Using Acute Oral Toxicity Data to Estimate Acute Dermal Hazard Classification and Labeling of Pesticide Actives

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Abstract

The U.S. Environmental Protection Agency (EPA) requires acute dermal systemic toxicity testing for hazard classification and labeling of pesticides to protect human health and the environment during the handling and use of chemicals. This study considered whether acute oral LD_{50} data could be used to determine EPA acute dermal hazard classifications. Oral and dermal LD_{50} data were collected for 225 pesticide active ingredients. Two approaches were used to predict dermal hazard classifications. First, oral hazard categories based on oral LD_{50} were compared to dermal hazard categories based on dermal LD_{50}. Concordance with the reference dermal hazard categories was 65% (146/225), overclassification was 31% (70/225), and underclassification was 4% (9/225). In the second approach, the oral LD_{50} was used directly to assign the dermal hazard category. Concordance with the reference dermal hazard categories was 43% (96/225), overclassification was 56% (126/225), and underclassification was 1% (3/225). For substances in EPA Category IV the predictivity was 100% (22/22) with either approach. These data suggest that if only acute oral toxicity data are used for predicting both oral and dermal hazards, the dermal acute toxicity of many pesticide actives could be overstated.

Introduction

- Exposure to chemicals can occur during routine use and handling or during accidental releases. Dermal exposure can contribute considerably to the internal dose of workers exposed to hazardous substances (Drexler 1998). For some types of chemicals, such as pesticides, the dermal route can be the most important route of exposure (Grandjean 1990).
- The U.S. Environmental Protection Agency (EPA) requires labeling for dermal and oral hazards if the LD_{50} value (the dose expected to produce lethality in 50% of the animals tested) of a pesticide is less than or equal to 5000 mg/kg (EPA 2012). **Table 1** lists the four categories of the EPA hazard classification system; **Figure 1** describes the required hazard warnings and specific personal protective equipment recommended for each category to prevent skin exposure.
- LD_{50} values are determined using test guidelines for acute dermal systemic toxicity testing from the EPA (EPA 1998) and the Organisation for Economic Co-operation and Development (OECD 1987). Both guidelines recommend using a minimum of 20 animals for the main test, but there is interest in developing alternative procedures to reduce the number of animals used for this purpose.
- The National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) evaluated acute oral and dermal systemic rat toxicity data to determine whether acute oral systemic toxicity data can be used to classify pesticide active ingredients for acute dermal systemic toxicity hazard. The goal is to determine the feasibility of reducing the regulatory need for acute dermal systemic toxicity testing and thereby reduce the overall number of animals used, while providing equivalent or improved protection of human health.

Table 1 EPA Acute Oral and Dermal Hazard Categories

Route	Category I (mg/kg)	Category II (mg/kg)	Category III (mg/kg)	Category IV (mg/kg)
Oral	LD_{50} ≤50	>50 LD_{50} ≤50	>500 LD_{50} ≤5000	LD_{50} >5000
Dermal	LD_{50} ≤200	>200 LD_{50} ≤ 2000	>2000 LD_{50} ≤5000	LD_{50} >5000

Abbreviation: EPA = U.S. Environmental Protection Agency.

Figure 1 EPA Hazard Classification for Acute Oral and Dermal Toxicity[a]

Oral Classification					
Signal Word for Label	**DANGER-POISON**	**WARNING**	**CAUTION**	**CAUTION** (optional)	
Hazard Statement for Label	Fatal if swallowed	May be fatal if swallowed	Harmful if swallowed	NR or optionally "harmful if swallowed"	
EPA Oral Category	**I**	**II**	**III**	**IV**	
LD_{50} (mg/kg)	50	200	500	2000	5000	>5000

Dermal Classification				
EPA Dermal Category	**I**	**II**	**III**	**IV**
Signal Word for Label	**DANGER-POISON**	**WARNING**	**CAUTION**	**CAUTION** (optional)
Hazard Statement for Label	Fatal if absorbed through skin	May be fatal if absorbed through skin	Harmful if absorbed through skin	NR or optionally "harmful if absorbed through skin"
Personal Protective Equipment	Coveralls worn over long-sleeved shirt and long pants; socks; chemical-resistant footwear; chemical-resistant gloves	Coveralls worn over short-sleeved shirt and short pants; socks; chemical-resistant footwear; chemical-resistant gloves	Long-sleeved shirt and long pants; socks; shoes; chemical-resistant gloves	Long-sleeved shirt and pants; socks; shoes

Abbreviations: EPA = U.S. Environmental Protection Agency; NR = none required.

