Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Directive

DIR2005-01

Guidelines for Developing a Toxicological Database for Chemical Pest Control Products

The purpose of this document is to outline the current toxicological data requirements for chemical pest control products in Canada. The last comprehensive publication of toxicology data requirements was in Agriculture Canada Trade Memorandum T-1-245, *Guidelines for Developing a Pesticide Toxicology Data Base*, issued 19 September 1984, which was released before the creation of the Pest Management Regulatory Agency (PMRA). Revisions have been made to the guidelines to reflect current scientific and operational practices and policies, move towards international harmonization of data requirements, where possible, and clarify testing requirements. No new toxicology data requirements have been established in this regulatory directive. Data requirements outlined under the data code (DACO) tables for each use-site category (USC) will be modified to reflect the update to the guidelines as well as to correct existing discrepancies.

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1.0 Introduction

The PMRA is responsible for the assessment of health risks from pesticide residues in food as well as from occupational and residential exposure to pest control products. This activity is carried out under the authority of both the *Pest Control Products Act* and *Food and Drugs Act* and their respective Regulations.

The PMRA requires extensive data to address dietary, occupational and residential risks. These data are required to evaluate new active ingredients or end-use products, new uses of existing products, in the re-evaluation of currently registered products or for the establishment of import maximum residue limits for a product not otherwise registered in Canada. It should be noted, however, that the PMRA considers applicants and registrants to be responsible for demonstrating the safety of any pest control product. The guidelines for pest control products in this document are intended to assist applicants/registrants in developing a toxicological database, essential for evaluating hazards and risks. These guidelines do not address data requirements for microbial pest control products or pheromones. Further guidance on requirements for these products can be found in Regulatory Directive DIR2001-02, *Guidelines for the Registration of Microbial Pest Control Agents and Products* (30 March 2001), and Regulatory Directive DIR97-02, *Guidelines for the Research and Registration of Pest Control Products Containing Pheromones and Other Semiochemicals* (29 September 1997).

The data requirements outlined in this document represent Canada's national requirements. They also reflect extensive consultation with the United States Environmental Protection Agency (USEPA) and are harmonized with the American requirements to a high degree. Furthermore, the Canadian toxicology data requirements are similar to those in other countries within the Organisation for Economic Cooperation and Development (OECD). The USEPA has recently proposed revisions to their data requirements for the registration of conventional pesticide products under the United States Code of Federal Regulations, (CFR, Part 158 of Title 40). Upon promulgation of the revised toxicology data requirements under the American Code of Federal Regulations, revisions to this regulatory directive may be required in order for it to remain harmonized.

These guidelines, outlined in Appendix I, are intended to clarify the types of tests generally needed in characterizing the toxicity of a chemical and the potential hazards it poses to humans. The submission of this data is critical to the Agency's ability to make scientifically sound regulatory decisions about the human health risks of pesticide products. The *Pest Control Products Act* and Regulations provide the PMRA with flexibility to require, or not require, data and information for the purposes of making regulatory judgements for pesticide products. The actual data required by the PMRA may be modified on an individual basis to fully elaborate the characteristics or effects of specific products under review. The PMRA encourages applicants and registrants to engage in pre-submission consultations to discuss data requirements. Applicants and

registrants are advised that the PMRA may require the submission of additional data or information beyond that specified in this regulatory directive if such data or information are needed to appropriately evaluate a product.

Although no new data requirements have been outlined in this regulatory directive, changes have been made to some of the existing DACO titles to reflect modern terminology and to clarify or standardize study descriptors. These changes will be made upon publication of this regulatory directive and are outlined in Appendix II. The DACO tables will also be modified to correct existing discrepancies in data requirements as well as to add DACO titles as placeholders for supplemental data that may be available.

There are no Canadian test guidelines for toxicity studies. The PMRA relies on internationally recognized test guidelines published by the USEPA[1] or the OECD[2]. It is recommended that proposed protocols, particularly those that may deviate from internationally recognized guidelines, be discussed with PMRA officials prior to initiating the toxicity studies to ensure the studies will be satisfactory for consideration of Canadian product registration. The PMRA prefers an information-based approach to testing, which utilizes the best available knowledge of the chemical (hazard, toxicokinetic or mechanistic data) to determine whether a standard guideline study, an enhanced guideline study or an alternative study should be conducted to assess potential hazards. Where testing is needed to develop scientifically adequate data, the PMRA is committed to reducing or replacing, wherever possible, the numbers of animals used for testing by incorporating in vitro (non-animal) test methods or other alternative approaches that have been scientifically validated and have received regulatory acceptance.

