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PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

03-APR-1998

MEMORANDUM

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

FROM: Jess Rowland, Executive Secretary
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)

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

TO: Steven Knizner, Branch Senior Scientist
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PC Code: 123000

The Health Effects Division (HED) FQPA Safety Factor Committee met on March 23, 1998 to evaluate the hazard and exposure data for Isoxaflutole and recommend application of the FQPA Safety Factor (as required by FQPA), to ensure the protection of infants and children from exposure to this chemical. The Committee's recommendations follow.

I. HAZARD ASSESSMENT

1. Determination of Susceptibility

(i) Developmental Toxicity

In the prenatal developmental toxicity study in **rats, enhanced susceptibility** of rat fetuses as compared to maternal animals **was seen** following *in utero* exposures. Increased sensitivity manifested as growth retardation characterized as decreased fetal body weight and increased incidence of delayed ossification of sternebrae, metacarpals and metatarsals.

In the prenatal developmental toxicity study in **rabbits, enhanced susceptibility** of rabbit fetuses as compared to maternal animals **was seen** following *in utero* exposures. Increased sensitivity manifested as fetuses with increased pre-sacral vertebrae at the lowest dose tested as well as fetuses with increased incidences of skeletal anomalies at the next tow higher doses tested. A NOEL for developmental toxicity was not established in this study. Consequently, a 3x uncertainty factor was applied by the HIARC.

(ii) Reproductive Toxicity

In the two generation reproduction study in rats, **no enhanced susceptibility was seen;** effects in the offspring were observed only at, or at higher doses than those that caused parental toxicity.

(iii) Neurotoxicity

Neurobehavioral findings were observed in the acute and subchronic neurotoxicity studies in rats. These included decreased foot splay in the acute and subchronic studies and decreased hind- and forelimb grip strength in the subchronic study.

Increased incidences of axonal/myelin degeneration of the sciatic nerve were observed in the chronic toxicity study in rats. Focal degeneration/inflammation of the thigh muscle was seen at the same treatment levels.

No evidence of abnormalities in the development of the fetal nervous system, were observed in the prenatal developmental toxicity studies in either rats or rabbits, at maternally toxic oral doses up to 500 or 100 mg/kg/day, respectively.

Neither brain weight nor histopathology (perfused or nonperfused) of the central or peripheral nervous system were affected in the subchronic toxicity studies in several species or in the acute and subchronic neurotoxicity studies in rats.

2. Adequacy of Database

There are no data gaps for the standard Subdivision F Guideline requirement for a food-use chemical by 40 CFR Part 158. Acute and subchronic neurotoxicity studies in rats are available. The developmental toxicity of Isoxaflutole has been tested *in utero* following oral administration rats and rabbits. HIARC determined that a developmental neurotoxicity study in rats is required (*Memorandum:* J. Rowland to B. Madden, dated December 22, 1997).

3. Doses Selected for Risk Assessments

For acute dietary risk assessment, a developmental LOEL of 5 mg/kg based on increased incidence of fetuses with 27th pre-sacral vertebrae in a rabbit developmental toxicity study; a NOEL was not established. This dose was identified for this risk assessment for Females 13+.

For acute dietary risk assessment for the general Population including Infants and Children, a NOEL of 125 mg/kg based on significant decreases in mean fore limb grip strength in males at 500 mg/kg (LOEL) in an acute neurotoxicity study.

For chronic dietary risk assessment, a NOEL of 2 mg/kg/day based on hepato, thyroid, ocular and neurotoxicity in males and hepatotoxicity in females at 20 mg/kg/day (LOEL) in a chronic toxicity/carcinogenicity study in rats.

II. EXPOSURE ASSESSMENT

1. Dietary Exposure Considerations

Tolerances are proposed for the combined residues of the herbicide Isoxaflutole and its metabolites 1-(2-methylsulfonyl-4-trifluoromethylphenyl-2-cyano-3-cyclopropyl propane-1,3-dione and 2-methylsulfonyl-4-trifluoromethyl benzoic acid, calculated as the parent compound, in/on corn (field, grain, stover and forage). Tolerances are also required for meat and fat of cattle, goat, hogs, and sheep. The required tolerances for these commodities, 0.20 ppm for meat and fat, are based on the LOQ of the proposed analytical enforcement method.

Isoxaflutole is a new chemical proposed for use on corn, therefore no monitoring data are available for dietary risk assessment. Anticipated residues from field trials were used in

acute and chronic dietary risk assessments. Field trials show the average level of Isoxaflutole and its metabolites for grain to be 0.015 ppm; in silage, 0.11 ppm; in forage, 0.087 ppm; and in stover, 0.057 ppm.

HED DRES System was used for dietary exposure analysis. For the chronic (non-cancer) dietary risk, using tolerance level residues and assuming 100 percent crop treated, non-nursing infants (< 1 year old) is the subgroup that utilized the greatest percentage of the RfD at 81%. By refining the chronic dietary risk assessment assuming 34 percent of the corn crop treated and anticipated residues (ARs) for corn, animal RACs and processed commodities; less than 1 percent of the RfD for the general population and 1 percent of the RfD for nursing infants is used. These same refinements (using ARs and 34 percent crop treated information) were used for the dietary risk assessments for cancer.

