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

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

July 13, 1999

MEMORANDUM

SUBJECT: **Pirimiphos-methyl**. (Chemical ID No. 108102/List B Reregistration Case No. 2535). Revised Human Health Risk Assessment and Supporting Documentation for the Reregistration Eligibility Decision Document (RED). No MRID #. DP Barcode No. D256633

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BACKGROUND

Pirimiphos-methyl [O-(2-diethylamino-6-methyl-pyrimidinyl) O,O-dimethyl phosphorothioate] is an organophosphate (OP) insecticide belonging to the phosphorothioate subclass of

is equal to the acute or chronic RfD divided by the FQPA Safety Factor. The dietary exposure risk estimate is now expressed as a percentage of the PAD, instead of the RfD as in the previous version. The aPAD refers to the acute population dose and the cPAD refers to the chronic population adjusted dose.

SUMMARY/CONCLUSIONS

Highly refined acute and chronic dietary risk assessments for pirimiphos methyl generally result in risks that are below the Agency level of concern. Monitoring data from the USDA Pesticide Data Program (PDP) were used for high fructose corn syrup and from FDA for corn grain. Controlled magnitude of residue studies combined with usage data were used for other commodities. The apparent chronic dietary risk could be reduced even further if the outstanding toxicology data gaps for chronic studies were fulfilled (refer to the Detailed Considerations). Additional usage data for popcorn would also refine the acute and chronic dietary risk estimates. An aggregate exposure/risk assessment (i.e., including residential exposure and dietary exposure through drinking water) is not applicable, based on registered use patterns for pirimiphos-methyl.

Data summarized in a 10/97 report, "Evaluation of Pirimiphos-methyl: Evaluation of Use in Agriculture, Horticulture, Food Storage Practice and Home Gardens," completed by the UK Ministry of Agriculture, Fisheries and Food (MAFF), indicate there is likely to be some dietary risk associated with imported commodities treated with pirimiphos-methyl. Although the UK monitoring data are not adequate to quantify dietary risk using from imported commodities, the data suggest that residues in imported commodities are generally low or below the limit of detection. FDA monitoring data for numerous imported fruits and vegetables also showed non-detectable residues. Dietary risk from imported commodities has not been included in the human health risk assessment completed by HED as the exposure is expected to be minimal.

Short-term and intermediate-term occupational exposure and concomitant risk associated with mixing, loading and applying products containing pirimiphos-methyl for bin disinfestation and top-dress treatments exceed the Agency's level of concern. Due to a lack of chemical-specific data, occupational exposure/risk assessment for handlers was accomplished using data of varying quality from the Pesticide Handlers Exposure Database (PHED), label information (i.e., for iris bulb fogging), and cultural practices information.

The Margins of Exposure (MOEs) exceeding the level of concern for short- and intermediate-term exposure represent the maximum level of mitigation through additional personal protective equipment (PPE) and engineering controls currently applied in HED. Occupational risk for handlers could be refined via submission of additional information such as typical application rates, the amount of grain handled, data pertaining to dermal absorption, and chemical- or scenario-specific data.

DETAILED CONSIDERATIONS

TOXICOLOGY

The toxicology database for pirimiphos-methyl is not complete, but can be used for human health risk assessments. The available toxicology data show that pirimiphos-methyl inhibits cholinesterase activity in various species, including humans, rabbits, guinea pigs, rats and mice. Pirimiphos-methyl causes dose-related inhibition in plasma, red blood cell (RBC) and brain cholinesterase (ChE) activity by all routes of exposure and following exposure for various durations. Clinical symptoms associated with exposure to pirimiphos-methyl include tremors, ataxia, leg paralysis, abnormal gait and salivation. However, none of the animal studies submitted to EPA indicate changes in brain weight or histopathology. Cholinesterase inhibition occurs at very low dose levels, and is reversible when exposure is discontinued. Pirimiphos-methyl has relatively low acute oral, dermal and inhalation toxicity; both eye and skin irritation was observed in rabbits (Table 1). The HIARC concluded that the chronic/carcinogenicity studies submitted to EPA are not adequate to determine the carcinogenic potential of pirimiphos-methyl; however, acceptable mutagenicity studies indicate no genotoxicity concerns.

