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WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

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DATE: March 25, 2004

MEMORANDUM

SUBJECT: **FLUMIOXAZIN** - Second Report of the Hazard Identification Assessment Review Committee

FROM: Alan C. Levy Alan C. Levy 3-26-2004
Registration Action Branch 2
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair
and
Karen Whitby, Co-Chair 3/30/04
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Margarita Collantes, Risk Assessor
Registration Action Branch 2
Health Effects Division (7509C)

PC Code: 129034

On December 9, 2003, The potential for increased susceptibility of infants and children from exposure to FLUMIOXAZIN was re-evaluated as required by the Food Quality Protection Act (FQPA) of 1996 according to the 2002 Office of Pesticide Program (OPP) 10X guidance document. In addition, the HIARC reevaluated the toxicological database for Flumioxazin with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The conclusions of the committee are presented in this report.

RC 04/04

Committee Members in Attendance

Members present were: Ayaad Assaad, William Burnam, Jonathan Chen, William Dykstra, Pamela Hurley, Ray Kent, Jessica Kidwell, John Liccione, Susan Makris, Elizabeth Mendez, Jess Rowland, PV Shah and Brenda Tarplee.

Member(s) in absentia: Karen Whitby

Data evaluation prepared by: Alan C. Levy of Registration Action Branch 2.

Also in attendance were: William Drew and Charles Stafford

Data Evaluation / Report Presentation

Alan C. Levy
Toxicologist

INTRODUCTION

On December 9, 2003, the potential for increased susceptibility of infants and children from exposure to FLUMIOXAZIN was re-evaluated as required by the Food Quality Protection Act (FQPA) of 1996 according to the 2002 Office of Pesticide Program (OPP) 10X guidance document. In addition, the HIARC reevaluated the toxicological database for Flumioxazin with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The conclusions of the committee are presented in this report.

I FQPA - HAZARD CONSIDERATIONS

1. Adequacy of the Toxicity Database

The HIARC concluded that the toxicology data base for flumioxazin is adequate for an FQPA evaluation. The following studies are available:

Oral (gavage) developmental toxicity study in the rat
Dermal developmental toxicity study in the rat
Oral (gavage) developmental toxicity study in the rabbit
Oral (dietary admix) two-generation reproduction toxicity study in the rat
Oral (gavage) "critical period" developmental toxicity study in the rat

2. Evidence of Neurotoxicity

The HIARC concluded that there is no concern for neurotoxicity resulting from exposure to flumioxazin. None of the acute, subchronic, chronic, developmental or reproduction studies indicated an effect on the nervous systems.

3. Developmental Toxicity Study Conclusions

Oral (gavage) Developmental Toxicity Study in Rats

MRID No.: 42684930 (pilot); 42684925 (main study)

Executive Summary: In an oral developmental toxicity study, the test substance, S-54382 (94.8% purity), was administered once daily by gavage to pregnant female Scl:SD (Sprague-Dawley) rats on days 6-15 of gestation (with the day of mating defined as gestation Day 0) at dose levels of 0, 1, 3, 1 0 and 30 mg/kg/day. The rats were observed for signs of toxicity; body weight and food consumption values were recorded. On day 20 of gestation, the rats were sacrificed and necropsied; gravid uterine weights were recorded. The uteri were examined, implantation sites were counted, and the numbers of

corpora lutea were determined. The fetuses were removed, weighed, sexed, and examined for external anomalies. They were then processed for visceral or skeletal evaluation.

There were no treatment-related effects on maternal mortality, clinical observations, body weight, food consumption or gross pathology data. **Maternal LOAEL = Not determined; Maternal NOAEL ≥ 30 mg/kg/day.**

