



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

07/08/03

MEMORANDUM

Subject: EPA Id # 059102. Chlorpyrifos methyl: Current status of toxicity data gaps and bridging studies from chlorpyrifos.

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The Health Effects Division (HED) has reconsidered the available toxicology data base for chlorpyrifos methyl (CPM) to see if studies submitted for the active ingredient, chlorpyrifos (CPY), can be used to address the data gaps identified in the CPM Toxicology Chapter for the RED dated April 19, 2000.

The Reregistration Branch III (RRBIII) met on April 14, 2003 with the Co-Chairs of Health

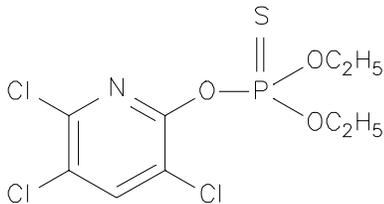
Effects Division (HED) Hazard Identification Assessment Review Committee, Jess Rowland and Elizabeth Doyle, to discuss and compare the relative toxicity to laboratory animals of CPY versus CPM. Of these two chemicals, CPY has a more extensive and for many studies a more current toxicity data base than the structurally, closely related chemical CPM. It was concluded that if anything, CPM would be less toxic than CPY based on comparison of cholinesterase inhibition particularly in rats and as would be predicted based on structure activity relationships. Thus, the extensive data base for CPY may serve as a surrogate for CPM. Only data gaps for CPY should now be considered as data gaps for CPM. As additional studies are submitted for CPY, they will also serve to address CPM data gaps, with the exception of the acute studies.

For risk assessment purposes, it was recommended that CPM continue to be regulated based on its current selection of endpoints and continued use of the 10 X uncertainty factor. It is noted that CPY currently has a 10 X FQPA uncertainty factor based on potential increased susceptibility to infants and children.

Comments.

1. The decision that CPM is regarded as less toxic than CPY is illustrated in Table I which shows the doses selected for the acute and chronic dietary endpoints.

Table 1. Comparison of selected studies in the toxicity data bases and other factors to support bridging of data from CPY to CPM.

Parameter	Chlorpyrifos (CPY)	Chlorpyrifos Methyl (CPM)	Comments
Completeness of the data base.	Essentially complete. Most studies are modern.	17 data gaps and many studies are older.	
Structure		<p>No electronic structure available in files.</p> <p>CPM has methyl groups in place of the ethyl groups on the phosphorous.</p>	Replacement of methyl groups may alter the metabolism and stability and make one chemical a more potent inhibitor of ChE than the other.
Key Endpoint Selection			
Acute Dietary RfD (endpoint dose).	<p>NOAEL = 0.5 mg/kg</p> <p>LOAEL = 1 mg/kg based on ChE inhibition in a special rat ChE study to determine the time to peak effect of inhibition.</p> <p>(1998, 44648101)</p>	<p>NOAEL = 1 mg/kg</p> <p>LOAEL = 12.5 mg/kg based on ChE inhibition in the dams in a development toxicity study.</p> <p>(1992 ,44680603)</p>	The selected dose levels are based on different types of studies but still supports implication that CPY is more potent a ChE inhibitor than CPM.

Parameter	Chlorpyrifos (CPY)	Chlorpyrifos Methyl (CPM)	Comments
Chronic Dietary RfD (endpoint dose)	NOAEL = 0.03 mg/kg/day Based on the comparison of several studies and no single LOAEL is assigned. Refer to HIARC report for list of studies used.	NOAEL = 0.1 mg/kg/day. LOAEL = 1.0 mg/kg/day based on ChE inhibition. (1991, 42269001)	Doses are not that different and still supports implication that CPY is more potent a ChE inhibitor than CPM.
Total uncertainty factor.	1000 10 X FQPA for increased susceptibility	1000 10 X for data base uncertainty factor	Also includes 10 X intraspecies and 10 X for interspecies.
Acute Toxicity - Caution - studies for both chemicals are very old.			
Acute Oral	LD ₅₀ = 163 mg/kg ♂ 137 mg/kg ♀ Vehicle not specified. (1963, Acc # 112115)	LD ₅₀ = 2140 (1530-2900) mg/kg ♂ 1090 (694-1710) mg/kg ♀ Corn oil (1969, Acc #242152)	Caution-large difference may be deceiving since strain of rat and other conditions may not be similar.
Acute Dermal	LD ₅₀ = 202 mg/kg (rat) (not identified in one liners)	LD ₅₀ > 2000 mg/kg (1964, Acc #242152)	Indicates CPY is more toxic than CPM
Neurotoxicity Testing			
Delayed type neurotoxicity - hens	Not neurotox at 50, 100 or 110 mg/kg/day in hens (00097144, 00405106)	Acute study (1979, 00029503) is considered equivocal at higher doses but 13 week study (1984, 00145060) did not show delayed type neuro-toxicity at 500 mg/kg/day.	Toxicity to hens is greater for CPY than for CPM.
Subchronic and Chronic Toxicity in Rats			
Subchronic - rat	LOAEL < 0.025 mg/kg/day for ChE. (1985, 40436406)	NOAEL = 0.1 mg/kg/day LOAEL = 1 mg/kg/day based on ChE inhibition by dietary route. (1990, 44906902, 45048301)	Supports implication that CPY is a more potent ChE inhibitor than CPM.
Chronic - rat	NOAEL = 0.132 mg/kg/day LOAEL = 0.33 mg/kg/day based on plasma ChE. (1990, 42172802)	NOAEL = 0.1 mg/kg/day LAOEL = 1 mg/kg/day based on both plasma and RBC ChE (1975, 00028752)	
Developmental and Reproductive Studies.			
Developmental - rat	NOAEL = 0.1 mg/kg/day LOAEL = 3 mg/kg/day based on ChE inhibition in dams. (1983, 00130400)	NOAEL = 1 mg/kg LOAEL = 12.5 mg/kg based on ChE inhibition in the dams. (1992 ,44680603)	Supports implication that CPY is a more potent ChE inhibitor than CPM.

