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TOXIC SUBSTANCES

DATE: December 22, 1997

MEMORANDUM

SUBJECT: ISOXAFLUTOLE - *REASSESSMENT OF THE FQPA REQUIREMENT* - Report of the Hazard Identification Assessment Review Committee.

FROM: Jess Rowland 12/22/97
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THROUGH: K. Clark Swentzel, Chairman,
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TO: Barbara Madden, Branch Senior Scientist
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BACKGROUND: On December 17, 1997, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) met to determine the Uncertainty Factors and the Margins of Exposure for dietary and non-dietary risk assessments as required by the Food Quality Protecting Act (FQPA) of 1996. The Committee's decisions are presented in this report.

I. INTRODUCTION

On April 24, 1997, the Health Effects Division's RfD/Peer Review Committee evaluated the toxicology data base of Isoxaflutole and established the Reference Dose by applying an Uncertainty Factor (UF) of 300. The RfD Committee applied an additional UF of 3 x to the conventional UF of 100 (10 x for inter-and 10 x for intra-species variation) since the dose used for deriving the RfD was a LOEL (i.e, lack of a NOEL in the critical study) and the data base showed a potential for increased sensitivity to fetuses following *in utero* exposure in rabbits (Memorandum: G. Ghali, HED to P. Errico, RD, dated 07/16/97).

On April 29, 1997, the Health Effects Division's Toxicology Endpoint Selection Committee (TESC) selected the doses and endpoints for acute dietary as well as occupational and residential exposure risk assessments.

On December 4, 1997, the risk assessment document on Isoxaflutole was reviewed by HED's Risk Assessment Review Committee (RARC). The RARC recommended that the Hazard Identification Review Committee (HIARC) re-evaluate the rationale used for the additional UF of 3 x. The RARC was unsure as to whether the 3 x applied for the lack of a NOEL in the critical study and/or because of the observance of increased sensitivity in *in utero* developmental toxicity studies in rats and rabbits. The RARC also needed clarification on the need for the developmental neurotoxicity study in light of the increased sensitivity observed in rats and rabbits .

Consequently, on December 12, 1997, the HIARC: 1) re evaluated the toxicology data base; 2) re-assessed the doses and endpoints selected; 3) determined the Margins of Exposures for the various exposure scenarios (dietary as well as occupational exposure risk assessments); 4) addressed the enhanced sensitivity of infants and children as required by FQPA; and 5) determined the need for a developmental neurotoxicity study in rats.

This report supersedes the previous RfD and the TES documents for the dose and endpoints selected as well as the Margins of Exposure (MOEs) determined for dietary as and non dietary risk assessments.

II. HAZARD IDENTIFICATION

A 1. Acute Dietary (One-Day) Females 13 +

Study Selected:	Developmental Toxicity - Rabbit	§83-3b
MRID No	43904808	

Executive Summary: In a developmental toxicity study, pregnant New Zealand White rabbits received oral administration of Isoxaflutole (99.6%) in 1% methylcellulose at dose levels of 0, 5, 20 or 100 mg/kg/day during gestation days 6 through 19.
For maternal toxicity, the NOEL was 20 mg/kg/day and the LOEL was 100 mg/kg/day based on increased incidence of clinical signs and decreases in body weight gain (23%) and food consumption (5%). For developmental toxicity, the LOEL was 5 mg/kg/day based on increased incidence of fetuses with 27th pre-sacral vertebrae; a NOEL was not established. The fetal incidence of this anomaly was dose-depended and exceeded the concurrent as well as the historical control incidences. Also at the next higher dose (20 mg/kg/day) there was an increased incidence of fetuses with reduced ossification. It was noted that the developmental anomalies occurred below the dose that caused maternal toxicity (100 mg/kg/day).

Dose/Endpoint for Risk Assessment: Developmental LOEL= 5 mg/kg/day based on increased incidence of fetuses with 27th pre-sacral vertebrae; a NOEL was not established.

Comments about Study/Endpoint: This anomaly is anticipated to occur following a single exposure (dose).