At the 30 mg/kg/day dose level, a treatment-related increase in fetal death (5.6% resorptions in control versus 20.4% at the high-dose), a 21% decrease in mean live litter size, and a decrease in male (14.3%) and female (15.2%) fetal body weights were noted as compared to control. A dose and treatment-related increase in the incidence of fetuses with cardiovascular abnormalities, particularly ventricular septal defect, was observed. Ventricular septal defect was noted in the following numbers of fetuses (litters) for the control, 1, 3, 10 and 30 mg/kg/day dose groups, respectively: 2(2), l(l), 2(2), 6(6), and 26(12); combined cardiovascular abnormalities were noted with the following distribution: 8(6), 7(6), 10(8), 13(9), and 36(14). These findings were both statistically significant at 30 mg/kg/day, and the increased incidence of cardiovascular abnormalities was judged to be biologically significant at 10 mg/kg/day. Appropriate historical control data submitted by the performing laboratory support and confirm these conclusions. Also at the 30 mg/kg/day dose level, significantly increased incidences of wavy ribs (27 fetuses, representing 12 of 18 litters) and curvature of the scapula (10 fetuses in 4 litters) and a significant 4-7% decrease in the number of ossified sacrococcygeal vertebral bodies as compared to control were attributed to treatment. **Developmental LOAEL = 10 mg/kg/day; Developmental NOAEL = 3 mg/kg/day,** based on a biologically significant increase in cardiovascular abnormalities, particularly ventricular septal defect; at 30 mg/kg/day, statistical significance was achieved for these observations and the following additional findings were noted: increased resorptions and decreased number of viable fetuses, decreased fetal body weight, increased abnormalities of the ribs (wavy) and scapula (curvature), and decreased numbers of ossified sacrococcygeal vertebral bodies.

The above findings were generally similar to those observed in the dermal developmental toxicity study in rats conducted with S-53482 (MRID No. 42684926, Teratology Study of S-53482 Administered Dermally to Rats, performed by Sumitomo Chemical Co. Ltd., for Valent U.S.A. Corporation, project No. 2018, March 14, 1991). **[SEE BELOW]** In that study, a dose- and treatment-related increase in the incidence of cardiovascular abnormalities, particularly ventricular septal defect, was noted for fetuses of dams treated by 6-hour dermal exposure to the test substance on days 6-15 of gestation.

CORE CLASSIFICATION: **not acceptable/guideline; does not satisfy the requirement (83-3) for an oral developmental toxicity (teratology) study in rats;** this study can be upgraded to acceptable following the receipt of the following acceptable

individual fetal observation data: body weight, external observations, visceral findings, and skeletal findings.

Dermal Developmental Toxicity Study in Rats

MRID No. 42684929 (pilot); 42684926 (main study)

Executive Summary: In a dermal developmental toxicity study, the test substance, S-54382 (94.8% purity), was administered by 6-hour daily dermal application to pregnant female Scl: SD (Sprague-Dawley) rats on days 6-15 of gestation (with the day of mating defined as gestation Day 0) at dose levels of 0, 30, 100, and 300 mg/kg/day. The rats were observed for signs of toxicity; body weight and food consumption values were recorded. On day 20 of gestation, the rats were sacrificed and necropsied; gravid uterine weights were recorded. The uteri were examined, implantation sites were counted, and the numbers of corpora lutea were determined. The fetuses were removed, weighed, sexed, and examined for external anomalies. They were then processed for visceral or skeletal evaluation.

There were no systemic treatment-related effects on maternal mortality, clinical observation, body weight, food consumption, or gross pathology data. **Maternal LOAEL = not determined; Maternal NOAEL ≥300 mg/kg/day.**

A dose- and treatment-related increase in the incidence of fetuses with cardiovascular abnormalities, particularly ventricular septal defect, was observed. Ventricular septal defect was noted in the following numbers of fetuses (litters) for the control, 30, 100, and 300 mg/kg/day dose groups, respectively: 1(1), 1(1), 2(2), and 13(9); combined cardiovascular abnormalities were noted with the following distribution: 5(5), 4(4), 10(7), and 19(9). These findings were both statistically significant at 300 mg/kg/day, and the increased incidence of cardiovascular abnormalities was judged to be biologically significant at 100 mg/kg/day. Appropriate historical control data submitted by the performing laboratory support and confirm these conclusions. At the 300 mg/kg/day dose level, an increase in fetal death (40.7% resorptions as compared to 6.0% in controls), a 40% decrease in live litter size, and a 6-9% decrease in fetal body weights were attributed to treatment. At the same dose level, significantly increased incidences of wavy ribs (18 fetuses, representing 10 of 17 litters) and a 3.4% decrease in the mean number of ossified sacrococcygeal vertebral bodies were attributed to treatment. **Developmental LOAEL = 100 mg/kg/day; Developmental NOAEL = 30 mg/kg/day,** based on a biologically significant increase in cardiovascular abnormalities, particularly ventricular septal defect; at 300 mg/kg/day, statistical significance was achieved for these observations and the following additional findings were noted: increased resorptions and decreased number of viable fetuses, decreased fetal body weight, increased abnormalities of the ribs (wavy), and decreased numbers of ossified sacrococcygeal vertebral bodies.