Table 1. Acute Toxicity Profile

OPPTS GDLN	MRID	Study Type	Species	Results	Tox Category
870.1100	00126257	Acute Oral	rat	LD_{50} = 2.4 g/kg	III
870.1200	00126257	Acute Dermal	rabbit	LD_{50} = >3.5 g/Kg for females and between 2.2-3.5 g/Kg for males	III
870.1300	41556304	Acute Inhalation	rat	LC_{50} = >4.7 mg/L	IV
870.2400	00126257	Primary Eye Irritation	rabbit	Irritant	II
870.2500	00126257	Primary Skin Irritation	rabbit	Moderate Irritant	III
870.2600	00126257*	Dermal Sensitization	guinea pig	Non-sensitizer	N/A

N/A = Not applied; * With the exception of this study, all other acute toxicity studies were conducted on the 75% formulation of pirimiphos-methyl.

RBC and brain ChEI) seen at the lowest dose tested.

The acute reference dose (RfD) is 0.015 mg/kg/day. The acute population adjusted dose is 0.005 mg/kg/day.

Chronic Dietary Endpoint for Risk Assessment

The chronic dietary endpoint was selected from a subchronic neurotoxicity study conducted in the rat (MRID No. 43608201). Test groups of Sprague-Dawley rats were fed diets containing pirimiphos-methyl (89.8%) at dose levels of 0, 0.2, 2.1 or 21.1 mg/kg/day for males and 0, 0.2, 2.4 or 24.7 mg/kg/day for females, respectively for 90-days. Plasma cholinesterase inhibition (ChEI) was observed in all test groups. The No Observed Adverse Effects Level (NOAEL) for brain and RBC ChEI was 2.1 mg/kg/day.

Longer-term studies reflecting exposure to the test material for a year or more are typically used to set the endpoint on which chronic risk assessments are based. However, no adequate chronic studies are available. Therefore the sub-chronic study, reflecting 90-day exposure, was used for the chronic risk assessment. Use of the study is supported by other longer-term studies, the two-generation reproduction study in rats and the carcinogenicity study in mice, in which the endpoint selected, cholinesterase inhibition, was observed at Weeks 3, 7, and 13. The uncertainty factor includes a 10x for intra-species variation, 10x for inter-species extrapolation, and 10x for the use of LOAEL and data gaps for long-term studies.

The chronic reference dose (RfD) is 0.0002 mg/kg/day. The chronic population adjusted dose is 0.00007 mg/kg/day.

Dermal and Inhalation Endpoints for Occupational Risk Assessment

Since endpoints were selected from oral studies, dermal and inhalation absorption rates, both assumed to be 100%, are applied to dermal and inhalation exposures in assessing risk associated with these exposures. Comparison of the acute oral and acute dermal LD_{50} from studies conducted in rats and rabbits indicates that the assumption of 100% dermal absorption (relative to oral absorption) is not likely to be conservative.

Short-term dermal and inhalation exposure

The acute neurotoxicity study used to select the endpoint for the acute dietary assessment was used for the short-term dermal and inhalation assessment as well. Please refer to the previous section for a description of the study. The HIARC determined that a MOE of 1000 is required for occupational (there are no residential uses) exposure risk assessments. This includes the conventional UF of 100 and an additional UF of 10 for the use of the use of a LOAEL as well as severity of the effects (marked plasma, RBC and brain cholinesterase inhibition observed at the lowest dose tested).