This risk assessment is required.

Acute Dietary Risk Assessment: The TESC selected this dose and endpoint and recommended a MOE of 300 for this risk assessment because of the use of a LOEL. The HIARC re-affirmed the dose and endpoint and the additional UF of 3 x under FIFRA.

The HIARC, however, determined that for acute dietary risk assessment for this sub population (13+), the **10 x factor** to account for enhanced sensitivity of infants and children (as required by FQPA) **should be retained.** Thus, **a MOE of 3000 is required**. This MOE of 3000 includes: the conventional 100; 10 x for FQPA; and 3 x for FIFRA.

The HIARC determined that although the toxicology data based is complete and there was no increased sensitivity in pups as compared to adults in the two-generation reproduction study in rats, **the FQPA 10 x factor should be retained because:**

(i) 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). In rats, increased sensitivity manifested as growth retardation characterized as decreased fetal body weight and increased incidence of delayed ossification of sternebrae, metacarpals and metatarsals.

In rabbits, increased sensitivity was 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 two higher doses tested; also a NOEL for developmental toxicity was not established in this study.

(ii) There is concern for the developmental neurotoxic potential of Isoxaflutole. This is based on the demonstration of neurotoxicy in FOB measurements in the acute and subchronic neurotoxicity as well as evidence of neuropathology in the combined chronic toxicity/ carcinogenicity studies.

(iii) The need for a developmental neurotoxicity study based on the evidence of neurotoxicity as well as the lack of assessment of susceptibility of the offspring in functional/neurological development in the standard developmental/reproduction toxicity studies.

A 2..Acute Dietary (One-Day) General Population including Infants and Children

Study Selected: Acute Neurotoxicity - Rat §81-8

MRID No 43904804

Executive Summary: In an acute neurotoxicity study, CD rats (10/sex/dose) received a single oral administrations of Isoxaflutole (99.2%) in 0.5% aqueous methylcellulose at doses of 0, 125, 500 or 2000 mg/kg/day. No treatment-related effects were observed on survival, body weight, body weight gain or food consumption. There were significant decreases in landing foot splay measurements in males at 2000 mg/kg during FOB tests indicating impairment of neuromuscular function. At 500 mg/kg, males exhibited significant decreases in mean forelimb grip on day 8 and in landing foot splay measurements on day 15. The NOEL was 125 mg/kg and the LOEL was 500 mg/kg based on significant decreases in mean hindlimb grip and in landing foot splay on day 15.

Dose/Endpoint for Risk Assessment: NOEL= 125 mg/kg/day based on significant decreases in mean fore limb grip strength on day 8 and in landing foot splay on day 15 in males at 500 mg/kg.

Comments about Study/Endpoint: This dose and endpoint is selected for acute dietary risk assessments for general populations including infants and children since a developmental endpoint was selected for females 13+. A dose and endpoint was not previously identified for this population subgroup.

This risk assessment is required.

Acute Dietary Risk Assessment: The HIARC determined that for acute dietary risk assessment for the general population, the **10 x factor** to account for enhanced sensitivity of infants and children (as required by FQPA) **should be retained**. Thus, **a MOE of 1000 is required** and includes the conventional 100 and 10 x for FQPA. Since a NOEL was used the FIFRA factor is not applicable. The MOE of 1000 is supported by the same reasons discussed under Acute Dietary Risk Assessment - Females 13+ (see above).

The Committee determined that the Data Evaluation Records for the Acute Neurotoxicity study should be revised to reflect the following changes in the NOELs and LOELs: NOEL = 125 mg/kg; LOEL = 500 mg/kg based on significant decreases in hind limb grip strength and landing foot splay on day 15.