PMRA Regulatory Directive DIR2003-01, *Organizing and Formatting a Complete Submission for Pest Control Products*, dated 11 April 2003, outlines the format for organizing all data in submissions for pest control products. In addition, Regulatory Directive DIR98-01, *Good Laboratory Practice*, dated 27 July1998, should be consulted for the PMRA's regulatory position on implementing good laboratory practice requirements. Submission of reviews conducted by other governments or agencies to the PMRA is encouraged to facilitate the Canadian review process.

2.0 Required Data, Conditionally Required Data and Data Waivers

The PMRA DACO tables for specific USCs indicate whether data are required (R), conditionally required (CR) or not required (NR). All data requirements identified as R must be addressed with appropriate studies or information, with references to previously submitted data or with scientifically based waiver requests.

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1 www.epa.gov/docs/OPPTS_Harmonized/870_Health_Effects_Test_Guidelines/Series

2 www.oecd.org/document/22/0,2340,en_2649_34377_1916054_1_1_1_1,00.html

The term CR is used in more than one manner in this document. When the USC triggers the data requirement based on how or where the product is used, the term CR has been used in Appendix I along with the test note "Refer to DACO requirement for specific USC". Where applicable, the DACO table for the relevant USC will specify the requirement with an R designation, and applicants and registrants will address the requirement.

The CR designation also identifies the conditions under which the data would be required. These conditions are provided in the "Test Notes" column of Appendix I and will be reflected in the "Conditions" column of the DACO tables. If the applicant or registrant realizes that a particular condition is applicable, it is essential that the CR data or a request for a waiver with a scientific rationale be supplied with the submission. Where conditions do not apply to a particular product, it is not necessary to reference these DACOs in the index or provide requests for waivers.

In certain cases, the CR designation is used as a placeholder. These placeholders identify the DACO against which additional data, if available, should be identified. It is not necessary to reference these DACOs in the index or provide requests for waivers if no data are available for these DACOs.

The PMRA encourages applicants and registrants to apply for data waivers if they believe that the test or recommended species is unsuitable for a certain pest control product. However, it is essential that where data waivers are sought, that the applicant or registrant provide a scientifically sound justification in support of the waiver request.

3.0 Comprehensive Data Summaries

Applicants and registrants should submit comprehensive data summaries of the toxicology profile as per PMRA Regulatory Directive DIR96-05, *Comprehensive Data Summaries*, published 11 October 1996, and Regulatory Directive DIR97-01, *Comprehensive Data Summaries*, published 15 August 1997. These summaries of all the available toxicology data including any literature references (to be included in the documentation) serve to facilitate efficient PMRA review processes.

4.0 Test Substance

Generally, the test substance used in toxicity testing will be the technical grade of the active ingredient that is produced during typical manufacturing processes. Under certain circumstances, it may be required that the following also be tested:

- an analytically pure grade of the active ingredient;
- a contaminant or impurity;
- a metabolite or degradation product;
- a formulant; or
- any combination of those listed above.

Toxicity tests performed with end-use products should utilize the formulation that is to be sold or used in Canada.

It is essential that all toxicology studies adequately identify the test material used in each study. For studies performed with the technical grade material, the purity must be specified. Where product purity or composition differs from that detailed on the Statement of Product Specification form, the specifications of the tested product must be provided to establish the relevance of the study. For studies performed with the end-use product, the applicant or registrant should indicate if the composition of the tested product is identical to the formulation to be sold or used in Canada, or otherwise identify the composition of the tested formulation.

If the identification of the test material is not readily available within each toxicology study, the applicant/registrant may wish to compile a central document identifying the test material used in each study in order to facilitate the review.

