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PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

05-APR-1999

MEMORANDUM

SUBJECT: *CHLORPYRIFOS* - Report of the FQPA Safety Factor Committee.

FROM: Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)

THROUGH: Ed Zager, Chair
FQPA Safety Factor Committee
Health Effects Division (7509C)

TO: Deborah Smegal, Risk Assessor
Reregistration Branch 3
Health Effects Division (7509C)

PC Code: 059101

The Health Effects Division (HED) FQPA Safety Factor Committee met on November 8, 1998, February 22, 1999, and March 8, 1999 to evaluate the hazard and exposure data for chlorpyrifos, and recommended that the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996) be reduced to 3x in assessing the risk posed by this chemical.

I. HAZARD ASSESSMENT

1. Adequacy of Toxicity Database

There are no data gaps for the assessment of the effects of chlorpyrifos following *in utero* and/or postnatal exposure. In addition to the core studies submitted to the Agency, a Developmental Neurotoxicity Study has been submitted and reviewed for chlorpyrifos.

2. Developmental and Reproduction Studies

Developmental toxicity studies on chlorpyrifos were conducted in mice, rats, and rabbits. Additionally, a two-generation dietary study and a three-generation reproduction study in rats were submitted and reviewed. The data submitted to the Agency under Subdivision F Guidelines provided no indication of increased susceptibility to *in utero* exposure in developmental toxicity studies and/or to pre- and post-natal exposure in reproduction studies with chlorpyrifos.

3. Developmental Neurotoxicity Study

The HIARC concluded that *quantitatively* (i.e., based on NOAELs/LOAELs in dams vs. pups), there was no evidence of increased susceptibility in the developmental neurotoxicity study in rats. *Qualitatively,* however, there was evidence of increased susceptibility at the high dose (5 mg/kg/day) based on the concern for the severity of effects seen in the dams and pups. Maternal toxicity, manifested as increased signs of autonomic function toxicity was apparent at the end of gestation as fasciculations, and during lactation as fasciculations, hyperpnea, and hyperactivity. Offspring toxicity was manifested as decreases in body weight/body weight gain and food consumption in both sexes, reductions in pup viability, delays in development (pinna unfolding and sexual maturation), decreased brain weight, and alterations in morphometric measurements of the pup brains (*Memorandum:* J. Rowland to D. Smegal, dated December 7, 1998).

4. Studies Reported in the Open Literature

Moser and Padilla (1998) reported that following oral (gavage) administration of 75 to 80% of the maximum tolerated dose, neonatal rats were 5 times more sensitive than adult rats. Following a single oral dose to pups (postnatal day 17) and adults (about 70 days), although the degree of cholinesterase inhibition (blood, brain and peripheral tissues) and behavioral measurements were similar, the effective dose was five-fold lower for the pups (15 mg/kg/day) when compared to adults (80 mg/kg/day). In the same study, 10 day old pups were approximately 7 times more sensitive than adults based on the maximum tolerated dose (15 mg/kg verses 100 mg/kg, respectively). This report is one of several studies from the open literature. For complete information on these reports, refer to the HIARC Reports for Chlorpyrifos dated February 2, 1998 and December 7, 1998.

5. Determination of Susceptibility

The HIARC acknowledged that while young rats (and by extrapolation, young humans) appear to be more sensitive to the acute toxicity of high doses of chlorpyrifos, sensitivity to neurochemical and/or neurobehavioral changes following repeated, low-dose exposure should be of more concern for risk assessment and regulatory decisions making, especially in light of the FQPA. Based on weight-of-evidence consideration and the lack of data with lower, "real world" exposure to chlorpyrifos in the diet, the HIARC concluded that the current available data demonstrated that exposure to chlorpyrifos results in increased susceptibility of young rats and this evidence cannot be discounted (*Memorandum:* J. Rowland to D. Smegal, dated December 7, 1998).

II. EXPOSURE ASSESSMENT AND RISK CHARACTERIZATION

1. Dietary (Food) Exposure Considerations

Tolerances are established for the combined residues of the insecticide, chlorpyrifos (and for some commodities, its metabolite, TCP) in/on many raw agricultural commodities at levels ranging from 0.01 to 13 ppm (40 CFR §180.342). However, these tolerances will be reassessed in terms of chlorpyrifos, *per se*, since "HED has determined that TCP is not of toxicological concern and can be excluded from the tolerance expression (PP3F2884 and 3F2947; FAP3H5396; 3H5411/R1191, Final Rule, D.Barolo, 4/1/93)". Food and feed additive tolerances are established in (40 CFR §185.1000 and 186.1000, respectively) at levels ranging from 0.4 to 25 ppm.

Chlorpyrifos is used on many foods which are highly consumed by infants and children, including milk, apples, oranges, peaches, pears, beans, soybeans, and wheat (1993 NAS report, Pesticides in the Diets of Infants and Children). Residues of chlorpyrifos, however, are not systemic and are, therefore, likely to be significantly removed during normal preparation such as washing and peeling.

