approaches, depending on the toxicological profile of the group of pesticides. The ARI method has been added to the SPN2018-02.

26. Comments related to the need for access to exposure monitoring data

Some commenters want to ensure that Canadian monitoring programs have capacity and funding to collect information, strengthen reporting, and co-ordinate programs to meet the needs of the PMRA.

PMRA Response:

The PMRA is engaged with partners to generate and collect information relevant to pesticide exposures. This includes monitoring and surveillance activities conducted under the CMP, such as the Canadian Health Measure Survey (CHMS), food residue monitoring conducted by the

CFIA under the National Chemical Residue Monitoring Program, demographic instruments such as the Canadian Community Health Surveys, and water quality monitoring data collected by Federal, Provincial and Territorial partners. The PMRA supports these publicly funded monitoring and surveillance activities, and is active in providing recommendations on the selection of monitored parameters. However, the funding and capacity-building aspects are broader than the PMRA's role, and fall more within the scope of Government of Canada initiatives such as the CMP. Where appropriate, the PMRA may also rely on data from international programs such as the United States Department of Agriculture's Pesticide Data Program (USDA PDP) for residues on foods imported into Canada, and the Centers for Disease Control and Prevention's NHANES for food intake estimates.

Monitoring and surveillance programs can provide data critical for the refinement of exposure estimates, however, pesticide registrants have the responsibility to provide the toxicology and exposure data required to support their registered products. The PMRA will use the most reliable and relevant available data to inform cumulative health assessments, which is consistent with the approach currently used for individual pesticide risk assessments. That is, the data sources will include both publicly generated information, as well as registrant-supplied data.

27. Comment related to criteria for identifying co-exposures

Several commenters asked for clarification of how, and at which point in the process, co-exposures will be identified. Another commenter requested that the "critical time window" be defined and the approach to assessing cumulative chronic exposure be clarified.

PMRA Response:

Exposure scenarios and the likelihood of co-exposure, along with the common toxicity determination, will be considered by the PMRA at the beginning of the cumulative health assessment process. At the earliest stages of the cumulative health assessment, it will be determined whether there is dietary or residential exposure, or whether exposure is limited to occupational scenarios. This initial analysis will determine if the cumulative health risk assessment is required and if so, whether it can be addressed within the individual pesticide documentation. For those groups that are addressed within the individual pesticide documentation, co-exposures are assessed concurrently with the review of exposure information supporting the individual pesticide. For groups for which the assessments are anticipated to be more complex, co-exposures will be identified, along with a common toxicity determination, at a scoping and problem formulation step. This step also represents a decision point at which there is a determination of whether a cumulative health risk assessment is required.

Timing of exposures to multiple pesticides sharing a common mechanism of toxicity is a major determinant of risks in cumulative health assessment. Co-exposures will be identified on the basis of the data that demonstrate temporality of exposure. The routes, pathways, amounts, frequency and intensity of exposure are all factors that must be considered in determining the likelihood of co-exposure. Relevant co-exposures target the same population within the same timeframe. The exposure period should be concordant with the exposure duration for which adverse effects are observed in animal toxicity studies. Toxicokinetic and toxicodynamic data can inform whether consecutive, separate or partially-overlapping exposures need to be considered in a cumulative health assessment. The critical time window will be based on actual or anticipated conditions of use and will be included in the problem formulation, if the information is available to make that determination. Otherwise, information will be requested to determine the critical time window during the information gathering step.