Table 2. Toxicological Endpoints for Risk Assessment [1]

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY	MOE
Acute Dietary	LOAEL=15 UF = 1000	Marked plasma, RBC and brain cholinesterase inhibition at the lowest dose tested	Acute Neurotoxicity-Rat Study	Not Relevant
	Acute RfD =0.015 mg/kg/day FQPA Acute Population Adjusted Dose (aPAD) = 0.005 mg/kg/day [2]			
Chronic Dietary	LOAEL=0.2 UF= 1000	Plasma cholinesterase inhibition in both sexes at the lowest dose tested.	Subchronic-Rat	Not Relevant
	Chronic RfD =0.0002 mg/kg/day FQPA Chronic Population Adjusted Dose (cPAD) = 0.00007 mg/kg/day [2]			
Dermal Absorption	100%, based upon the comparisons of LOAELs in the oral developmental toxicity (24 mg/kg/day) and the 21-day dermal (4 mg/kg/day) toxicity studies in rabbits based on the common endpoint (cholinesterase inhibition)			
Short-Term (Dermal & Inhalation) [3]	Oral LOAEL=15	Marked plasma, RBC and brain cholinesterase inhibition at the lowest dose tested	Acute Neurotoxicity-Rat Study	1000 [4]
Intermediate-Term (Dermal & Inhalation) [3]	Oral LOAEL=0.2	Plasma cholinesterase inhibition in both sexes at the lowest dose tested.	Subchronic-Rat	300 [5]
Long-Term (Dermal & Inhalation) [3]	Oral LOAEL=0.2	Plasma cholinesterase inhibition in both sexes at the lowest dose tested.	Subchronic-Rat	300 [5]

[1] NOAEL = No Observed Adverse Effect Level; LOAEL = Lowest Observed Adverse Effect Level; ChE = Cholinesterase

[2] Population Adjusted Dose (PAD) = RfD/FQPA factor (for this chemical FQPA factor = 3x)

[3] Oral values were selected, therefore route-to-route extrapolation is used (100% dermal and 100% inhalation absorption).

[4] MOE of 1000 due to severity of the effects (marked plasma, RBC and brain ChEI at the LOAEL)

[5] MOE of 300 due to the use of the LOAEL

The anticipated residues for popcorn were calculated four different ways. BEAD estimated the percent crop treated for corn as <1%, with no separate distinction for popcorn. (It should be noted that popcorn does not expressly appear on the product label, only corn.) Out of 70 samples analyzed for residues of pirimiphos methyl over the past 7 years, FDA had a detection rate of 34% in popcorn. A somewhat higher detection rate (than percent crop treated) would be expected since there is likely to be blending of untreated popcorn with treated, which would result in residue levels in the blended commodity that would be lower than those found in the residue trials, where there is no blending. Average residue levels in the monitoring samples were lower than the average from residue trials (2.5 vs. 1.4 ppm), but not as much as expected. FDA data for popcorn could not be used directly since the Agency typically requires a minimum of 100 monitoring samples.

Assessment 1, the least conservative analysis, which could possibly underestimate the risk, assumes average residues from magnitude of residue trials and <1% crop treated. The remaining three analyses are increasingly conservative in the assumptions. The second assessment uses the same residue value, but assumes 34% crop treated (based on the rate of detection in the FDA monitoring samples). No adjustments for percent crop treated were made in the remaining two assessments. Assessment 3 uses the average value of the detects in the FDA monitoring data as the residue value, and Assessment 4 uses the average value from the corn grain residue trials.

The most highly exposed population sub-groups after refinement of residues Children 1-6 years and Children 7-12 years. The most conservative refined assessment, which the Agency believes is an overestimate, resulted in a risk that exceeded 100% of the population adjusted dose for both the acute and chronic analyses. The risk was below the level of concern in the other three refined assessments for all population sub-groups. As a result, the Agency does not have a risk concern from dietary exposure to pirimiphos-methyl.