[a] Hazard classifications and label requirements according to the EPA Label Review Manual (EPA 2012). The LD_{50} dose range is not to scale.

NICEATM Acute Systemic Toxicity Database

- NICEATM collected acute oral and acute dermal LD_{50} values for 291 pesticide active ingredients.
- Pesticide active ingredients were removed if the oral LD_{50} >5000 mg/kg, based on a limit test or a point estimate (e.g., 6800 mg/kg), and the corresponding dermal LD_{50} >2000 mg/kg was based on a limit test (66 pesticide active ingredients).
    - These 66 pesticide active ingredients would require dermal hazard labeling in EPA Category III, but would not provide an accurate comparison of oral and dermal LD_{50} values because the highest doses tested for the two routes are not the same.
- The acute oral and dermal rat LD_{50} values for the remaining 225 pesticide active ingredients came from the following sources:
    - Creton et al. 2010 (data from the UK Pesticides Safety Directorate [PSD; now Chemicals Regulation Directorate]): 167 pesticide active ingredients
    - European Chemicals Agency (ECHA) database: 35 pesticide active ingredients
    - EPA Office of Pesticide Programs Reregistration Eligibility Decision (RED) documents: 13 pesticide active ingredients
    - EPA Office of Pesticide Programs (toxicity test reports): 10 pesticide active ingredients

Table 2 Chemical Class and Product Use for Pesticide Active Ingredients in NICEATM Database[a]

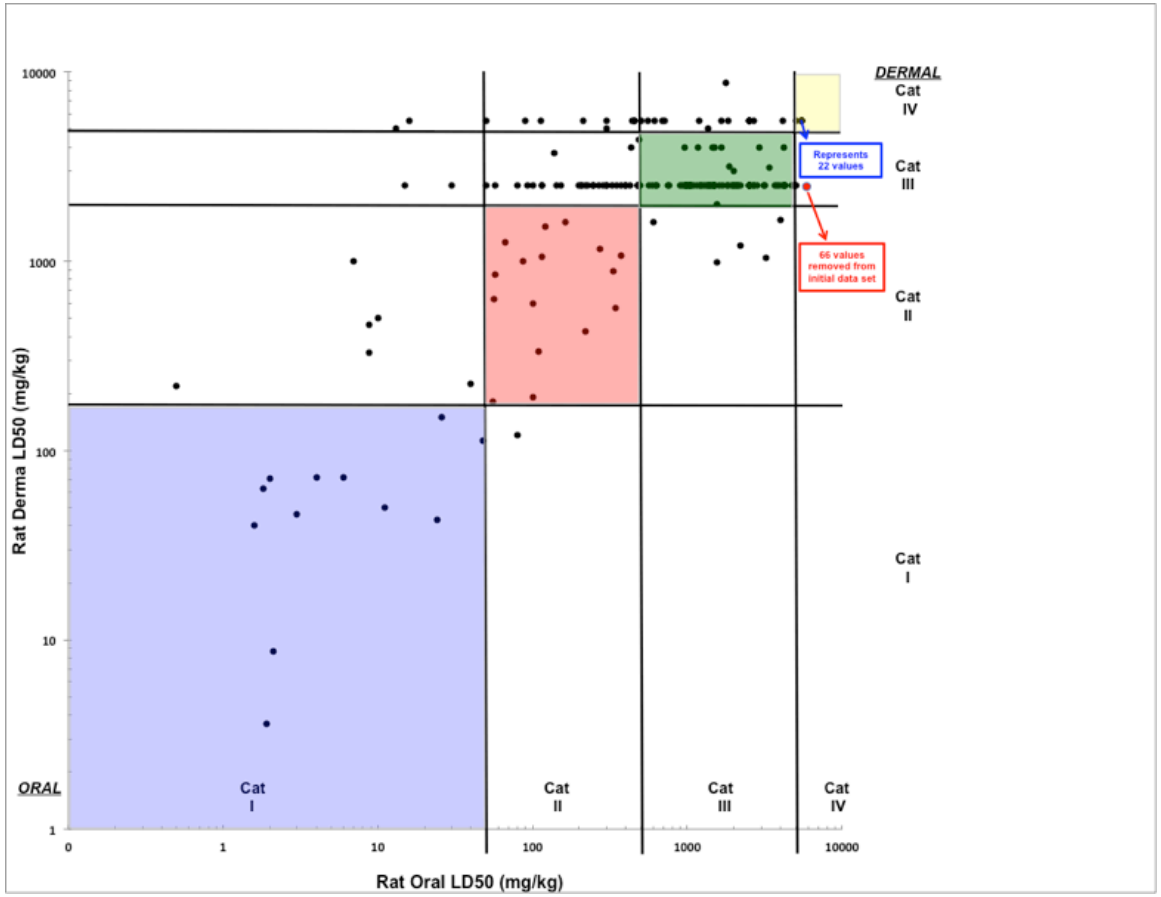
Chemical Class	Acaricide	Fungicide	Herbicide	Insecticide	Nematicide	Other Pesticides	Algicide	Plant Growth Regulator
Acylamino acid		3						
Amide			3					
Anilide		4	1					
Benzofuranyl methylcarbamate				3				
Chloroacetanilide			4					
Conazole		11						
Copper		5						
Dichlorophenyl dicarboximide		3						
Fumigant		1	1	3	2			
Growth inhibitors								5
Inorganic		1		1		3		
Morpholine		3						
Organochlorine	2			1				
Organophosphate	1	2	2	1	2			
Organothiophosphate	10		1	17	1			
Phenoxyacetic			3					
Phenoxypropionic			3					
Phenylurea			5					
Pyrethroid ester	3			6				
Triazinylsulfonylurea			4					
Unclassified		6	1	1				3
Urea		1	4	1	2			1
Other	12	30	32	25	4	19	4	9
TOTAL[b]	28	70	64	59	11	23	4	18