5.0 Acute Toxicity Studies

Acute toxicity studies on active ingredients and end-use products are necessary to determine the potential hazards from acute exposures. Acute data are used for classification purposes and for the development of appropriate precautionary statements for product labels. Acute studies identify relative acute toxicities by different routes of exposure as well as the potential to produce irritation and sensitization. It should be noted that the PMRA does not endorse irritation testing that seriously compromises animal welfare. Waivers should be requested if the test material is known to be severely irritating or corrosive, or if irritation potential can be estimated from other reliable information.

6.0 Short-term Studies

These studies provide information on the toxic potential of the pest control product through daily repeated exposure. A short-term study has been defined as having a duration lasting up to 10% of the animal's lifespan, 90 days in rats and mice, or 1 year in dogs. The data obtained from these short-term studies are useful in determining possible cumulative or delayed toxicity, and variability in species sensitivity as well as in identifying effects in organs or systems that are vulnerable to the chemical insult. They also provide guidance for selecting dosages for long-term studies. Post-treatment recovery phases assist in detecting reversibility or persistence of adverse effects. The use pattern and physical properties of the product as well as toxicokinetic considerations will assist in determining the appropriate route of exposure and duration of study.

7.0 Long-term Studies

Long-term daily repeated exposure studies are generally designed to investigate the chronic toxicity and oncogenic potential of the pest control product when administered to

test animals over the major portion of their lifespan. Ideally, the data thus generated should identify dose-response relationships and possible effects of cumulative toxicity as well as permit assessment of the potential for neoplastic development.

8.0 Reproduction Studies

These studies provide information on the potential of the pest control product to influence the reproductive performance and function of the male and female parental animals, through assessment of effects on gonadal function, estrus cycles, mating behaviour, conception, parturition, lactation and weaning. Observation of progeny from conception through lactation and weaning may enable the detection of possible adverse effects on survival, viability, development and behaviour. These studies have a pivotal role in determining the potential sensitivity of the young animal.

9.0 Developmental Toxicity Studies

These studies, referred to in the past as teratogenicity studies, permit assessment of the potential of the pest control product to induce adverse effects on the developing embryo and fetus when administered to the pregnant female test animal during critical periods of organogenesis. Studies are generally conducted in a rodent and a non-rodent species. The teratogenic potential of the pest control product may be measured by the increased incidence or induction of congenital malformations. These studies also have a pivotal role in determining the potential sensitivity of the young animal.

10.0 Genotoxicity Studies

Tests for genetic damage are designed to assess both gene mutations and chromosomal changes as well as the competency of DNA repair mechanisms. The basic criteria considered when evaluating the genotoxic activity of a pest control product are as follows:

1. determine whether the pest control product is genotoxic in some biological system by means of sensitive in vitro short-term tests;

2. through the prudent use of in vivo tests in mammalian somatic cells, establish whether the pest control product is a mammalian genotoxic agent; and

3. ascertain if the genotoxic activity of the pest control product is expressed as an adverse health effect.

With respect to the latter, it is necessary to determine if cancer or heritable mutations are induced by evaluating the data from the appropriate bioassays for carcinogenicity and the induction of heritable mutations. Appendix I presents the genotoxicity tests typically preferred for pest control products. There are, however, some pest control products for which another test could be justified scientifically as a substitute. In these instances, it

would be necessary to substitute a valid alternative test for the same endpoint, i.e., gene mutation or chromosome aberration.

11.0 Toxicokinetic Studies

Toxicokinetic studies provide data on the absorption, distribution, metabolism and excretion of the pest control product. This information may be valuable in interpreting toxic effects, or lack thereof, and may assist in the extrapolation of animal toxicity data to humans. A good understanding of the toxicokinetics of the pest control product may also enable more judicious selection of appropriate routes of administration and dose levels in long-term studies. Studies should be conducted in the most appropriate animal model(s).

The variability of test material absorption by different routes of exposure should be considered. In general, toxicokinetic studies should be performed using the same route of administration as that used in the majority of studies. Although dermal adsorption studies are not included as part of the current toxicology data requirements, they often play a pivotal role in the risk assessment. These studies are included under the data requirements for occupational and/or bystander exposure (DACO 5).