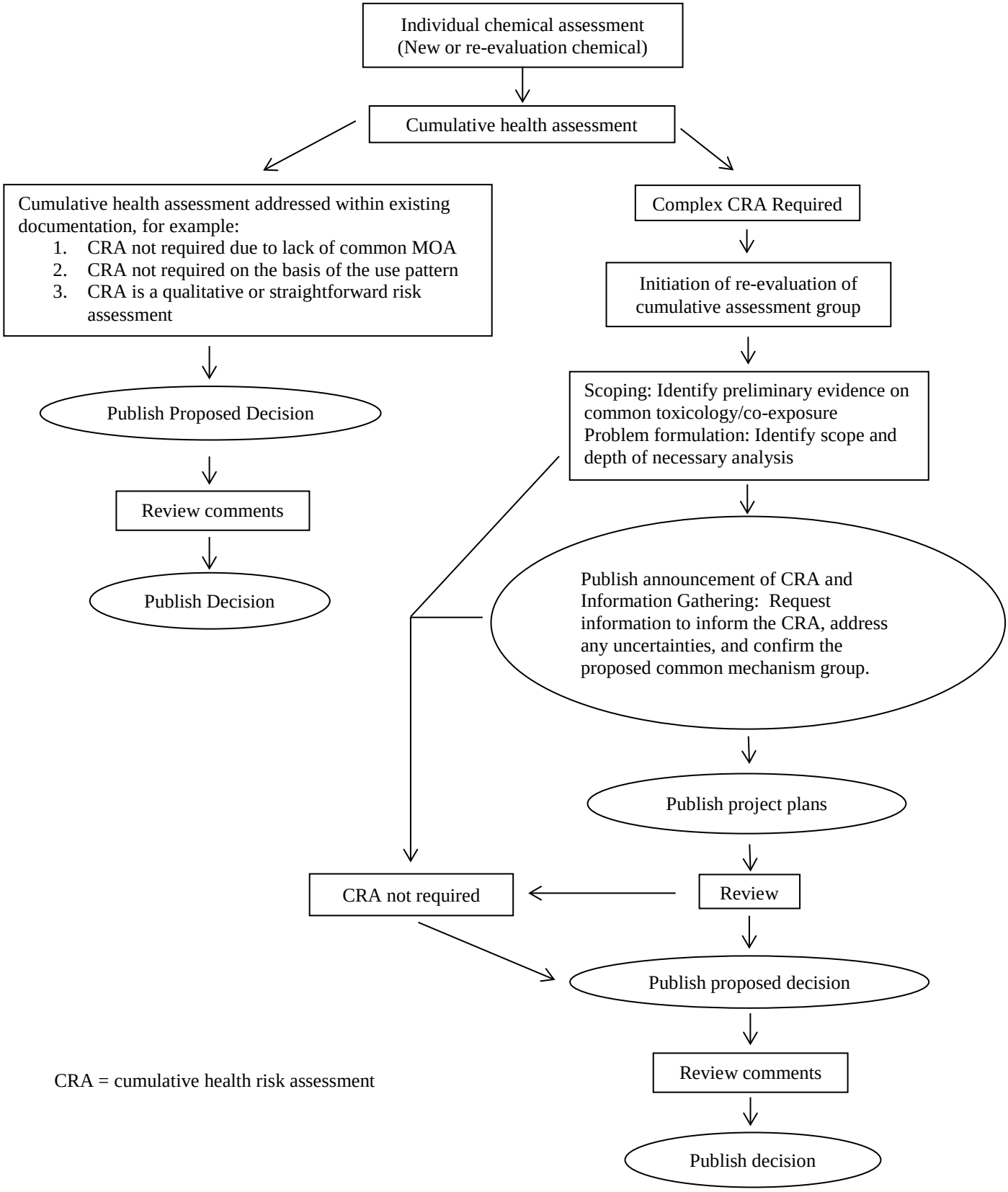
28. Comment related to overly conservative risk assessments

One commenter recommended not summing exposures from too many separate scenarios for the screening-level residential exposure analysis. They indicated that the cumulative health risk assessment should not assume that multiple active ingredients with the same mode of action are concurrently applied to the same sites in the same temporal period.

PMRA Response:

The focus of the cumulative health risk assessments will be on exposures that are likely to co-occur, rather than those that may possibly co-occur. Information on product use and co-use profiles is essential for determining a realistic scenario of combined exposure for a given population and avoiding overestimation of exposure. Principles for inclusion or exclusion of exposure scenarios, similar to those used in aggregate risk assessments (SPN2003-04), will be applied to the cumulative health risk assessments. As the PMRA will be consulting on the outcomes of cumulative health assessments, stakeholders will have the opportunity to provide further comments on the likelihood of any given co-exposures.

Appendix III Process Map for Cumulative Health Assessment



CRA = cumulative health risk assessment

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Glossary

Adverse Outcome Pathway: A linear representation of key events between a molecular initiating event and an adverse outcome

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

Common Mechanism Group: Pertains to two or more chemicals 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 chemicals that are known to cause the same toxic effect (that is, concordant in the nature of the effect) in or at the same anatomical or physiological site or location (for example, same organ or tissue).

Composite Assessment Factor: The product of the uncertainty factors and the PCPA factor; used to establish reference values for use in dietary, aggregate and cumulative risk assessments.

Cumulative Assessment Group: Two or more chemicals grouped together for the purpose of conducting a cumulative health assessment.

Cumulative Toxic Effect: The net change in magnitude of a common toxic effect resulting from the exposure to two or more chemicals acting by a common mechanism, relative to the magnitude of the common toxic effect caused by exposure to any of the chemicals individually.

Hazard Index: The sum of the individual hazard quotients of individual chemicals in a cumulative assessment group

Hazard Quotient: The ratio of an individual chemical’s exposure to its reference value.