[a] Chemical classifications and product use information were obtained from the Compendium of Pesticide Product Names (http://www.alanwood.net/pesticides/index.html) and the database of EPA pesticide active ingredients with registered products (personal communication).

[b] The total number of pesticide active ingredients exceeds 225 because many had multiple product uses.

- **Figure 2** shows the distribution of the pesticide active ingredients by EPA hazard classifications when oral LD_{50} is graphed against dermal LD_{50}.
  - If a pesticide active ingredient had more than one LD_{50} value reported, it was categorized according to the lowest LD_{50}.
  - If a pesticide active ingredient had an LD_{50} value reported as a range, it was categorized according to the lowest LD_{50} of the range.
  - If a pesticide active ingredient had an LD_{50} value reported as greater than a finite value, it was categorized according to the finite value (e.g., $LD_{50} > 5000$ mg/kg was placed in Category IV).

Figure 2 Distribution of Pesticide Active Ingredients by Hazard Category[a]



Abbreviation: Cat = U.S. Environmental Protection Agency hazard category

[a] If an LD_{50} value was listed as a range, e.g., >2000 or >5000 mg/kg, for ***illustrative purposes only*** it is represented in the plot as having an LD_{50} value of 2500 or 5500 mg/kg to emphasize categorization of the endpoint. Twenty-two pesticide active ingredients with the same LD_{50} values in oral and dermal Category IV appear as one point (see blue text box). The red dot shows the 66 pesticide active ingredients with oral LD_{50} >5000 mg/kg and the corresponding dermal LD_{50} >2000 mg/kg (based on a limit test) removed from the analyses.

Approaches to Predicting Dermal Hazard Classifications

- **Approach 1**: Oral hazard categories based on acute oral toxicity LD_{50} values were compared to dermal hazard categories based on acute dermal toxicity LD_{50} values.
- **Approach 2**: Acute oral toxicity LD_{50} values were used directly to assign the acute dermal toxicity hazard category.