B. Chronic Dietary Risk Assessment

For chronic dietary risk assessment, the RfD Committee selected a NOEL of 2 mg/kg/day based on hepato, thyroid, ocular and neurotoxicity in males as well as hepatotoxicity in females at 20 mg/kg/day (LOEL) following dietary administration of Isoxaflutole (99.2%) at 0, 0.5, 2, 20 or 500 mg/kg/day for 104 weeks to male and female Sprague-Dawley rats (MRID No. 43904806). The NOEL/LOEL of this study is supported by the parental systemic toxicity NOEL of 1.76 mg/kg/day and the LOEL of 17.4 mg/kg/day established in the two-generation reproduction study in rats; the LOEL was based on increased liver weights and hypertrophy in both sexes in both generations.

The RfD Committee applied a UF of 300 to the NOEL of 2 mg/kg/day to derive the RfD of 0.0067 mg/kg/day (2 mg/kg/day ÷ 300 = 0.0067 mg/kg/day). The UF of 300 included 10 x for inter, 10 x for intra-species variations and an additional 3 x for the lack of a NOEL in the developmental rabbit study and the potential for increased sensitivity to fetuses following *in utero* exposure. Because of the clarification needed on the UF of 300, this RfD was re-assessed by the HIARC as discussed below.

Re-Assessment of the RfD : The HIARC concurred with the RfD Committee on the dose and endpoint selected but did not concur on the UF of 300. Instead, the HIARC determined that the **10 x factor** to account for enhanced sensitivity of infants and children (as required by FQPA) **should be retained.** Thus, for chronic dietary risk assessment a **UF of 1000 is required** (10 x for inter-species variation, 10 x for intra-species variation, and 10 x for FQPA). **Consequently the revised RfD is 0.002 mg/kg/day.**(NOEL of 2 mg/kg/day ÷ UF of 1000 = RfD, 0.002 mg/kg/day) and supersedes the previous RfD.

The HIARC determined that although the toxicology data based is complete and there was no increased sensitivity in pups as compared to adults in the two-generation reproduction study in rats, **the FQPA 10 x factor should be retained because:**

(i) 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). In rats, increased sensitivity manifested as growth retardation characterized as decreased fetal body weight and increased incidence of delayed ossification of sternebrae, metacarpals and metatarsals. In rabbits, increased sensitivity was 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 two higher doses tested; also a NOEL for developmental toxicity was not established in this study.

(ii) There is concern for the developmental neurotoxic potential of Isoxaflutole. This is based on the demonstration of neurotoxicy in FOB measurements in the acute and subchronic neurotoxicity as well as evidence of neuropathology in the combined chronic toxicity/ carcinogenicity studies.

(iii) The need for a developmental neurotoxicity study based on the evidence of neurotoxicity as well as the lack of assessment of susceptibility of the offspring in functional/neurological development in the standard developmental/reproduction toxicity studies.

C. Occupational/Residential Exposure Risk Assessments

On April 29, 1997, the TESC determined that: 1) the Short-and Intermediate-Term Dermal risk assessments are not required due to lack of dermal or systemic toxicity following repeated dermal applications of Isoxaflutole at doses up to and including 1000 mg/kg/day, for 8 hours/day, 7 days/week over a three week period; 2) a NOEL of 2 mg/kg/day established in the combined chronic toxicity/carcinogenicity study (used for deriving the RfD) along with a dermal absorption factor of 0.2% (since an oral dose was identified) should be used for Long-Term dermal s risk assessment; and 3) risk assessments via the inhalation route was not necessary because of the low toxicity (LC50 of >5.26 mg/L;Toxicity Category IV) potential of Isoxaflutole via this route.

At the present meeting, the HIARC re-evaluated the doses and endpoints for dermal as well as inhalation exposures. **These doses and endpoints supersede the TESC of April 29, 1997.**

1). Dermal Absorption

Study Selected: Dermal Absorption of ^{14}C-Isoxaflutole in Male Rats §85-3

MRID No. 44044702

Executive Summary: In a dermal absorption study ^{14}-C-Isoxaflutole(99.7%) as a 1% carboxy methylcellulose aqueous suspension was administered to male Crl:CDBR rats (4/dose) as a single dermal application at 0.865, 7.32 or 79 mg/cm^2). Dermal absorption was measured sacrificed after 0.5, 1, 2, 4, 10 and 24 hours of exposure. Results are summarized below:

	Percent Absorbed		
Average Dose	1 hour	10 hours	24 hours
0.865 mg/cm^2	<1	**3.46**	4.42
7.32 mg/cm^2	<1	<1	<1
7.9 mg/cm^2	<1	<1	<1

Dermal Absorption Factor: 3.5% at 10 hours.