The above findings were generally similar to those observed in the oral developmental toxicity study in rats conducted with S-53482 (MRID No. 42684925, Teratology Study of S-53482 Administered Orally to Rats, performed by Sumitomo Chemical Co. Ltd., for Valent U.S.A. Corporation, project No. 1759, August 28, 1990). **[SEE ABOVE]** In that study, a dose- and treatment-related increase in the incidence of cardiovascular abnormalities, particularly ventricular septal defect, was noted for fetuses of dams treated on days 6-15 of gestation.

CORE CLASSIFICATION: **not acceptable/guideline; does not satisfy the requirement (83-3) for a dermal developmental toxicity (teratology) study in rats;** this study can be upgraded to acceptable following the receipt of the following acceptable individual fetal observation data: body weight, external observations, visceral findings, and skeletal findings.

Oral Developmental Toxicity Study in Rabbits

MRID No. 42684927 (range-finding); 42684928 (main study)

Executive Summary: In a developmental toxicity study, New Zealand White rabbits received V-53482 (94.8% purity) daily via gavage at doses of 0, 300, 1000, or 3000 mg/kg/day on gestational days (GDs) 7-19, inclusively.

Group mean body weight gain (kg) during dosing (gestation days 7-19) were as follows (0, 300, 1000 or 3000 mg/kg/day): 0.17, 0.18, 0.14 and 0.05 ($p<0.05$). Group mean food consumption (g/kg/day) during dosing were as follows: 42.9, 42.1, 39.4 and 35.7 ($p<0.05$). No other parameters (maternal or developmental) were considered to have been affected by test article administration.

Maternal LOAEL = 3000 mg/kg/day based on decreased body weight and food consumption mostly during the dosing period
Maternal NOAEL = 1000 mg/kg/day

Developmental LOAEL = not determined
Developmental NOAEL = 3000 mg/kg/day

This study is considered to be **acceptable/guideline** and meets the requirements to fulfill 83-3 for a developmental toxicity study in rabbits.

SPECIAL STUDY

Critical Period for Developmental Toxicity Induced by S-53482 in Rats

MRID No. 42884006

Executive Summary: This study was designed to provide supplementary information on the developmental toxicity of S-53482 in rats. A single 400 mg/kg oral dose of S-53482 was administered to five groups of pregnant 4-5 Crj:CD Sprague-Dawley rats on day 11, 12, 13, 14 or 15 of gestation. On day 20 of gestation, the rats were sacrificed and necropsied. The uteri were examined, implantation sites were counted, and the numbers of corpora lutea were determined. The fetuses were removed, weighed, sexed, and examined for external anomalies. They were then processed for visceral evaluation, and the heart of each fetus was examined for the presence of ventricular septal defect.

Mean incidences of embryonic death (resorptions) for each day of administration (days 11, **12,** 13, 14 and 15) were 2.7, **39.4,** 16.1, 9.9 and 6.3%, respectively. For the same groups, mean male fetal body weights were 3.34, **3.23,** 3.73, 3.59 and 3.67 g; and mean female body weights were 3.22, **2.95,** 3.49, 3.14 and 3.46 g, respectively. The incidences of ventricular septal defects were 6.9, **14.0,** 5.8, 4.7 and 2.2%, respectively, for each day of administration. For the induction of each effect (embryolethality, retarded growth, and the cardiovascular anomaly, ventricular septal defect), the most sensitive developmental stage was identified as gestation **day 12.** This conclusion is supported by the study data for the conditions of this study. Other conclusions proposed by the study, that 1) the mechanism of perturbation could be common to all three endpoints and that 2) S-53482 does not have a primary effect on fetal heart tissue, are reasonable speculation; however, this study neither confirmed nor disproved these hypotheses.

This study was determined to be **acceptable/supplementary.** Although **this study does not satisfy the requirement (83-3) for an oral developmental toxicity (teratology) study in rats,** it provides acceptable supplementary information related to that guideline; this study **cannot be upgraded.**

4. Reproductive Toxicity Study

A Two-Generation Reproduction Study (dietary admix) in Rats

MRID No. 42684934 and 42684936 (pilot studies); 42684935 (main study)

Executive Summary: In a two-generation reproduction study, Sprague-Dawley rats were fed V-53482 (94.8% purity) in the diet at dosage levels of 0, 50, 100, 200 or 300 ppm (during premating, at least 0, 3.2, 6.3, 12.7, and 18.9 mg/kg/day in males and 0, 3.8, 7.6, 15. 1, and 22.7 mg/kg/day in females, respectively).