A variety of residue data sources are available for chlorpyrifos, including field trial data, Pesticide Data Program (PDP) monitoring data, FDA surveillance data, and FDA Market Basket Survey sampling and analysis data. Information on percent of crop treated (%CT) is also available from the Biological and Economic Analysis Division (BEAD) for this pesticide.

PDP monitoring data (1996) indicate quantifiable residues of chlorpyrifos in approximately 9% of the samples tested (433 samples with detections in a total of 4831 samples), including apples, apple juice, carrots, grapes, green beans, oranges, peaches, spinach, sweet corn, sweet peas, sweet potatoes, and tomatoes.

The registrant initiated a market basket survey in 1993 for nine food items (apples, applesauce, apple juice, orange juice, tomatoes, peanut butter, whole milk, ground beef,

and pork sausage) to better determine the acute dietary exposure of chlorpyrifos to consumers. The data were submitted and reviewed by the Agency and found to be acceptable. These market basket survey data are incorporated into the acute dietary exposure analysis for chlorpyrifos using Monte Carlo-type probabilistic analysis techniques. Probabilistic techniques enhance risk estimates by more fully incorporating the available information on the range of possible values that an input variable could take, and weighting these values by their probability of occurrence. The resulting output of a probabilistic determination is a distribution of risk values with probability assigned to each estimated risk which in turn, results in a more realistic reflection of the expected exposure.

The chronic dietary analysis uses market basket survey data, PDP and FDA monitoring data in conjunction with percent crop treated and field trial data to calculate anticipated residues (Tier IV). This analysis is unlikely to underestimate exposure for the majority of the U.S. population.

2. Dietary (Drinking Water) Exposure Considerations

The environmental fate database for chlorpyrifos is largely complete. Based on available data, chlorpyrifos appears to degrade slowly in soil under both aerobic and anaerobic conditions. Available field data indicate that chlorpyrifos has a half-life in the field of less than 60 days, with little or no leaching observed. The environmental fate data for the major chlorpyrifos degradate, TCP, indicate it to be mobile in soils; and persistent in soils when not exposed to light. Because of its low solubility and high soil binding capacity, there is potential for chlorpyrifos residues sorbed to soil to runoff into surface water via erosion.

Monitoring data for residues of chlorpyrifos in ground and surface water are available. Monitoring data for ground water were from all uses of chlorpyrifos. The termiticide use studies were targeted to wells and ponds adjacent to treatment areas which resulted in the highest detection concentrations.

EFED performed modeling to calculate estimated environmental concentrations (EECs) in order to bolster the monitoring data using SCI-GROW Tier 1 for ground water; and GENEEC and PRZM/EXAMS for surface water. EFED states that these estimates are reasonably conservative for the majority of the U.S. population, and could be further reduced in finished drinking water (activated charcoal). Residues in surface water could be higher in areas where usage is pervasive in the watershed. EFED concluded that if chlorpyrifos is used for termite control within 100 feet of a drinking water well, then contamination at levels up to 2000 ppb is possible.

3. Residential Exposure Considerations

Chlorpyrifos is currently registered for many residential uses including: lawns and ornamentals; vegetable gardens and fruit trees; pet treatments; indoor crack and crevice treatments; and as a residential termiticide. The registrant recently canceled uses

including indoor total-release foggers, broadcast application on floors, direct application pet care products (i.e., shampoos, dips and sprays), and paint additive products.

Chemical-specific data were used to assess post-application exposure to residents. Most exposures to children are calculated based on state-of-the-art biomonitoring studies conducted in adults (i.e. exposure following lawn or crack and crevice treatment), while other exposures were estimated based on environmental measurements (i.e., air concentrations following termite treatment). The most significant exposures have been characterized, although *not all* exposure scenarios have been characterized due to the widespread use of this chemical and the absence of data (i.e., residues tracked indoors from outdoor use, garden use, etc.). Where data are lacking or are incomplete, the DRAFT Standard Operating Procedures (SOPs) for Residential Exposure Assessments are used to estimate the potential exposure. Thus, it is the Committee's understanding that all residential exposure scenarios will be assessed either through the use of chemical-specific data or the SOPs for Residential Exposure Assessments.

4. Poisoning Incident Data

As a result of the widespread use of chlorpyrifos, there have been numerous exposures and poisonings. Detailed analysis of the poisoning data has been used to identify specific use patterns that are more likely to be associated with pesticide poisoning. In addition to acute poisoning, chlorpyrifos has been reported to be associated with chronic effects in humans, including peripheral neuropathy, chronic neurobehavioral effects, and multiple chemical sensitivity.

Poison Control Center data combined for the years 1993-1996 were examined to determine hazards from organophosphate pesticides used in residential settings. Thirteen organophosphate insecticides were analyzed with at least 100 incidents reported over the four year period. By most measures, Chlorpyrifos did not pose a greater hazard than other organophosphates used in residential settings. For complete information on human incident data for chlorpyrifos, refer to the HIARC Report for Chlorpyrifos dated December 7, 1998.