12.0 Neurotoxicity

The neurotoxic potential of the pest control product may be assessed on the basis of behaviour, neurophysiology, neurochemistry and neuropathology. Neurotoxicity screening tests may be incorporated into several of the standard protocols for acute toxicity as well as short- and long-term repeated exposure toxicity studies. This may be accomplished through expanded histopathological examination of the brain, spinal cord and peripheral nervous system, a functional observational battery of tests for general behaviour and neurology as well as autonomic and sensory assessment. Appropriate tests may also be incorporated into the standard protocol for reproduction studies for the purpose of assessing the neurotoxic potential of the pest control product in the progeny. Further testing may be appropriate for pest control products known or suspected to be neurotoxicants. For pest control products requiring an assessment of delayed neurotoxicity, studies are performed in the most susceptible animal species, the adult hen.

13.0 Immunotoxicity

The potential of the pest control product to affect the immune system may be discerned from hematology, blood chemistry, organ weights and histopathology, routinely investigated in short-term repeated exposure studies. The assessment of potential immunomodulating effects of the pest control product may be supplemented by immunotoxicological assessments such as a host resistance assay. Since data generated to date suggest that chemically induced functional adverse effects on the immune system may be present at doses below those producing clinical and histopathological alterations, additional assays may be triggered by immune-related effects noted in available toxicity

studies. If deemed appropriate, specific aspects of the immune response or elucidation of immunomodulation mechanisms may be investigated through additional assays to help predict a chemically induced functional effect on the immune system. These assays may be considered to further investigate lymphocyte subsets, humoral antibody mediated immunity as well as cell-mediated and non-specific immunity.

14.0 Mechanism of Action

Ancillary studies designed to elucidate specific mechanisms of action in the test animal may be key in interpreting the toxicological properties of the pest control product. Such information may permit a more comprehensive assessment of potential health hazards and risks to humans.

15.0 Combination of Active Ingredients

For end-use formulations in which more than one active ingredient is present, a full complement of acute studies are necessary to identify acute hazards and assist in determining acceptable labelling statements. In addition, where the combination of active ingredients is suspected to be of greater than additive toxicity based on known information (e.g., acute testing results, mode of action, quantitative structure-activity relationships or other), additional information such as a short-term toxicity study may be required.

16.0 Additional Comments

To facilitate the review of submissions, ranges of reference values (i.e., historical control data) for blood chemistry, hematology, tumour incidences, developmental variations and other malformations should be submitted, if available, with their respective studies. These reference values should be specific to the testing laboratory, route of exposure, species and strain in the study as well as relevant with respect to the date of study conduct.

List of Abbreviations

CR	conditionally required
DACO	data code
EP	end-use product
NR	not required
OECD	Organisation for Economic Co-operation and Development
OPPTS	Office of Prevention, Pesticides and Toxic Substances (USEPA)
PMRA	Pest Management Regulatory Agency
R	required
TGAI	technical grade active ingredient
USC	use-site category
USEPA	United States Environmental Protection Agency

Appendix I Guidelines for Toxicology Data for a Pest Control Product

NOTE: Text in italics will appear in the "Conditions" column of the data requirements for the USC, where applicable.

DACO	Study Type	Data Required	Test Notes	Available Guideline
4.1	Summaries	R		
4.2	Acute Studies—TGAI			
4.2.1	Acute Oral	R	The preferred species is the rat. Not required if the test substance is a gas or highly volatile liquid.	OPPTS 870.1100 OECD 420 OECD 423 OECD 425
4.2.2	Acute Dermal	R	The preferred species is the rat or the rabbit. Not required if the test substance is a gas or highly volatile liquid. Not required if the test substance is corrosive to skin or has a pH lower than 2 or greater than 11.5.	OPPTS 870.1200 OECD 402
4.2.3	Acute Inhalation	R	The preferred species is the rat. Required if the test substance consists of, or under conditions of use will result in, a respirable material (e.g., gas, vapour, aerosol or particulate).	OPPTS 870.1300 OECD 403 OECD 433 (draft)
4.2.4	Primary Eye Irritation	R	The preferred species is the rabbit. Not required if the test substance is corrosive to skin or has a pH lower than 2 or greater than 11.5.	OPPTS 870.2400 OECD 405
4.2.5	Primary Dermal Irritation	R	The preferred species is the rabbit. Not required if the test substance is a gas or highly volatile liquid. Not required if the test substance is corrosive to skin or has a pH lower than 2 or greater than 11.5.	OPPTS 870.2500 OECD 404