Lower Confidence Limit on a Benchmark Dose: The lower confidence limit on a benchmark dose. The benchmark dose is the dose or concentration that corresponds with a specified level of response. Both the benchmark dose and its lower limit are derived through statistical modelling of dose-response data.

Lowest Observed Adverse Effect Level: The lowest level of exposure in an organism that causes an adverse alteration of morphology, function, capacity, growth, development or lifespan.

Maximum Cumulative Ratio: The ratio of the hazard index of a group of chemicals (that is, the sum of the hazard quotients of each chemical in that group) to the maximum hazard quotient within that group, where the hazard index is used to normalize exposures across chemicals.

Margin of Exposure: The ratio of a chemical’s point of departure to its predicted or estimated exposure.

Mechanism of Toxicity or Action: The molecular sequence of events that produces a specific biological outcome.

Mode of Action: A plausible hypothesis about measurable key events by which a chemical exerts it biological effects. It does not imply full understanding of mechanism of action at the molecular level. In the context of this document, mode of action refers to the key cytological and biochemical events by which a pesticide is toxic to humans or experimental animals, and not the mode of action by which it is toxic to target or intended species (that is, its pesticidal action).

No Observed Adverse Effect Level: A level of exposure in an organism at which there is no biologically or statistically significant increase in the frequency or severity of an adverse effect.

Point of Departure: A dosage or concentration of a single chemical used in regulatory toxicology for estimating tolerable exposures to humans. The point of departure is typically based on a NOAEL, No observed Adverse Effect Concentration (NOAEC) or benchmark dose.

Reference Value: The reference value is the point of departure, (that is, the NOAEL, LOAEL, or BMDL), divided by the composite assessment factor (that is, the product of the uncertainty factors and the PCPA factor).

Relative Potency Factor: The ratio of the toxic potency of a given chemical to that of an index chemical in a cumulative assessment group.

Site of Toxic Action: The anatomical or physiological site(s) or location(s) at which the interaction of the chemical with its biological targets occurs that leads to a toxic effect.

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

Target Margin of Exposure: The product of the uncertainty factors and the PCPA factor; used in occupational, residential, aggregate and cumulative risk assessments.

Toxic Action: The interaction of a given chemical with biological targets that leads to a toxic effect.

Toxic Effect: An effect known (or can reasonably be expected) to occur from exposure to a chemical 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.

Toxophore: A structural feature or moiety of a chemical that bestows the toxic property through interaction with a molecular site (e.g., receptor) in cells of tissue or organs. The resulting biochemical changes or alterations lead to the disruption of physiological processes performed by the tissue or organs and, ultimately, to the toxic effect. The toxophoric portion of a chemical may interact reversibly or irreversibly with its molecular site, depending upon its reactivity and the molecular site. For some chemicals, toxicity results from the metabolism of a structural substituent to a toxophore. Metabolic pathways that lead to toxicity are often called bioactivation pathways.

Weight-of-Evidence: A qualitative evaluation that takes into account the nature and quality of scientific information regarding a chemical for a specific purpose. A weight-of-evidence evaluation can involve 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.

List of Abbreviations

ARI: Aggregate Risk Index

BMDL: Lower Confidence Limit on a Benchmark Dose

CAG: Cumulative Assessment Group

CARES NG: Cumulative and Aggregate Risk Evaluation System Next Generation

CFIA: Canadian Food Inspection Agency

CHMS: Canadian Health Measure Survey

CMG: Common Mechanism Group

CMP: Chemical Management Program

CPMA: Canadian Pest Management Association

EC: European Commission

ED: Effective Dose

EFSA: European Food Safety Authority

HI: Hazard Index

HQ: Hazard Quotient

LOAEL: Lowest Observed Adverse Effect Level

MCR: Maximum Cumulative Ratio

MOA: Mode of Action

MOE: Margin of Exposure

MRL: Maximum Residue Limit

NAFTA: North American Free Trade Agreement

NOAEC: No Observed Adverse Effect Concentration

NOAEL: No Observed Adverse Effect Level

NHANES: National Health and Nutrition Examination Survey

OECD: Organization for Economic Development

PCPA: Pest Control Products Act

PMRA: Pest Management Regulatory Agency

POD: Point of Departure

PRD: Proposed Registration Decision

PRO: Regulatory Proposal

PRVD: Proposed Re-evaluation Decision

REJV: Residential Join Venture

RPF: Relative Potency Factor

SHEDS: Stochastic Human Exposure and Dose Simulation

SPN: Science Policy Note

UF: Uncertainty Factor

USEPA: United States Environmental Protection Agency

WHO/IPCS: World Health Organization/International Program on Chemical Safety

WOE: Weight of Evidence

USDA PDP: United States Department of Agriculture’s Pesticide Data Program