***** Public Review Draft *****

Guidance for Waiving Acute Dermal Toxicity Tests for Pesticide Technical Chemicals & Supporting Retrospective Analysis

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Related Authority**:**	7 U.S.C. 136 *et seq*. The overall purpose of this analysis is to address the utility of the acute dermal toxicity study for single technical chemicals in pesticide labelling, such as the signal word and precautionary statements as described in 40 CFR 156.64 and 40 CFR 156.70.
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Guidance for Waiving Acute Dermal Toxicity Tests for Pesticide Technical Chemicals & Supporting Retrospective Analysis

1.0 Introduction

This guidance document follows upon the final dermal waiver guidance published in November 2016 for pesticide formulations. This document expands the potential for data waivers for acute dermal studies to single active ingredient technical chemicals (technical chemicals) used to formulate end user products. The reasoning and analysis in this dermal waiver guidance for technical chemicals is similar to what was presented in the 2016 guidance for end-use products. While more acute toxicity studies are submitted to OPP annually for formulated pesticide products than for technical chemicals, there is still the potential for animal and resource savings from waivers for technical chemical acute toxicity studies. Further, this guidance allows OPP to harmonize with the Pest Management Regulatory Agency (PMRA) of Canada, which published guidance[1] on dermal waivers for both formulations and technical chemicals in 2017.

OPP and the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) have conducted a retrospective analysis of oral and dermal acute lethality studies that fit the regulatory context relevant for OPP, and considered the EPA pesticide categorization scheme, which uses acute study results (see 40 CFR 156.212 and *OPP Label Review Manual*[2]). The OPP/NICEATM analysis was designed to evaluate the relative consistency of the findings of paired oral and dermal studies for technical chemicals (Section 2.0). ***The Agency has used this analysis to support a policy statement in Section 5.0 to waive all acute lethality dermal studies for pesticide technical chemicals***.

The 2016 guidance focused on formulated pesticide product testing because ecological risk assessments for endangered and threatened species typically rely in part on acute studies for the technical chemical. After further consideration of these data needs, EPA has determined that the Agency is now able to provide waivers for acute dermal studies for technical chemicals.

2.0 Dataset for Analysis

The Agency developed a dataset of rat acute oral and acute dermal LD_{50} studies for 249 active ingredients. The spreadsheet of data used in the analysis is provided in *Dermal Data Spreadsheet for Pesticide Active Ingredient Technical Chemicals Final.xlsx*, and is available in the docket[3]. The active ingredients include conventional pesticides, antimicrobials, and biopesticides across numerous chemical classes and Toxicity Categories (Appendix 1). Fumigants and rodenticides were excluded because of their

[1] https://www.canada.ca/content/dam/hc-sc/documents/services/consumer-product-safety/reports-publications/pesticides-pest-management/policies-guidelines/science-policy-notes/2017/acute-dermal-toxicity-waiver-spn2017-03-eng.pdf

[2] Chapter 7: https://www.epa.gov/sites/production/files/2018-04/documents/chap-07-mar-2018.pdf

[3] https://www.regulations.gov/docket?D=EPA-HQ-OPP-2016-0093

physical forms and the types of exposures that would be anticipated; this policy does not apply to these types of pesticides.

3.0 Comparison of Toxicity Category Between Oral and Dermal Studies

As shown in the blue boxes in Table 1 below, for 167 of the 249 technical chemicals, the paired oral and dermal studies provide the same Toxicity Category. For 80 chemicals, the oral study provides a lower (i.e., more potent) category than the dermal study (grey boxes).

Table 1. Results of comparison analysis for oral & dermal technical chemical acute studies

Rat Dermal Hazard Category (mg/kg)	Rat Oral Hazard Category (mg/kg)			
	EPA I ≤50	**EPA II >50 – ≤500**	**EPA III >500 – ≤5000**	**EPA IV >5000**
EPA I ≤200	10	1	0	0
EPA II >200 – ≤2000	6	15	1	0
EPA III >2000 – ≤5000	4	40	114	0
EPA IV >5000	2	6	22	28
Total	**22**	**62**	**137**	**28**

For 2 chemicals, the dermal study provides a lower (i.e., more potent) Category than the oral study (yellow boxes). One chemical (xylenol) had a Toxicity Category II for dermal (LD_{50}: 1040 mg/kg), and Toxicity Category III for oral (LD_{50}: 3200 mg/kg) (*i.e.*, a more potent Category for dermal compared to oral) and one chemical, dichlorvos (DDVP), in the dataset has a Toxicity Category I for dermal (LD_{50}: 75 mg/kg) and a Toxicity Category II for oral (LD_{50} 56 mg/kg). EPA's Label Review Manual[4] provides information on how acute toxicity information is used in pesticide labeling, including the hazard statements, signal word, first aid, and precautionary statements that appear on technical labels. The results from all six acute toxicity tests are considered, and the lowest category determines the signal word, whereas the other precautionary/first aid statements are determined by the category for each endpoint.