III. SAFETY FACTOR RECOMMENDATION AND RATIONALE

1. FQPA Safety Factor Recommendation

The Committee recommended that the **FQPA safety factor** for protection of infants and children (as required by FQPA) be **reduced to 3x.**

2. Rationale for Requiring the FQPA Safety Factor

The Committee concluded that an additional safety factor is required for chlorpyrifos due to:

- concern for the extensive use of this organophosphate insecticide and resulting potential for exposure to infants and children;
- concern for the qualitative evidence of increased susceptibility at the high dose (5 mg/kg/day) in the developmental neurotoxicity study in rats based on the comparison of the severity of effects seen in the dams and pups;
- the uncertainty associated with the five-fold difference in sensitivity observed at high doses in the Moser and Padilla susceptibility study since there are no comparable studies that examine age-related sensitivity at lower doses.

However, based on the weight-of-evidence for chlorpyrifos, the Committee recommended that the **FQPA safety factor** be **reduced** to 3x since:

- the assessments for the most significant chlorpyrifos exposures are well-characterized; actual data are available for dietary (food and water) and residential exposure assessments; acute and chronic dietary risk assessments are very refined and state-of-the-art techniques are used for some residential scenarios; where data are lacking or are incomplete for residential exposure scenarios, the DRAFT SOPs for Residential Exposure Assessments (using upper-percentile assumptions) will be used to estimate the potential exposure;
- the toxicology database is complete for assessing the effects of chlorpyrifos following *in utero* and/or postnatal exposure;
- the data submitted to the Agency under Subdivision F Guidelines provided no indication of increased susceptibility to *in utero* exposure in developmental toxicity studies and/or to pre- and post-natal exposure in reproduction studies with chlorpyrifos;
- there was no quantitative evidence of increased susceptibility in the developmental neurotoxicity study in rats;
- the qualitative evidence of increased susceptibility (developmental neurotoxicity study) was only observed at the high dose (5 mg/kg/day) and not at the effects levels for developmental and maternal toxicity;
- the five-fold difference in sensitivity (Moser and Padilla study) was observed at very high doses (15 and 80 mg/kg/day) which were the only doses tested.

The major concerns of the Committee were for the possible increased susceptibility demonstrated in young rats that cannot be discounted, coupled with the widespread use of this organophosphate insecticide and resulting potential for exposure. The exposure concerns centered on ensuring that the exposure assessments will adequately account for all potential chlorpyrifos exposures and that when relying on the chemical specific studies submitted by the registrant, the results do not underestimate the actual potential for exposure to infants and children. The Committee agreed that if all residential exposure scenarios are assessed, either through the use of chemical-specific data or the DRAFT SOPs for Residential Exposure Assessments, the FQPA safety factor could be reduced to 3x.

3. Population Subgroups for Application of the Safety Factor

The Committee determined that the FQPA safety factor is applicable for the following subpopulations:

Acute Dietary Assessment: The FQPA safety factor is applicable for all population subgroups due to the concern for the possible increased susceptibility of infants and children to adverse effects resulting from a single exposure to chlorpyrifos (as demonstrated in the Moser and Padilla study) coupled with the extensive use of this organophosphate insecticide and resulting potential for exposure.

Chronic Dietary Assessment: The FQPA safety factor is applicable for all population subgroups due to the concern for the possible increased susceptibility of infants and children to adverse effects resulting from repeated exposure to chlorpyrifos (as demonstrated in the developmental neurotoxicity study) coupled with the extensive use of this organophosphate insecticide and resulting potential for exposure.

Residential Exposure Assessment: The FQPA safety factor is applicable for all population subgroups due to the concern for the possible increased susceptibility of infants and children to adverse effects resulting from the extensive residential use of this organophosphate insecticide and resulting potential for exposure.

FQPA Safety Factor Committee Meeting
08MAR1999
Chemical: CHLORPYRIFOS (Revisit)

Name	Division/Branch
[illegible]	EFED/ERB1
Rick Keigwin	RD
Ray Kent	HED
Kathy Monk	SRRD
Jon Fleuchaus	OGC
Susan Makris	HED/TOX1
Debbie McCall	RD
[illegible]	HED
[illegible]	HED
[illegible]	HED
Debbie Smegal	HED
[illegible]	HED/SAB

FQPA Safety Factor Committee Meeting
22FEB1999
Chemical: CHLORPYRIFOS (Revisit)

Name	Division/Branch
Jess Rowland	HED/RCAB
Ed Zaghi	HED
Rick Keigwin	RD
Kathy Monk	SRRD
Daniel Rieder	EFED
Tina Levine	RD
Debbie Smegal	HED
Bill Sette	HED/SAB
Susan Makris	HED/TOX
Jon Fleuchaus	OGC
W J Burnam	HED
Ray Hunt	HED
Brenda Tarplee	HED/SAB

FQPA Safety Factor Committee Meeting
09NOV1998
Chemical: Chlorpyrifos - Revisit

Name	Division/Branch
Jean Holmes	EI=ED/ERB2
	SAB / HED
Ray West	HED/CBB2
	OGC
Bill Sette	HED / SAB
Margaret Rice	SRRD
Tina Levine	RD / IRB
Susan Makris	HED/TOX I
Steve Knizer	HED/RCAB
Rick Keigwin	RD
Debbie McCall	RD
Ed Rugh	HED
	HED
Barbara Tarplee	HED