Results

- **Tables 3 (Approach 1)** and **4 (Approach 2)** provide concordance analyses for the oral and dermal hazard categories. Neither approach correctly identified all categories. However, predictivity of pesticide active ingredients to be classified as EPA dermal Category IV was 100% (22/22) for both approaches.
- **Approach 1**
  - 65% (146/225) concordance
  - 31% (70/225) overclassification of the dermal toxicity
  - 4% (9/225) underclassification of the dermal toxicity
- **Approach 2**
  - 43% (96/225) concordance
  - 56% (126/225) overclassification of the dermal toxicity
  - 1% (3/225) underclassification of the dermal toxicity

Table 3 Concordance of Oral and Dermal Hazard Categorization Using Approach 1

	EPA Oral Cat I[a] (≤50)	EPA Oral Cat II (>50 – ≤500)	EPA Oral Cat III (>500 – ≤5000)	EPA Oral Cat IV (>5000)	Total Pesticide Active Ingredients	Concordant Dermal and Oral Hazard	Dermal Hazard Overpredicted by Oral Hazard	Dermal Hazard Underpredicted by Oral Hazard
EPA Dermal Cat I (≤200)[b]	12[c]	3	0	0	15 (7%)	80% (12/15)	NA	20% (3/15)
EPA Dermal Cat II (>200 – ≤2000)	6	14	6	0	26 (12%)	54% (14/26)	23% (6/26)	23% (6/26)
EPA Dermal Cat III (>2000 – ≤5000)	4	33	98	0	135 (60%)	73% (98/135)	27% (37/135)	0% (0/135)
EPA Dermal Cat IV (>5000)	2	7	18	22	49 (22%)	45% (22/49)	55% (27/49)	NA
Total (Predictivity)	24 (50% [12/24])	57 (25% [14/57])	122 (80% [98/122])	22 (100% [22/22])	225	65% (146/225)	31% (70/225)	4% (9/225)

Abbreviations: Cat = category; EPA = U.S. Environmental Protection Agency; NA = not applicable: overprediction or underprediction is not possible in these situations.

[a] Numbers in parentheses refer to the range of oral hazard classification category in mg/kg.

[b] Numbers in parentheses refer to the range of dermal hazard classification category in mg/kg.

[c] Gray shaded boxes contain the numbers of pesticide active ingredients with concordant oral and dermal hazard categories.

Table 4 Concordance of Oral and Dermal Hazard Categorization Using Approach 2

	EPA Oral Cat I (≤200)[a]	**EPA Oral Cat II (>200 – ≤2000)**	**EPA Oral Cat III (>2000 – ≤5000)**	**EPA Oral Cat IV (>5000)**	**Total Pesticide Active Ingredients**	**Concordant Dermal and Oral Hazard**	**Dermal Hazard Overpredicted by Oral Hazard**	**Dermal Hazard Underpredicted by Oral Hazard**
EPA Dermal Cat I (≤200)[b]	15[c]	0	0	0	15 (7%)	100% (15/15)	NA	0% (0/15)
EPA Dermal Cat II (>200 – ≤2000)	15	8	3	0	26 (12%)	31% (8/26)	58% (15/26)	11% (3/26)
EPA Dermal Cat III (>2000 – ≤5000)	14	70	51	0	135 (60%)	38% (51/135)	62% (84/135)	0% (0/135)
EPA Dermal Cat IV (>5000)	4	15	8	22	49 (22%)	45% (22/49)	55% (27/49)	NA
Total (Predictivity)	48 (31% [15/48])	93 (9% [8/93])	62 (82% [51/62])	22 (100% [22/22])	225	43% (96/225)	56% (126/225)	1% (3/225)

Abbreviations: Cat = category; EPA = U.S. Environmental Protection Agency; NA = not applicable: overprediction or underprediction is not possible in these situations.

[a] Numbers in parentheses refer to the range of oral hazard classification category in mg/kg.

[b] Numbers in parentheses refer to the range of dermal hazard classification category in mg/kg.

[c] Gray shaded boxes contain the number of pesticide active ingredients with concordant oral and dermal hazard categories.

Underpredicted Pesticide Active Ingredients

- **Table 5** provides the classifications for nine pesticide active ingredients that were underpredicted for dermal toxicity by **Approach 1**.
  - The dermal irritancy/corrosivity classification of these compounds was identified to assess whether corrosiveness might be a contributing factor to the underprediction.
    - Three of nine compounds were corrosive and one compound was a severe/moderate irritant.
    - Under current test guidelines, a corrosive chemical would not be tested in an *in vivo* assay to assess acute dermal toxicity.
  - Fumigants may be underpredicted due to their volatile nature, which could compromise acute dermal toxicity testing.
    - Three of nine compounds were fumigants.