To further characterize dietary exposure/risk, the Agency generated an acute critical exposure contribution analysis and a chronic commodity contribution analysis for the worst-case scenario, Assessment 4. These analyses indicate that at the 99.9th percentile of exposure, both popcorn and corn grain are significant contributors to the estimated acute dietary risk, but estimated chronic dietary risk is almost entirely due to residues in popcorn. The highest detected residue in the corn grain FDA monitoring data appears to have a greater impact on the estimated acute exposure and risk at the 99.9th percentile than excessive consumption events for individual survey respondents. Additional usage data for popcorn would help to further refine the risk assessment. It should be noted that heating and popping data are not available, which would further refine the assessment as well.

Table 4. Pirimiphos-methyl: Probabilistic Acute Dietary Exposure and Risk Estimates[1]

Population Subgroup	Deterministic Analysis (95th Percentile of Exposure Reported)				Probabilistic Analysis (99.9th Percentile of Exposure Reported)							
	Acute Reassessed Tolerances 1		Acute Reassessed Tolerances 2		Acute ARs Refined Assessment 1		Acute ARs Refined Assessment 2		Acute ARs Refined Assessment 3		Acute ARs Refined Assessment 4	
	Exposure (mg/kg/day)	%aPAD	Exposure (mg/kg/day)	%aPAD	Exposure (mg/kg/day)	%aPAD	Exposure (mg/kg/day)	%aPAD	Exposure (mg/kg/day)	%aPAD	Exposure (mg/kg/day)	%aPAD
General U.S. Population	0.019524	390	0.003348	67	0.002559	51	0.002678	54	0.003102	62	0.004591	92
All infants (<1 yr)	0.049357	990	0.002008	40	0.002664	53	0.002664	53	0.002664	53	0.002664	53
Nursing infants (<1 yr)	0.016215	320	0.000654	13	0.000584	12	0.000584	12	0.000584	12	0.000584	12
Non-nursing infants (<1 yr)	0.052105	1,000	0.002208	44	0.002884	58	0.002884	58	0.002884	58	0.002884	58
Children (1-6 years)	0.037433	750	0.005705	114	0.004017	80	0.004168	83	0.004774	95	0.007040	141
Children (7-12 years)	0.027216	540	0.005140	103	0.003158	63	0.003214	64	0.003415	68	0.005029	101
Females (13-19)	0.016340	330	0.003201	64	0.002684	54	0.002698	54	0.002701	54	0.003549	71
Females (20+ years)	0.011013	220	0.002332	47	0.001568	31	0.001773	35	0.002185	44	0.003563	71
Females (13-50 years)	0.013017	360	0.002671	53	0.001786	36	0.001990	40	0.002531	51	0.003755	75
Males (13-19 years)	0.019612	390	0.003721	74	0.002225	44	0.002314	46	0.002749	55	0.004309	86
Males (20+ years)	0.012203	240	0.002768	55	0.002121	42	0.002192	44	0.002471	49	0.003645	73
Description of Assessment	Tolerance level residues and 100%CT[2] for all commodities		Tolerance level residues and 100%CT[2] for most commodities; excludes HFCS and sugar/molasses.		Used anticipated residues for most commodities; assumed <1%CT and average residue trial values for popcorn.		Used anticipated residues for most commodities; assumed 34%CT and average residue trial values for popcorn.		Used anticipated residues for most commodities; used average of FDA monitoring detects; and no adjustment for %CT		Used anticipated residues for most commodities; used average residue trial value; and no adjustment for %CT	

limited the maximum number of applications to carrots, and continued to monitor residues in both composite and single serving samples of carrots. Reductions in the residues detected were observed, but the MAFF determined that "some erosion of safety margins for consumers still existed." Therefore, the restriction on the maximum number of applications to carrots has been retained, and the WPPR continues to monitor residues in carrots.

The UK report suggests that there is likely to be some dietary risk associated with pirimiphos-methyl uses in other countries. It is not possible to quantify the risk using the available information; however, the UK monitoring data suggest that residues are generally low or near the limit of detection.