2. Drinking Water Exposure Considerations

Parent Isoxaflutole is not expected to persist in surface water or to reach ground water. However, the metabolites RPA 202248 and RPA 203328 are expected to reach both ground and surface water, where they are expected to persist and accumulate.

The Environmental Fate and Effects Division (EFED) provided estimates of exposure for Isoxaflutole and its metabolites RPA 202248 and RPA 203328 for both surface and ground water based on available modeling. Since there are no registered uses for Isoxaflutole in the U.S., there are no monitoring data to compare against the modeling. The estimated environmental concentrations (EECs) for surface water were generated using Tier 2 modeling from PRZM/EXAMS. A Tier II EEC can provide a reasonable upper bound on the concentration found in drinking water if not an accurate assessment of the real concentration.

Acute and chronic ground water concentrations were estimated from the SCI-GROW model. SCI-GROW is a model that provides an upper bound of EEC's in shallow ground water. For surface water, the maximum concentrations should be used for acute risk calculations. The annual means (1-10 years) are available for chronic risk calculations. For ground water, the SCI-GROW numbers for each compound should be used for acute, chronic, and cancer risk assessment.

Since modeling data was used, HED calculated drinking water levels of concern (DWLOC) for the general population and children for acute exposures to Isoxaflutole in surface and ground water. The maximum estimated concentrations of Isoxaflutole and its metabolites in surface and ground water were less than HED's levels of concern for acute exposure in drinking water.

3. Residential Exposure Considerations

Isoxaflutole is a new chemical, proposed for use on corn. **Currently there are no residential uses associated with this chemical.**

III. RISK CHARACTERIZATION

1. Determination of the Factor

The Committee recommended that the **10x factor** or enhanced sensitivity to infants and children (as required by FQPA) for Isoxaflutole should be **retained.**

2. Rationale for Selection of the FQPA Factor

- There is increased sensitivity of rat and rabbit fetuses as compared to maternal animals following *in utero* exposures in prenatal developmental toxicity studies. In both species, the developmental effects were seen at doses which were not maternally toxic (i.e., developmental NOELs were less than the maternal NOELs).

- There is concern for the developmental neurotoxic potential based on the demonstration of neurotoxicity in FOB measurements in the acute and subchronic neurotoxicity, as well as evidence of neuropathology in the combined chronic toxicity/carcinogenicity studies.

- There is concern for the lack of a postnatal exposure study to confirm the *in utero* effects observed in the prenatal study. The developmental neurotoxicity (which is required) might provide data to alleviate this concern.

- There is concern for the developmental effects observed and exposure to infants and children which requires the FQPA factor.

- There are no monitoring data for drinking water risk assessments. Since only modeling data are available for surface and ground water, quantitative estimates were not included in the dietary risk assessments.

Retaining the 10x factor results in a total Uncertainty Factor of 3000 for acute dietary risk assessment (10x for interspecies extrapolation, 10x for intraspecies variability, 10x for FQPA and 3x for the use of a LOEL).

For acute dietary risk assessment, the 10x FQPA safety factor cannot subsume the 3x factor for the use of a LOEL because: 1) that would essentially lower (to 3x) the FQPA factor; 2) the lack of a NOEL requires a "modifying" factor since the "true NOEL" could have been lower (approximately 3 fold); and 3) even if a NOEL would have been established in the study, the 10x factor would have been retained (stand alone) due to the enhanced susceptibility in two species plus the need for a developmental toxicity study.

3. Identification of Population Subgroup

The Committee determined that the FQPA Safety Factor (10x) is applicable for the following subpopulations:

Acute Dietary: **For Females 13 +**, because the endpoint is developmental toxicity and are presumed to occur following "acute"exposures. Also for **All Populations which include Infants and Children**, because the endpoint is neurotoxicity seen following a single exposure and Isoxaflutole is a neurotoxic chemical.

Chronic Dietary Risk Assessment: **All Populations which include Infants and Children** because the NOEL (2 mg/kg/day) selected for this risk assessment is similar to the NOEL (1.76 mg/kg/day) established for parental systemic toxicity in the two-generation reproduction study. Although there was no increased susceptibility, since the NOELs (1.76 mg/kg/day) and the LOELs (17.4 mg/kg/day) were the same for parental systemic toxicity and offspring toxicity, the effects seen in the offsprings (decreased litter viability at birth) were more notable than those seen in the mothers (increase in liver weights and hypertrophy).

Occupational/Residential Risk Assessments: No registered residential uses exist at this time for Isoxaflutole. Occupational exposure is not considered when determining the FQPA safety factor, however, the factor should be considered when characterizing the risks to pregnant female workers exposed to the chemical.

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FQPA Safety Factor Committee Meeting
23-MAR-1998
Chemical: Isoxaflutole

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