Table 5 Pesticide Active Ingredients with Underpredicted Dermal Hazard using Approach 1

Substance	CASRN	EPA Toxicity Category Oral	EPA Toxicity Category Dermal	EPA Toxicity Category Dermal Irritant/Corrosive[a]	Source for Irritant/ Corrosivity Data
Dichlorvos[b]	62-73-7	II	I	IV	EPA RED
Furfural[b]	98-01-1	II	I	III	EPA Pesticide Fact Sheet
Methane, isothiocyanato-[b]	556-61-6	II	I	I	PesticideInfo.org
Amitraz	33089-61-1	III	II	IV	EPA RED
Cinnamaldehyde	104-55-2	III	II	III	EPA Pesticides: Registration Review website
Dodemorph	1593-77-7	III	II	II/III	Sigma-Aldrich
Ethephon	16672-87-0	III	II	I	EPA RED
Thiamethoxam	153719-23-4	III	II	IV	MSDS
Xylenol	1300-71-6	III	II	I	EPA RED

Abbreviations: CASRN = Chemical Abstracts Service Registry Number; EPA = U.S. Environmental Protection Agency; MSDS = material safety data sheet; RED = Office of Pesticide Programs Reregistration Eligibility Decision document.

[a] EPA dermal corrosivity/irritation classifications are defined as: I, corrosive; II, severe irritant; III, moderate irritant; IV, mild irritant or nonirritant.

[b] Methane, isothiocyanato- is classified as a fumigant (http://www2.epa.gov/soil-fumigants/regulatory-status-fumigants), as are dichlorvos and furfural (personal communication).

Conclusions

- Using only oral LD_{50} values will not accurately classify the acute dermal hazard of pesticide active ingredients across all hazard categories.
- The dermal hazard of many pesticide active ingredients could be overstated if only oral LD_{50} values are used for predicting both oral and dermal hazards (**Tables 3** and **4**).
- Oral LD_{50} >5000 mg/kg (Category IV) correctly predicted dermal classification as Category IV for all 22 pesticide active ingredients with oral LD_{50} >5000 mg/kg using either approach to predicting acute dermal toxicity hazard.
- Acute oral toxicity information may provide relevant information on dermal hazard, which may contribute to a reduction in the number of animals used for dermal acute toxicity testing.
- Future goals include:
  - Collection and curation of additional *in vivo* data
  - Reanalysis of the dataset after excluding fumigants and volatile materials
  - Analysis of pesticide formulations

References

Creton S, Dewhurst IC, Earl LK, Gehen SC, Guest RL, Hotchkiss JA, et al. 2010. Acute toxicity testing of chemicals-Opportunities to avoid redundant testing and use alternative approaches. Crit Rev Toxicol 40(1): 50–83.

Drexler H. 1998. Assignment of skin notation for MAK values and its legal consequences in Germany. Int Arch Occup Environ Health. 71(7): 503–505.

EPA. 1998. Health Effects Test Guidelines: OPPTS 870.1200 - Acute Dermal Toxicity. EPA 712-C-98-192. Washington, DC:U.S. Environmental Protection Agency. Available: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0156-0004.

EPA. 2012. Label Review Manual [Internet]. U.S. Environmental Protection Agency, Washington, DC. Available: http://www.epa.gov/oppfead1/labeling/lrm/

Grandjean P. 1990. Skin Penetration: Hazardous Chemicals at Work. London:Taylor & Francis.

OECD. 1987. Test Number 402: Acute Dermal Toxicity. In: OECD Guidelines for the Testing of Chemicals, Section 4: Health Effects. Paris:OECD Publishing. Available: http://www.oecd.org/chemicalsafety/risk-assessment/1948333.pdf

OECD. 2005. OECD Series on Testing and Assessment No. 34. Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment. ENV/JM/MONO(2005)14. Paris:OECD Publishing. Available: http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?doclanguage=en&cote=env/jm/mono%282005%2914.

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