Parameter	Chlorpyrifos (CPY)	Chlorpyrifos Methyl (CPM)	Comments
Mutagenicity Testing and Concern (if any)			
Data base	Apparently complete and without a mutagenicity concern.	Data base considered adequate - one study positive with metabolic activation.	Neither chemical has a mutagenicity concern.

2. The current status of the data gaps for CPM is shown in Table 2. The following comments should be noted.

(a). **Acute toxicity.** The acute toxicity data bases for both CPY and CPM are based on studies conducted in the 1960s and early 1970s. Thus, the acute oral, dermal, inhalation and irritation studies should be repeated for both chemicals and cannot be bridged. It is strongly advised that these acute toxicity studies (except for the irritation studies) be conducted concurrently using all the same parameters.

(b). **Subchronic inhalation.** The subchronic inhalation study with CPY (1988, 40908401) did not demonstrate a NOAEL. Thus this study should not be bridged to support CPM.

(c) **Rabbit developmental toxicity study.** The rabbit developmental toxicity study (1987, 404354408) is considered a data gap for CPY and therefore cannot be bridged to support the uses of CPM.

(d) **Dermal absorption.** The dermal absorption factor for CPY is set at 3% based on the weight of evidence of the toxicity data for CPY. The HIARC report (May 17, 1999) also assigned 3% as the dermal absorption factor for CPY using CPY as a comparative model.

Table 2. Status of Data Gaps for CPM.

Study Type	Reason for Chlorpyrifos Methyl Data Gap	Bridge #
870.1100. Acute oral toxicity.	1969 study. Old technical preparation used. Newer methods of synthesis may change toxicity.	No (a)
870.1200. Acute dermal toxicity	1964 study. Old technical preparation used. Newer methods of synthesis may change toxicity.	No (a)
870.1300. Acute inhalation toxicity	No valid study with current technical grade.	
870.2400. Primary ocular irritation	1974 study. Old technical preparation used. Newer methods of synthesis may change toxicity.	No (a)
870.2500. Primary dermal irritation	1964 study. Old technical preparation used. Newer methods of synthesis may change toxicity.	No (a)
870.2600. Dermal sensitization.	1985 Study (44906901 and 4498001) is classified as unacceptable.	No (a)

Study Type	Reason for Chlorpyrifos Methyl Data Gap	Bridge #
870.6100. Acute delayed type neurotoxicity - hens	1979 acute study is "equivocal" with some evidence of sciatic nerve at higher doses. A 1984 13 week study with CPM does not show effect at 500 mg/kg/day (classified as Acceptable).	Yes 00097144 and 00405106
870.6200. Acute neurotoxicity screen.	No CPM study. CPY study has time to peak effect.	Yes (1992, 42669101)
870.6200. Sub-chronic neurotoxicity screen	No CPM study. CPY study did not include ChE assessments and was acceptable for FOB and motor activity etc only. An acceptable CPM subchronic study (1990, 44906902 and 45048301) established the NOAEL and LOAELs for plasma, RBC and brain ChE for CPM.	Yes - for FOB, motor activity etc. (1993, 42929801)
870.3200. Sub-chronic dermal	No CPM study.	Yes (1988, 40972801)
870.3250. Sub-chronic inhalation	No CPM study.	No (b)
870.4100. Chronic non-rodent (dog)	1974 CPM study (00029477). Study is considered unacceptable for ChE assessment.	No (c)
870.3700. Developmental toxicity - rabbits	1976 CPM study (00030758). According to the HIARC report (5/17/99), this study is considered a data gap because of several deficiencies.	No (d)
870.3800. Multi-generation reproduction study.	1975 CPM study (00030757). According to the HIARC report (5/17/99), this study is considered a data gap because of several deficiencies including that only 2 doses were assessed. Note: A replacement study (MRID No.: 45826201) has been received and is currently under review by the contractor (due 9/30/03).	Yes (1991, 41930301)
870.6300. Developmental neurotoxicity - rat	No CPM study.	Yes (1998, 44556901, 44661001, 44787301)
870.7485. General metabolism - rat	(1971, 0029484). Study classified as unacceptable and not upgradeable. Uses only two males in a preliminary study.	Yes (e) (1987, 40458901)
870.7600. Dermal absorption.	1995 Study (44913001). In vitro studies are not acceptable for demonstration of dermal absorption.	Yes (f)

The MRID number for the study with CPY that is considered acceptable for bridging to support CPM is identified.

(a) The acute studies for both CPY and CPM are based on very old data and should be repeated for each chemical. Note the Acc # for all the acute studies is 242152.

(b) The study (1988, 40908401) with CPY did not demonstrate a NOAEL and is therefore a data gap for both CPY and CPM.

- (c) The dog studies with both CPY and CPM were conducted at approximately the same time (early seventies) and the study with CPY demonstrated much variability in the ChE assessments and thus contributing to problems in bridging the study. This remains a gap for both CPY and CPM.
- (d) The rabbit developmental toxicity study (1987, 404354408) is considered a data gap for CPY and therefore cannot be bridged to support the uses of CPM.
- (e) The differences in toxicity between CPY and CPM may be related to differences in the pharmacokinetics for each chemical but it is not necessary to prove this difference at this time.
- (f) The dermal absorption of 3% for CPY was based on a weight of the evidence approach that includes a study with humans. The HIARC (refer to report dated May 17, 1999) used the CPY approach as a model and also assigned 3% as the dermal absorption factor for CPM.