DACO	Study Type	Data Required	Test Notes	Available Guideline
4.2.6	Dermal Sensitization	R	The preferred species is the guinea pig (e.g., maximization or Buehler assays) or mouse (local lymph node assay). Not required if the test substance is corrosive to skin or has a pH lower than 2 or greater than 11.5.	OPPTS 870.2600 OECD 406 OECD 429
4.2.7	Potentiation/ Interaction	CR	Data should be submitted *if available.*	
4.2.8	Antidote	CR	Data should be submitted *if available.*	
4.2.9	Other Acute Studies	CR	DACO 4.2.9 is a place-holder for other available studies that elaborate on the toxicity profile of a test substance. Data should be submitted if available.	
4.3	Short-term Studies—TGAI			
4.3.1	Short-term Oral (90-day rodent)	R	The preferred species is the rat. Consideration should be given to incorporating a post-treatment recovery phase.	OPPTS 870.3100 OECD 408

DACO	Study Type	Data Required	Test Notes	Available Guideline
4.3.2	Short-term Oral (90-day and/or 12- month dog)	CR	Required when the product is to be used on food or likely to come in contact with food. Refer to DACO requirement for specific USC. Study duration for dog is 12 months. Consideration of a 90-day study in lieu of a 12-month study will be given if: i) based on the results from a 90-day dog study, this species has been demonstrated to be the least sensitive laboratory animal and there is no evidence for the potential of cumulative or delayed toxicity; or ii) based on the results from a 90-day dog study and structure-activity considerations, the test substance elicits no specific effects on target organ toxicity when fed at dietary levels achieving 1–5% of the total diet composition.	OPPTS 870.3150 OPPTS 870.4100 OECD 409 OECD 452
4.3.3	Short-term Oral (28-day)	CR	DACO 4.3.3 is a place-holder for other available studies of shorter duration including range-finding studies that elaborate on the toxicity profile of a test substance. Data should be submitted *if available.*	OPPTS 870.3050 OECD 407
4.3.4	Short-term Dermal (90-day)	CR	Required for some use patterns. Refer to DACO requirement for specific USC.	OPPTS 870.3250 OECD 411
4.3.5	Short-term Dermal (21/28-day)	CR	Required for some use patterns. Refer to DACO requirement for specific USC. Not required if an acceptable 90-day dermal toxicity study is performed and submitted.	OPPTS 870.3200 OECD 410

DACO	Study Type	Data Required	Test Notes	Available Guideline
4.3.6	Short-term Inhalation (90-day)	CR	*Required if there is the likelihood of significant repeated inhalation exposure to the product as a gas, vapour or aerosol.* Based on estimates of the magnitude and duration of human exposure, studies of shorter duration, e.g., 21 or 28 days, may be sufficient to satisfy this requirement. Registrants should consult with the PMRA to determine whether studies of shorter duration would meet this requirement.	OPPTS 870.3465 OECD 413
4.3.7	Short-term Inhalation (21/28-day)	CR	DACO 4.3.7 is a place-holder for other available studies of shorter duration including range-finding studies that elaborate on the toxicity profile of a test substance. Data should be submitted *if available.*	OECD 412
4.3.8	Other Short-term Studies	CR	DACO 4.3.8 is a place-holder for other available studies that elaborate on the toxicity profile of a test substance. Data should be submitted *if available.*	
4.4	Long-Term Studies—TGAI			
4.4.1	Chronic (rodent)	R	The preferred species is the rat. The oral route is recommended when the product is to be used on food or likely to come in contact with food. Minimum study duration for the rat is 24 months. *DACOs 4.4.1 and 4.4.2 can be submitted as a combined study under DACO 4.4.4.*	OPPTS 870.4100 OECD 452