2. Short-Term Dermal (1-7 days)

Study Selected: Developmental Toxicity - Rabbit §83-3b

MRID No 43904808

Executive Summary: See Acute Dietary

Dose/Endpoint for Risk Assessment: Developmental LOEL= 5 mg/kg/day based on increased incidence of fetuses with 27th pre-sacral vertebrae; a NOEL was not established.

Comments about Study/Endpoint: The TESC in their April, 1997 meeting did not select a dose or endpoint for this risk assessment due to the lack of dermal or systemic toxicity in the 21-dermal toxicity study in rats following repeated dermal applications at doses up to and including 1000 mg/kg/day (Limit-Dose)(MRID No. 43573219).

Although the HIARC recognized the lack of systemic toxicity in the 21-day dermal toxicity study as well as the low absorption potential, a developmental LOEL was selected because: 1) of the concern for the increased sensitivity observed following *in utero* exposures in rats and rabbits; 2) developmental LOEL was lower than maternal NOEL in rabbits; 3) fetal effects can occur after a single exposure; 4) developmental effects are not evaluated in the dermal study and 5) adequate protection is needed for pregnant occupational workers.

Since an oral dose was selected a dermal absorption rate of 3.5% should be used in risk assessments.

This risk assessment is required.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: 21-Day Dermal Toxicity - Rat §83-b

MRID No 43904808

Executive Summary: See Acute Dietary

Dose/Endpoint for Risk Assessment: Developmental LOEL= 5 mg/kg/day based on increased incidence of fetuses with 27^{th} pre-sacral vertebrae; a NOEL was not established.

Comments about Study/Endpoint: See Short-Term

This risk assessment is required.

4. Long-Term Dermal (Several Months to Life-Time)

Study Selected: Combined Chronic Toxicity/Carcinogenicity §83-5

MRID No. 43904806

Executive Summary: In a combined chronic toxicity/carcinogenicity study, Sprague-Dawley rats (75/sex/dose) received dietary administration of Isoxaflutole (99.2%) at 0, 0.5, 2, 20 or 500 mg/kg/day for 104 weeks. For chronic toxicity, the NOEL was 2 mg/kg/day and the LOEL was 20 mg/kg/day based on hepato, thyroid, ocular and neurotoxicity in males as well as hepatotoxicity in females. The NOEL/LOEL of this study is supported by the parental systemic toxicity NOEL of 1.76 mg/kg/day and the LOEL of 17.4 mg/kg/day) established in the two-generation reproduction study in rats; the LOEL was based on increased liver weights and hypertrophy in both sexes in both generations.

Dose/Endpoint for Risk Assessment: NOEL= 2 mg/kg/day based on hepato, thyroid, ocular and neurotoxicity in males and hepatotoxicity in females at 20 mg/kg/day (LOEL).

Comments about Study/Endpoint: This dose/endpoint was used to establish the RfD. Also, this dose is supported by the identical parental systemic toxicity NOEL of 2 mg/kg/day and the LOEL of 20 mg/kg/day established in the two-generation reproduction study in rats. Since an oral dose was selected a dermal absorption rate of 3.5% should be used in risk assessments.

This risk assessment is required.

5. Inhalation (Any Time Period)

Although the LC_{50} of >5.26 mg/L (Toxicity Category IV) indicates low inhalation toxicity potential, the HIARC identified doses and endpoints for inhalation risk assessment due to the potential exposure via this route for occupational workers.

Dose/Endpoint for Risk Assessment: Oral Developmental LOEL= 5 mg/kg/day for Short-and Intermediate-Term. An oral systemic NOEL = 2 mg/kg/day for Long-Term .