Acute studies are primarily used by the Agency to determine the appropriate level of Personal Protective Equipment (PPE), hazard labeling, first aid, and precautionary statements for all product labels.

[4] https://www.epa.gov/pesticide-registration/label-review-manual

4.0 Discussion - Implications of Retrospective Analysis on Utility of Acute Dermal Technical Product Lethality Studies

The overall purpose of this analysis is to address the utility of the acute dermal toxicity study for single technical chemicals in pesticide labelling, such as the signal word and precautionary statements as described in 40 CFR 156.64 and 40 CFR 156.70. To this end, this analysis includes a large number of technical chemicals (249) from numerous chemical classes representing conventional pesticides, antimicrobials, and biopesticides. This guidance expands upon the work of the dermal waiver guidance published in November 2016 for pesticide formulations.

For 67% of the 249 technical chemicals, the results of both oral and dermal acute toxicity studies fall within the same Toxicity Category. For 32% of the chemicals, the oral study falls within a lower (i.e., more protective) Toxicity Category; thus, for 99% of the chemicals in the analysis, if the dermal study had not been available, and labelling had been based only on the Toxicity Category for the oral acute toxicity study, the labelling requirements would have been equally or more protective. For the two remaining chemicals (less than 1%), as noted above, factors other than the dermal acute toxicity may influence labelling requirements. In some cases, dermal irritation/corrosion studies or risk management decisions based on other factors may result in label requirements more protective than what would otherwise be required based on acute oral toxicity alone. When all these sources of information are considered together, in most cases, the dermal acute toxicity study for technical chemicals provides little to no added value in regulatory decision making.

5.0 Waiver Guidance

The Agency believes this retrospective analysis fully supports the conclusion that waivers may be granted for acute dermal toxicity studies for pesticide technical chemicals except for fumigants and rodenticides which were excluded because of their physical forms and the types of exposures that would be anticipated. Waivers may be accepted for fumigants and rodenticides but on a case by case basis with appropriate scientific rationale. Applicants should submit formal waiver requests as part of their registration application through existing processes and cite this guidance. The Agency maintains the ability to request acute dermal toxicity data on a case by case basis. The Agency anticipates allowing the waiver in most cases, however, a determination that a waiver request is unacceptable will be made upon consultation with the Agency's relevant internal peer review groups (*e.g.,* Hazard and Science Policy Committee (HASPOC) and Chemistry and Acute Toxicity Science Advisory Committee (CATSAC)) and/or OPP's science advisor.

Appendix 1. List of Active Ingredients in the Retrospective Analysis

1,3-Dibromo-5,5-dimethylhydantoin
1-Decanol
2,3-Dichlorobenzoic acid-methyl ester
2,4,4-Trimethylpentene
2,4-D, sodium salt
2,4-Dichlorophenoxyacetic acid (2,4-D)
2-Ethylhexanoic acid
2-Methyl-4-chlorophenoxy acetic acid (MCPA)
2-Methyl-4-chorophenoxybutyric acid (MCPB)
2-Phenylphenol
4-(2,4-Dichlorophenoxy)butyric acid (2,4-DB)
4,4-Dimethyloxazolidine
4,6-dinitro-o-cresol (DNOC)
4-Chloro-3-cresol
Abamectin

a-C11-15-sec-alkyl-omega-hydroxypoly(oxy-1,2-ethanediyl)
Acephate
Acetochlor
Acibenzolar-S-methyl (CGA 245704)
Aclonifen
Alachlor
Aldicarb
Alpha cypermethrin
Ametryn
Amidosulfuron
aminopyralid (xde-750)
Ammonium bromide
Ammonium chloride
Ammonium sulfate
Antimycin-a
asana (esfenvalerate)
Atrazine
Azinphos-methyl
bcs-aa10717 herbicide (indaziflam)
Benalaxyl
Benalaxyl-M
Benfluralin