DACO	Study Type	Data Required	Test Notes	Available Guideline
4.4.2	Oncogenicity (rodent species 1)	R	The preferred species is the rat. The oral route is recommended when the product is to be used on food or likely to come in contact with food. Minimum study duration for the rat is 24 months. *DACOs 4.4.1 and 4.4.2 can be submitted as a combined study under DACO 4.4.4.*	OPPTS 870.4200 OECD 451
4.4.3	Oncogenicity (rodent species 2)	R	The preferred species is the mouse. The oral route is recommended when the product is to be used on food or likely to come in contact with food. Minimum study duration for the mouse is 18 months.	OPPTS 870.4200 OECD 451
4.4.4	Combined Chronic/ Oncogenicity (rodent)	CR	The preferred species is the rat. The oral route is recommended when the product is to be used on food or likely to come in contact with food. *DACOs 4.4.1 and 4.4.2 can be submitted as a combined study under DACO 4.4.4.*	OPPTS 870.4300 OECD 453
4.4.5	Other Long-term Studies	CR	DACO 4.4.5 is a place-holder for other available studies that elaborate on the toxicity profile of a test substance. Data should be submitted *if available.*	

DACO	Study Type	Data Required	Test Notes	Available Guideline
4.5	Special Studies—TGAI			
4.5.1	Multigeneration Reproduction (rodent)	R	The preferred species is the rat. The oral route is recommended when the product is to be used on food or likely to come in contact with food. A second litter per generation should be considered when: i) any effect on routinely evaluated reproductive parameters required elucidation, particularly at dose levels below those causing minimal adverse effects in repeated exposure studies in the same species; ii) the observed effects in the first litters were induced post-implantation; or iii) the test substance is known or likely to be bioaccumulative, and where blood and tissue levels had not stabilized or attained plateau levels prior to mating. The use of a combined study that utilizes the two-generation reproduction study in rodents as a basic protocol for the addition of other endpoints or functional assessments in the immature animal is encouraged.	OPPTS 870.3800 OECD 416

DACO	Study Type	Data Required	Test Notes	Available Guideline
4.5.2	Prenatal Developmental Toxicity (rodent)	R	The preferred species is the rat. Unless the chemical or physical properties of the test substance or the pattern of human exposure suggest a more appropriate route of exposure, the oral route, by oral intubation, is preferred. Additional testing by other routes may be required if the test substance is determined to be a prenatal developmental toxicant after oral dosing.	OPPTS 870.3700 OECD 414
4.5.3	Prenatal Developmental Toxicity (non-rodent)	R	The preferred species is the rabbit. Unless the chemical or physical properties of the test substance or the pattern of human exposure suggest a more appropriate route of exposure, the oral route, by oral intubation, is preferred. Additional testing by other routes may be required if the test substance is determined to be a prenatal developmental toxicant after oral dosing.	OPPTS 870.3700 OECD 414
4.5.4	Genotoxicity: Bacterial Reverse Mutation Assay	R		OPPTS 870.5100 OECD 471

DACO	Study Type	Data Required	Test Notes	Available Guideline
4.5.5	Genotoxicity: In vitro Mammalian Cell Assay	R	Choice of assay using either of the following: i) mouse lymphoma L5178Y cells, thymidine kinase (tk) gene locus, maximizing assay conditions for small colony expression and detection (also addresses DACO 4.5.6); ii) Chinese hamster ovary (CHO) or Chinese hamster lung fibroblast (V79) cells, hypoxanthine-guanine phosphoribosyl transferase (HGPRT) gene locus (needs appropriate in vitro study submitted under DACO 4.5.6); or iii) CHO cell strain AS52, xanthine-guanine phosphoribosyl transferase (XPRT) gene locus.	OPPTS 870.5300 OECD 476
4.5.6	Genotoxicity: In vitro Mammalian Clastogenicity	CR	*Required if not addressed in study submitted for DACO 4.5.5.*	OPPTS 870.5375 OPPTS 870.5900 OECD 473 OECD 479
4.5.7	Genotoxicity: In vivo Cytogenetics	R	Choice of assays. Assays using rodent bone marrow, using either metaphase analysis (aberrations) or a micronucleus assay, are preferred.	OPPTS 870.5395 OPPTS 870.5385 OPPTS 870.5915 OECD 474 OECD 475