Comments about Study/Endpoint: HIARC selected these doses, the same doses used in respective dermal risk assessments, due to the lack of appropriate inhalation toxicity studies and the concern for the toxicity seen via the oral route. Since the doses identified for these (inhalation) risk assessments are oral dose the risk assessment should be as follows:

Step I. The inhalation exposure component (i.e., mg/L) using a 100 % absorption rate (default value) should be **converted to** an **equivalent oral dose** (mg/kg/day).

Step II.) The dermal exposure component (i.e., mg/kg/day) using 3.5% dermal absorption should be **combined with this converted oral equivalent dose** (mg/kg/day).

Step III. **This combined oral equivalent dose** should then **be compared to** the oral LOEL of 5 mg/kg/day for Short- and Intermediate-Term exposure and the NOEL of 2 mg/kg/day for Long-Term exposures to calculate the Margins of Exposure.

D. Margins of Exposure for Occupational Exposure Risk Assessments

For Short-and Intermediate-Term Dermal and Inhalation risk assessments, the HIARC determined that the **10 x factor** to account for enhanced sensitivity of infants and children (as required by FQPA) **should be retained.** An **additional UF of 3 x was applied under FIFRA** because of the use of the LOEL (i.e., lack of a NOEL in the critical study) for these risk assessments. Thus, **a MOE of 3000 is required** for the same reasons stated under the Acute Dietary Risk Assessment - Females 13+ (Section II.A.1). The MOE of 3000 includes: the conventional 100; 10 x for FQPA; and 3 x for FIFRA. Although there are no residential uses, the FQPA factor still applies to ensure protection against female occupational workers.

For Long-Term Dermal and Inhalation risk assessments, the HIRAC determined that the **10 x** factor to account for enhanced sensitivity of infants and children (as required by FQPA) **should be retained.** Thus, for these risk assessments **a MOE of 1000 is required** for the same reasons stated under the Chronic Dietary Risk Assessment (Section II.B). The MOE of 1000 includes the conventional 100 and 10 x for FQPA. In addition, although there are no residential uses, the FQPA factor still applies to ensure protection against female occupational workers.

E. Recommendation for Aggregate Exposure Risk Assessments

An aggregate systemic (oral) and dermal exposure risk assessment is not required since there are no residential uses for Isoxaflutole at the present time. Aggregate exposure will be limited to food + water only.

III. FQPA CONSIDERATIONS

1. Neurotoxicity Data:

In an acute neurotoxicity study, a single oral dose of Isoxaflutole at 500 mg/kg/day resulted in neurobehavioral effects. This study is discussed in Section 1. Acute Dietary (MRID No. 43904804).

In a subchronic neurotoxicity study, dietary administration of Isoxaflutole at 0, 25, 250 or 750 mg/kg/day resulted in significant decreases in mean hind limb grip strength in male rats at 25 mg/kg/day (LDT) during both trials at week 13. A non significant decreases in mean forelimb grip strength was also observed at week 13. A NOEL was not established in this study (MRID No. 43904805).

In a combined chronic toxicity/carcinogenicity study in rats, dietary administration of Isoxaflutole for 104 weeks resulted in neuropathological lesions in the sciatic nerve of males at 20 and 500 mg/kg/day and in females at 500 mg/kg/day. Sciatic nerve lesions were characterized as increased incidence of axonal/myelin degeneration and cholesterol cleft/granulomas in these rats (MRID No. 43904806).

2. Determination of Susceptibility:

The data from both the prenatal developmental toxicity study in rats and rabbits suggested the potential for increased susceptibility of fetuses to *in utero* exposure to Isoxaflutole. Additionally, the prenatal developmental study in rabbits did not establish a NOEL for developmental toxicity study in that species, thus an assessment of prenatal toxicity in a non-rodent species is not complete. The data from the two-generation reproduction study did not indicate increased sensitivity of rats following postnatal exposure to Isoxaflutole. Effects in the offspring were observed only at treatment levels which resulted in evidence of parental toxicity.