There were no definitive clinical signs attributed to test article administration in males of either generation. In F0 females only, there was an increase ($p<0.01$) in the incidence of "red substance in vagina" only at 300 ppm (9/25 versus 0-1/27-30 for the other 4 groups). The mortality in the F1 females was as follows for 0, 50, 100, 200 or 300 ppm: 0, 1, 0, 0 and 5 ($p<0.01$).

Group mean body weight gains were less than control ($p<0.05$ or 0.01) in F1 males and females during the first week of premating. During gestation, F0 and F1 females had lower body weight gain ($p<0.01$) during the last 5 days and for the entire period of gestation(28-31% decrease in gain). There was a decrease in food consumption in 300 ppm females of both generations: F0, 65-84% of control during lactation ($p<0.05$ or 0.01); F1, 92-95% of controls during gestation ($p<0.05$ or 0.01); and F1, 78-89% of control during lactation ($p<0.05$ or 0.01).

The incidence of grossly observable yellow livers was increased in 300 ppm F1 females that died ($p<0.01$, 3/30 versus 0/30 for controls). There was a decrease ($p<0.01$) in absolute only testis and epididymides weights in 300 ppm F1 males (not F0). [Study authors excluded all rats with small organs from the analysis.] No definitive histopathological changes were attributed to test article administration. There was the suggestion of atrophied/hypoplastic/hypospermia of the testes and/or epididymides in both generations of 300 ppm males (of 30 males examined in 0 and 300 ppm groups, the treated group had no more than one finding more than the control group). Tissues from the 100 and 200 ppm (and most of the 50 ppm) groups were not evaluated. In F1 300 ppm females that died, liver lobular necrosis and bile stasis was observed (2-3/4 examined).

Systemic LOAEL = 300 ppm (mg/kg/day: males = 18.9, females = 22.7) based on increased clinical signs (F0 females); increased mortality (Fl females), gross and histopathology findings in the liver (Fl females); decreased body weight/weight gain (F0 and Fl females during gestation, Fl males during the early portion of premating); and decreased food consumption (F0 and Fl females during lactation).

Systemic NOAEL = 200 ppm (mg/kg/day: males = 12.7, females = 15.1)

In both generations, the following reproductive parameters were affected primarily at 300 ppm and to a lesser extent at 200 ppm: females with liveborn (300 ppm, 16/21 for Fl pups and 16/18 for F2 pups; control, 23/23 and 23/23); mean number of live pups/litter on day one of lactation (300 ppm 7/9; control, 14/16); mean pup weight on lactation day one (300 ppm, 5.7/5.6 g; 200 ppm, 6.1/6.1; control, 6.9/6.4).

Reproduction/Offspring LOAEL = 200 ppm (mg/kg/day: males = 12.7, females = 15.1) based on decreased number of females with liveborn and mean number of pups/litter on lactation day 1, decreased pup body weight, testicular atrophy in F1 males and decreased mating index.

Reproduction/Offspring NOAEL = 100 ppm (mg/kg/day: males = 6.3, females = 7.6)

This study is classified **acceptable/guideline** and meets the requirements of 83-4 for a two generation reproductive toxicity study in rats.

NOTE: The HIARC had concern regarding statistical analyses of group mean absolute and relative male reproductive organ weights because analyses were performed after removal of values for all animals which were grossly abnormal. In addition, male mating and fertility indices were calculated after elimination of data from these affected males. The elimination of affected animals from summary calculations were considered inappropriate as it led to the masking of information that suggested a treatment-related effect on male reproduction at the highest dose tested (300 ppm; mg/kg/day = 18.9).

5. Additional Information from Literature Sources

The following literature sources were searched (October 12, 2000):

DialogClassic Web

Developmental and Reproductive Toxicology Databank (DART) from the National Library of Medicine TOX-NET system

Toxicology Literature Online Databank (TOXLINE) from the National Library of Medicine TOX-NET system.

The following published articles were found (these appeared to be presented in submitted studies and DERs have been generated):

Species difference in protoporphyrin IX accumulation produced by an N-phenylimide herbicide in embryos between rats and rabbits, Kawamura, S. *et al.* Toxicology and Applied Pharmacology, 1996, Dec.; 141(2):520-5.

Histological changes in rat embryonic blood cells as possible mechanism for ventricular septal defects produced by an N-phenylimide herbicide. Kawamura,S. *et al.* Teratology, 1996, Nov.; 54(5): 237-44.

Species difference in developmental toxicity of an N-phenylimide herbicide between rats and rabbits and sensitive period of the toxicity to rat embryos. Kawamura, S *et al.* Congenital Anomalies, 1995, Mar.; 35(l): 123-32.