DACO	Study Type	Data Required	Test Notes	Available Guideline
4.5.8	Other Genotoxicity Studies	CR	DACO 4.5.8 is a place-holder for other available studies that elaborate on the toxicity profile of a test substance. Data should be submitted *if available.*	OPPTS 870.5140 OPPTS 870.5195 OPPTS 870.5200 OPPTS 870.5250 OPPTS 870.5275 OPPTS 870.5380 OPPTS 870.5450 OPPTS 870.5460 OPPTS 870.5500 OPPTS 870.5550 OPPTS 870.5575 OECD 477 OECD 478 OECD 480 OECD 481 OECD 482 OECD 483 OECD 484 OECD 485 OECD 486
4.5.9	Metabolism/ Toxicokinetics in Mammals (laboratory animals)	R	Most appropriate species	OPPTS 870.7485 OECD 417
4.5.10	Acute Delayed Neurotoxicity (hen)	CR	*Required if the test substance is an organophosphorus substance or is structurally related to other substances that may cause the delayed neurotoxicity*, sometimes seen in this class of chemicals. Organophosphorus substances include the following: • uncharged organophosphorus esters, thioesters or anhydrides of organophosphoric, organophosphonic or organophosphoramidic acids; and • uncharged organophosphorus esters, thioesters or anhydrides of related phosphorothioic, phosphonothioic or phosphorothiamidic acids.	OPPTS 870.6100 OECD 418

DACO	Study Type	Data Required	Test Notes	Available Guideline
4.5.11	28-day Delayed Neurotoxicity (hen)	CR	*Required if results of the acute delayed neurotoxicity study indicate significant statistical or biological effects, or if other available data indicate the potential for this type of delayed neurotoxicity,* as determined by the PMRA.	OPPTS 870.6100 OECD 419
4.5.12	Acute Neurotoxicity (rat)	CR	*Required if there is neurotoxic potential.* Additional measurements such as cholinesterase activity determinations for certain test substances (e.g., organophosphates and carbamates) will also be required. The route of exposure must correspond to the primary route of human exposure.	OPPTS 870.6200
4.5.13	90-day Neurotoxicity (rat)	CR	*Required if there is neurotoxic potential.* Additional measurements such as cholinesterase activity determinations for certain test substances (e.g., organophosphates and carbamates) will also be required. The route of exposure must correspond to the primary route of human exposure. All 90-day short-term studies in rats can be designed to simultaneously fulfill the requirements of the 90-day neurotoxicity study using separate groups of animals for testing. Although the short-term guidelines include the measurement of neurological endpoints, they do not meet the requirement of the 90-day neurotoxicity study.	OPPTS870.6200 OECD 424

DACO	Study Type	Data Required	Test Notes	Available Guideline
4.5.14	Developmental Neurotoxicity	CR	*Required if neurological effects are observed in other studies.* *Should be considered if test substance:* *i) causes neuropathology or neurotoxicity in adults;* *ii) is hormonally active in vivo; or* *iii) causes other types of nervous system involvement at a developmental stage.* The use of a combined study that utilizes the two-generation reproduction study in rodents as a basic protocol for the addition of other endpoints or functional assessments in the immature animal is encouraged.	OPPTS 870.6300 OECD 426 (draft)
4.6	Acute Studies—EP			
4.6.1	Acute Oral	R	The preferred species is the rat. Not required if the test substance is a gas or highly volatile liquid.	OPPTS 870.1100 OECD 420 OECD 423 OECD 425
4.6.2	Acute Dermal	R	The preferred species is the rat. Not required if the test substance is a gas or highly volatile liquid. Not required if the test substance is corrosive to skin or has a pH lower than 2 or greater than 11.5.	OPPTS 870.1200 OECD 402
4.6.3	Acute Inhalation	R	The preferred species is the rat. Required if the test substance consists of, or under conditions of use will result in, a respirable material (e.g., gas, vapour, aerosol or particulate).	OPPTS 870.1300 OECD 403 OECD 433 (draft)