(i) Developmental Toxicity

In a prenatal developmental toxicity study, pregnant Sprague-Dawley rats (25/group) received oral administration of Isoxaflutole (99.2%) in 0.5% methylcellulose at dose levels of 0, 10, 100, or 500 mg/kg/day during gestation days 6 through 15. For maternal toxicity, the NOEL was 100 mg/kg/day and the LOEL was 500 mg/kg/day based on an increase in clinical signs of toxicity (salivation) and on reduced body weight gain and food consumption. For developmental toxicity, the NOEL was 10 mg/kg/day and the LOEL was 100 mg/kg/day based on a growth retardation (decreased fetal body weight, increased incidence of delayed ossification of sternebrae, metacarpals and metatarsals). In addition, an increased incidence of vertebral and rib anomalies and high incidence of subcutaneous edema were observed at 500 mg/kg/day (MRID No.43573220).

In a developmental toxicity study, pregnant New Zealand White rabbits received oral administration of Isoxaflutole (99.6%) in 1% methylcellulose at dose levels of 0, 5, 20 or 100 mg/kg/day during gestation days 6 through 19. For maternal toxicity, the NOEL was 20 mg/kg/day and the LOEL was 100 mg/kg/day based on increased incidence of clinical signs and decreases in body weight gain (23%) and food consumption (5%). For developmental toxicity, the LOEL was 5 mg/kg/day based on increased incidence of fetuses with 27^{th} pre-sacral vertebrae; a NOEL was not established. The fetal incidence of this anomaly was dose-depended and exceeded the concurrent as well as the historical control incidences. Additional findings at 20 and 100 mg/kg/day included increased number of post implantation loss and late resorptions, as well as growth retardations in the form of generalized reduction in skeletal ossification, and increased incidence of 13 pairs of ribs. At 100 mg/kg/day, an increase incidence of fetuses with incisors not erupted was also observed (MRID No. 43904808).

(ii) Reproduction Toxicity

In a two-generation reproduction study, Crl:CD BR VAF/Plus rats (30/sex/dose) were fed diets containing Isoxaflutole (98.7%) at 0, 0.5, 2, 20 or 500 mg/kg/day for two successive generations. These dose levels were equivalent to 0, 0.45, 1.76, 17.4 or 414 mg/kg/day in males and 0, 0.46, 1.79, 17.7 or 437 mg/kg/day in females. There was no evidence of increased sensitivity in pups as compared to parental animals. There was no evidence of

reproductive toxicity. Treatment-related effects included reductions in pup survival in F1 and F2 offsprings at 20 and 500 mg/kg/day and decreases in body weights of F1 and F2 pups throughout lactation, increased incidence of chronic keratitis, low incidence of inflammation of the iris, as well as retinal and vitreous bleeding in F2 pups and weanlings at 500 mg/kg/day. For parental systemic toxicity, the NOEL was 1.76 mg/kg/day) and the LOEL was 17.4 mg/kg/day based on increased liver weight and hypertrophy. For offspring toxicity, the NOEL was 2 mg/kg/ day and the LOEL was 20 mg/kg/day based on decreased litter viability at birth. (MRID No.43904809) .

3. Adequacy of Data Base:

There are no data gaps for the assessment of the effects of Isoxaflutole on developing animals following *in utero* and/or early postnatal exposure.

4.. Determination of Uncertainty Factor:

The Committee determined that for Isoxaflutole, the **10 x factor** to account for enhanced sensitivity of infants and children (as required by FQPA) **should be retained.** This conclusion was based on the following factors.

(i) 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). In rats, increased sensitivity manifested as growth retardation characterized as decreased fetal body weight and increased incidence of delayed ossification of sternebrae, metacarpals and metatarsals. In rabbits, increased sensitivity was 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 two higher doses tested; also a NOEL for developmental toxicity was not established in this study.

(ii) There is concern for the developmental neurotoxic potential of Isoxaflutole. This is based on the demonstration of neurotoxicy in FOB measurements in the acute and subchronic neurotoxicity as well as evidence of neuropathology in the combined chronic toxicity/ carcinogenicity studies.