FDA has monitored many imported commodities for residues of pirimiphos-methyl over the past several years. Residues have not been detected in any of these samples. The Agency generally believes that the exposure to pirimiphos-methyl from imported fruits and vegetables is minimal and was therefore not specifically included in the risk assessment.

OCCUPATIONAL RISK

No additional occupational exposure data were submitted after the preliminary assessment (10/98). Examination of use patterns on registered labels indicates exposure is expected to occur in the course of typical activities for occupational workers; exposure assessments have been completed for occupational handler and post-application scenarios. There are no products registered at this time for residential use. Short-term and intermediate-term occupational exposure assessments were conducted, but chronic occupational exposure scenarios are not expected to occur, based on use patterns supported through reregistration.

For occupational handlers, six scenarios served as the basis for the exposure/risk assessment. The registrant intends to propose a pour-on treatment for livestock (scenarios 4a and 4b in the ORE Chapter). The pour-on use was incorporated into the assessment dated 6/1/99, but is not included in the HED risk assessment for reregistration since it is not a registered use, and since it has not formally been submitted to the Agency. The potential for post-application exposure is expected only in conjunction with the fogging use on iris bulbs in Washington State; short-term inhalation exposure is of concern following this fogging operation. No other scenarios are expected to result in either dermal or inhalation post-application exposure.

Since there were no chemical-specific exposure data, unit exposures (dermal and inhalation) for occupational handler scenarios were derived from the Pesticide Handlers Exposure Database (PHED Surrogate Data Table, 5/97); several handler assessments were completed using "**low quality**" PHED data due to the lack of higher quality data. No data were available to assess exposure during application of ear tags to livestock. Several generic protection factors were used to calculate handler exposures, although protection factors for clothing layers have not been completely evaluated by HED. In calculating daily exposures, factors such as tons of grain

Table 5. Summary of Occupational Risk for Pirimiphos-methyl[1]

Exposure Scenario	Baseline Clothing[2]		Protective Clothing/PPE[3]		Engineering Controls[4]	
	Short-Term Risk (MOE)	Intermediate-Term Risk (MOE)	Short-Term Risk (MOE)	Intermediate-Term Risk (MOE)	Short-Term Risk (MOE)	Intermediate-Term Risk (MOE)
Mixer/Loaders						
Mixing/loading Liquids For Admixture Grain Treatment	Not feasible, since only closed loading system (considered to be an engineering control) are being supported in re-registration.				17,000 (min rate) 14,000 (max rate)	240 (min rate) 180 (max rate)
Mixing/loading Liquids For Seed Treatment					68,000	910
Loading Liquids For Fogging Treatment of Iris Bulbs	13	<1	2100	27	N/F	N/F
Applicators						
Fogging Treatment of Iris Bulbs	Not Feasible - See text					
Cattle Ear Tags	No Data	No Data	No Data	No Data	N/F	N/F
Mixer/Loader/Applicator						
Mixing/loading and Applying Liquids Using a Low Pressure Handwand [Top dress]	15	<1	4,200	55	Not feasible; no engineering controls have been identified for these occupational scenarios.	
Mixing/loading and Applying Liquids Using a Low Pressure Handwand [Bin Disinfestation]	8	<1	3,200	30		
Mixing/loading and Applying Liquids Using a Backpack Sprayer [Top dress]	600	8	940	13		
Mixing/loading and Applying Liquids Using a Backpack Sprayer [Bin Disinfestation]	330	4	500	7		
Mixing/loading and Applying Liquids Using a High Pressure Handwand [Top dress]	580	8	940	13		
Mixing/loading and Applying Liquids Using a High Pressure Handwand [Bin Disinfestation]	310	4	500	7		

[1] Only occupational risk is summarized, since there are no residential exposure patterns based on the registered uses. The data are summarized from the 6/1/99 ORE Chapter of the HED RED.