6. Pre-and/or Postnatal Toxicity

A. Determination of Susceptibility

There was evidence of quantitative susceptibility following oral and dermal exposures to rats. Following *in utero* exposures, developmental effects (cardiovascular anomalies) were seen at lower doses in the absence of maternal toxicity.

There was no evidence (quantitative or qualitative) of susceptibility following *in utero* oral exposure in rabbits. No developmental toxicity was seen at the highest dose tested (3 x the Limit-Dose).

There was quantitative evidence of susceptibility in the multigeneration reproduction study where effects in offspring were seen at doses lower than those which induced effects in parental animals.

B. Degree of Concern Analysis and Residual Uncertainties

Since there is evidence of increased quantitative susceptibility of the young following exposure to flumioxazin in the oral and dermal developmental toxicity studies, a Degree of Concern Analysis was performed to: 1) determine the level of concern for the effects observed when considered in the context of all available toxicity data; and 2) identify any residual concerns after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment of this chemical. If residual concerns are identified, HIARC examines whether these residual concerns can be addressed by a special FQPA safety factor and, if so, the size of the factor needed.

Although increased prenatal and postnatal quantitative susceptibility was seen in rats, the HIARC concluded that there is a low concern and no residual uncertainties for pre-and/or postnatal toxicity because: (1) developmental toxicity NOAELs/LOAELs are well characterized after oral and dermal exposure; (2) off-spring toxicity NOAEL/LOAEL are well characterized; (3) there is a well defined dose-response curve for the cardiovascular effects seen following oral exposure (i.e., critical period); and (4) the end points of concern are used for overall risk assessments for the appropriate route and population subgroups.

C. Special FQPA Safety Factor(s):

Based on the above described data, no special FQPA Safety Factor is needed (i.e. 1x) since there are no residual uncertainties for pre- and/or post-natal toxicity.

The Special FQPA Safety Factor recommended by the HIARC **assumes** that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk

assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

7. Recommendation for a Developmental Neurotoxicity Study

The HIARC concluded that a developmental neurotoxicity study is not required.

A. Evidence that suggests requiring a Developmental Neurotoxicity study:

- None
- The cardiovascular malformations are not indicative of neurotubular origin and therefore are not a concern for developmental toxicity.

B. Evidence that does not suggest a need for a Developmental Neurotoxicity study:

There was no evidence in any of the submitted studies (acute, subchronic, chronic, developmental or reproduction) that flumioxazin had an effect on the nervous systems.

II HAZARD IDENTIFICATION

1. Acute Reference Dose (aRfD) - General population including infants and children

No appropriate endpoint was found for the general population that was considered attributable to a single dose.

2. Acute Reference Dose (aRfD) - Subpopulation of Females 13-49 years of age

Studies: (1) Developmental Oral Toxicity Study in Rats

(2) Supplemental Information on Prenatal Developmental Toxicity (Critical Period for Developmental Toxicity Induced by S53482 in Rats)

MRID Nos.: (1) 42684930 (pilot study); 42684925 (main study)
(2) 42884006

Executive Summaries: See Section I.3, Developmental Toxicity Study Conclusions

Dose and Endpoint for Establishing RfD: Developmental NOAEL = 3 mg/kg/day based on a biologically significant increase in cardiovascular abnormalities, particularly ventricular septal defect, at a LOAEL of 10 mg/kg/day.

Uncertainty Factor(s): 100 (based upon 10x for intraspecies variability and 10x for interspecies extrapolation)

Comments about Study/Endpoint Uncertainty Factor(s): The cardiovascular effect (ventricular septal defect) that was noted at the LOAEL of 10 mg/kg/day may have been the result of a single dose of flumioxazin. At 30 mg/kg/day, statistical significance was achieved for these observations. The second (2) study (MRID No. 42884006) indicated that a single oral dose on gestation day 12 caused the cardiovascular effect. In this study, 400 mg/kg was administered on only one gestation day (either day 11, 12, 13, 14 or 15). Although the dose (400 mg/kg) was 40 times the LOAEL in the developmental study (10 mg/kg/day), the same effect was reported.