(iii) The need for a developmental neurotoxicity study based on the evidence of neurotoxicity as well as the lack of assessment of susceptibility of the offspring in functional/neurological development in the standard developmental/reproduction toxicity studies.

5. Recommendation for a Developmental Neurotoxicity Study

Although the recommendation of the 5/29/97 RfD Peer Review Committee was that a developmental neurotoxicity study in rats would not be required, a reevaluation of the neurotoxicity studies by the Committee identified significant neurobehavioral findings, supported by neuropathology observed in the chronic study in rats following long term exposure. With this information considered in the weight-of-the-evidence evaluation, the Committee revised the previous conclusion and recommended that a developmental neurotoxicity study in rats with isoxaflutole would be required. The following information was considered in support of this decision:

(i) Evidence that support requiring a developmental neurotoxicity study:

- Isoxaflutole is a neurotoxic chemical as shown below-
- 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.

(ii) Evidence that do not support asking for a developmental neurotoxicity study:

- 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.

IV. OTHER

The Committee determined that the Data Evaluation Records for the Acute and Subchronic neurotoxicity studies should be revised to reflect the following changes in the NOELs and LOELs.:

Acute Neurotoxicity: NOEL = 125 mg/kg; LOEL = 500 mg/kg based on significant decreases in hind limb grip strength and landing foot splay on day 15.

Subchronic Neurotoxicity: NOEL = not established; LOEL = 25 mg/kg/day based on significant decreases in mean hind limb grip strength in male rats at 25 mg/kg/day (LDT) during both trials at week 13 as well as a non significant decreases in mean forelimb grip strength at week 13.

V. DATA GAP

None

VI. ACUTE TOXICITY:

Guideline No.	Study Type	MRID NO.	Results	Toxicity Category
81-1	Acute Oral	43573225	LD_{50} = >5000 mg/kg	IV
81-2	Acute Dermal	43573226	LD_{50} > 2000 mg/kg	IV
81-3	Acute Inhalation	43573227	LC_{50} => 5.26 mg/L	IV
81-4	Primary Eye Irritation	43573228	Mild reversible irritation	III
81-5	Primary Skin Irritation	43573229	Non-irritant	IV
81-6	Dermal Sensitization	43573230	Non-sensitizer	N/A

VII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for Isoxaflutole and the Margins of Exposures for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY	MOE
Acute Dietary Female 13+	Developmental LOEL = 5.0	Increased incidence of 27th pre-sacral vertebrae	Developmental - Rabbit	3000
Acute Dietary General Population	NOEL= 125.0	Significant decreases in fore limb grip strength on day 8 and landing foot splay on day 15 in males.	Acute Neurotoxicity	1000
Chronic Dietary	NOEL= 2.0	Hepato, thyroid, ocular and neurotoxicity in males and hepatotoxicity in females	Combined/ Chronic Toxicity - Rat	UF= 1000
	Rfd = 0.002 mg/kg/day			
Short-Term (Dermal)	Oral LOEL = 5.0	Increased incidence of 27th pre-sacral vertebrae	Developmental Rabbit	3000
Intermediate-Term (Dermal)	Oral LOEL= 5.0	Increased incidence of 27th pre-sacral vertebrae	Developmental Rabbit	3000
Long-Term (Dermal)	Oral NOEL = 2.0	Hepato, thyroid, ocular and neurotoxicity in males and hepatotoxicity in females	Combined/ Chronic Toxicity - Rat	1000
Short-Term (Inhalation)	Oral LOEL =5.0	Increased incidence of 27th pre-sacral vertebrae	Developmental Rabbit	3000
Intermediate-Term (Inhalation	Oral LOEL =5.0	Increased incidence of 27th pre-sacral vertebrae	Developmental Rabbit	3000
Long-Term (Inhalation)	Oral NOEL = 2.0	Hepato, thyroid, ocular and neurotoxicity in males and hepatotoxicity in females	Combined/ Chronic Toxicity - Rat	1000