Benfuracarb
Bentazone
bifenthrin
Bispyribac-sodium
Bitertanol (KWG 0599)
Bromoxynil
Bromuconazole
Buprofezin
Butralin
Captan
Carbaryl
Carbofuran
Carbosulfan
Chlorfenapyr
Chloridazon
Chlorpropham
Chlorpyrifos
Cinidon ethyl
Citral
Clodinafop-propargyl
Clomazone
Copper as elemental
Copper carbonate, basic
Copper compounds

Cupric oxide
Cuprous oxide
Cyclanilide
Cyfluthrin
Cymoxanil
Cypermethrin
Cyproconazole technical
Cyprodinil
Cyromazine
Daminozide
Deltamethrin
Diazinon
Dicamba
Dichloroisocyanuric acid, sodium salt, dihydrate
Dichlorprop-P
Dichlorvos
Diclofop-Methyl
Dimethachlor
Dimethenamid
Dimethoate
Dimethomorph
Dimethoxane
Dinocap
Dinoterb

Diquat
Disulfoton (S 276)
Diuron
dpx-kjm44 herbicide (aminocyclopyrachlor-methyl)
emamectin benzoate
Endosulfan
Epoxiconazole
Ethephon
Ethoprophos
Ethoxysulfuron
Famoxadone
Fenamiphos
Fenarimol
Fenhexamid
Fenitrothion
Fenoxaprop
Fenpropidin
Fenpropimorph
Fenpyroximate
Fenthion
Ferric phosphate
Flonicamid insecticide
Fluazinam

Flufenacet
flufenpyr-ethyl-s-3153
flumethrin
Fluopicolide
Fluopyram
Fluoxastrobin
Fluroxypyr
Flurprimidol
Flusilazole
Flutolanil
Folpet
Forchlorfenuron
Formetanate
Fosthiazate
Fuberidazole
Furfural
Glufosinate
Glyphosate
Glyphosate trimesium
Haloxyfop-R
Imazalil
initium fungicide (ametoctradin)
Iodosulfuron
Ioxynil

ipconazole
Iprodione
Isoproturon
kixor herbicide (saflufenacil)
Lavandulyl senecioate
l-Cyhalothrin
Lindane
Linuron
Magnate (imazalil)
Malathion
Maleic hydrazide
mcm 437 (fipronil)
mcpp-p (mecoprop)
Mecoprop
Mecoprop-P
mecoprop-p acid
Mepiquat
Mesosulfuron-methyl
Metalaxyl-M
Metamitron
Metazachlor
Methamidophos
Methiocarb
Methomyl

Methoxyfenozide
Metrafenone
Metribuzin
metsulfuron methyl
Milbemectin
Mitin FF
mkh 3586 (amicarbazone)
Molinate
Monolinuron
Nipacide cmx (chloroxylenol)
nni-0001 (flubendiamide)
Nonanoic acid (CGA-133205 Technical)
Oxazolidine-E
Oxydemeton-methyl
Paraquat
Parathion
Parathion-methyl
Penconazole
Penflufen tc
Penthiopyrad
Permethrin
Pethoxamid
Phorate

Phosalone
Phosmet
Phosphides
Pirimicarb
Pirimiphos-methyl
Potassium silicate
Procymidone
Profenofos
Propamocarb
Propiconazole
Propineb
Propoxycarbazone sodium
Prosulfocarb
Prosulfuron
pyrasulfotole
Pyrazophos
Pyridalyl
Pyridate
Pyrimethanil
Pyroxasulfone
Quinoclamine
reldan f (chlorpyrifos-methyl)
rotam imidacloprid
Salicylic acid

Sedaxane
Sethoxydim
Simazine
Sodium ferric ethylenediaminetetraacetate
Sodium fluoride
Spinosad
Spiromesifen
Spirotetramet
Sulfur
sumione (metofluthrin)
tebuconazole fungicide (tebuconazole)
Tecnazene
Terbuthylazine
Tetraconazole

Thiabendazole
Thiacloprid
Thiamethoxam
Thidiazuron
Thiencarbazone-methyl
Thiodicarb
Thiram
Thymol
Tolclofos-methyl
Tolyfluanid
tpth (fentin)
Tralkoxydim
Triadimenol
Triallate
Triazamate
Tribenuron methyl
Tributyltin benzoate

Trichlorfon
Triclopyr
Trinexapac
Triphenyltin Hydroxide
Triticonazole
Tritosulfuron
Undecylenic acid
Urea, sulfate (1:1)
Vinclozolin
xde-742 (pyroxsulam)
Xemium fungicide (fluxapyroxad)
Xylenol
Zinc pyrithione
Ziram
Zoxamide