DACO	Study Type	Data Required	Test Notes	Available Guideline
4.6.4	Primary Eye Irritation	R	The preferred species is the rabbit. Not required if the test substance is corrosive to skin or has a pH lower than 2 or greater than 11.5.	OPPTS 870.2400 OECD 405
4.6.5	Primary Dermal Irritation	R	The preferred species is the rabbit. Not required if the test substance is a gas or highly volatile liquid. Not required if the test substance is corrosive to skin or has a pH lower than 2 or greater than 11.5.	OPPTS 870.2500 OECD 404
4.6.6	Dermal Sensitization	R	Preferred species is guinea pig (maximization and Buehler assays) or mouse (local lymph node assay). Not required if the test substance is corrosive to skin or has a pH lower than 2 or greater than 11.5; however, diluted EP testing may be required if the EP is diluted under conditions of use.	OPPTS 870.2600 OECD 406 OECD 429
4.6.7	Potentiation/ Interaction	CR	Data should be submitted *if available.*	
4.6.8	Other Acute Studies	CR	DACO 4.6.8 is a place-holder for other available studies that elaborate on the toxicity profile of a test substance. Data should be submitted *if available.*	
4.7	Short-term Studies—EP	CR	*Depending on use pattern, required if any component of the EP may increase absorption of the active ingredient(s) or increase toxic or pharmacologic effects.*	
4.7.1	Short-term Oral (90-day rodent)	CR	*See 4.7*	
4.7.2	Short-term Oral (90-day and/or 12-month dog)	CR	*See 4.7*	

DACO	Study Type	Data Required	Test Notes	Available Guideline
4.7.3	Short-term Dermal (90-day)	CR	*See 4.7*	
4.7.4	Short-term Dermal (21/28-day)	CR	*See 4.7*	
4.7.5	Short-term Inhalation (21/28 day)	CR	*See 4.7*	
4.7.6	Short-term Inhalation (90-day)	CR	*See 4.7*	
4.7.7	Other Special Studies	CR	*See 4.7*	
4.8	Other Studies/Data/ Reports	CR	DACO 4.8 is a place-holder for other available studies, including mechanistic data or immunotoxicity data, that elaborate on the toxicity profile of a test substance. Data should be submitted *if available.*	
4.9	Safety to Treated Animals	CR	May be required if the product's use will result domestic animals being exposed through, but not limited to, direct application or consumption of treated feed. Refer to DACO requirement for specific USC.	OPPTS 870.7200

Appendix II Name Changes to DACO Table Resulting from Update to Toxicology Data Requirements

DACO	Existing Name	Revised Name
4.3.2	Short-term Oral (6-12 month dog)	Short-term Oral (90-day and/or 12-month dog)
4.3.3	Short-term Oral (21-day, 30-day)	Short-term Oral (28-day)
4.3.4	Short-term Dermal (90-day rodent)	Short-term Dermal (90-day)
4.3.5	Short-term Dermal (21-day rodent)	Short-term Dermal (21/28-day)
4.3.7	Short-term Inhalation (21-day, 30-day)	Short-term Inhalation (21/28-day)
4.5.2	Teratogenicity (rodent)	Prenatal Developmental Toxicity (rodent)
4.5.3	Teratogenicity (non-rodent)	Prenatal Developmental Toxicity (non-rodent)
4.5.4	Genotoxicity: Microbial Point Mutation	Genotoxicity: Bacterial Reverse Mutation Assay
4.5.5	Genotoxicity: Mammalian (cell) Point Mutation	Genotoxicity: In vitro Mammalian Cell Assay
4.5.6	Genotoxicity: In vitro Chromosomal Aberration	Genotoxicity: In vitro Mammalian Clastogenicity
4.5.7	Genotoxicity: In vivo Chromosomal Aberration	Genotoxicity: In vivo Cytogenetics
4.5.10	Delayed Neurotoxicity Following Acute Exposure (28-day hen)	Acute Delayed Neurotoxicity (hen)
4.5.11	Delayed Neurotoxicity (28-day hen)	28-day Delayed Neurotoxicity (hen)
4.5.13	Subchronic Neurotoxicity (90-day rat)	90-day Neurotoxicity (rat)
4.7.1	90-day Rodent	Short-term Oral (90-day rodent)

DACO	Existing Name	Revised Name
4.7.2	90 day Dog	Short-term Oral (90-day and/or 12-month dog)
4.7.3	90 day Dermal	Short-term Dermal (90-day)
4.7.4	21/28 day Dermal	Short-term Dermal (21/28-day)
4.7.5	28 day Inhalation	Short-term Inhalation (21/28-day)
4.7.6	90 day Inhalation	Short-term Inhalation (90-day)
4.9	Safety of Treated Animals	Safety to Treated Animals