Acute RfD = $\frac{\text{3 mg/kg NOAEL)}}{\text{100 (UF)}}$ = **0.03 mg/kg**

3. Chronic Reference Dose (RfD)

Study: Combined Chronic Toxicity/Carcinogenicity Rat Feeding Study
83-5 (870.4300)

MRID No.: 44295028

Executive Summary: In a combined chronic/oncogenicity study (MRID 44295028), flumioxazin (technical, 94.8% a.i., S-53482) was administered in the diet for up to 24 months to 74 Sprague-Dawley rats/sex/dose at levels of 0, 50, 500, and 1000 ppm (equivalent to 0, 1.8, 18.0, and 36.5 mg/kg/day in male rats and 0, 2.2, 21.8, and 43.6 mg/kg/day in female rats). At approximately 52 and 78 weeks 10-14 rats per group were terminated and all remaining animals were terminated at approximately 104 weeks.

Survival rates, clinical observations, clinical chemistry, ophthalmoscopic, urinalysis, and gross pathologic parameters were unaffected by treatment with S-53482.

Minor changes (2-15%) in hematological parameters (hemoglobin, MCV, MCH, MCHC) in the mid- and high-dose females were consistent with a chronic mild anemia. The presence of circulating erythroblasts in peripheral blood, reticulocytosis, decreased bone marrow Myeloid/Erythroid ratio (↓49%, $p<0.05$) and splenic extramedullary hematopoiesis (8/10 treated; 6/10 controls, $p<0.05$) are consistent with a severe stress on

erythropoiesis similar to what might be observed in chronic iron deficiency. However, the relatively moderate decreases in hemoglobin and lack of progression to a more severe type of anemia such as aplastic anemia or pancytopenia indicate successful compensatory erythropoiesis.

Histopathological changes of the kidney indicative of slight to mild chronic nephropathy were found at the final necropsy in the 500 and 1000 ppm male groups (26-27/33 treated vs 13/31 controls, $p<0.01$).

The chronic LOAEL is 500 ppm (equivalent to 18.0 and 21.8 mg/kg/day in males and females, respectively) based upon decreased hemoglobin, MCV, MCH and MCHC in females and increased incidence of chronic nephropathy in males. The chronic NOAEL is 50 ppm (equivalent to 1.8 and 2.2 mg/kg/day in males and females, respectively).

Under the conditions of this study, there was no evidence of carcinogenic potential.

Dosing was considered adequate due to hematological and histopathological changes observed in the mid- and high-dose animals.

This study is classified as **acceptable/guideline (§83-5; 870.4300)** and satisfies the guideline requirements for a combined chronic toxicity study and a carcinogenicity study in rats.

Dose and Endpoint for Establishing RfD: NOAEL of 1.8 mg/kg/day based on the LOAEL of 18.0 mg/kg/day where there was decreased hemoglobin, MCV, MCH and MCHC in females and increased chronic nephropathy in males.

Uncertainty Factor(s): 100 (based on 10x for inter-species extrapolation and 10x for intra-species variability).

Comments about Study/Endpoint/Uncertainty Factor(s): The NOAEL that was selected for the chronic RfD was based on a study of appropriate duration and exposure.

Chronic RfD = $\frac{1.8 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}}$ = **0.018 mg/kg/day** [rounded to 0.02 mg/kg/day]

4. Incidental Oral Exposure: Short-Term (1-30 days)

Study: Two-generation Reproduction Study (dietary admix) in Rats 83-4 (870.3800)

MRID Nos.: 42684934 and 42684936 (pilot studies); 42684935 (main study)

Executive Summary: See Section I.4, Reproductive Toxicity Study

Dose and Endpoint for Risk Assessment: Offspring NOAEL of 6.3 mg/kg/day based on decreased pup body weight at 12.7 mg/kg/day (LOAEL).

Comments about study/Endpoint: The dose/endpoint is appropriate for the population (infants and children) and duration (1-30 days) of concern.

5. Incidental Oral Exposure: Intermediate-Term (1-6 Months)

Study: Two-Generation Reproduction Study in Rats 83-4 (870.3800)

MRID Nos.: 42684934 and 42684936 (pilot studies); 42684935 (main study)

Executive Summary: See Section I.4, Reproduction Toxicity Study

Dose and Endpoint for Risk Assessment: Offspring NOAEL of 6.3 mg/kg/day based on decreased pup body weight at 12.7 mg/kg/day (LOAEL).

Comments about Study/Endpoint: The dose/endpoint is appropriate for the population (infants and children) and duration (1-30 days) of concern.

6. Dermal Absorption

Dermal Absorption Factor: 8%

The maximum amount of dermal absorption is 8% based on the results of the three studies described below.

Studies:	(1) Dermal Absorption in the Rat	85-3 (870.7600)
	(2) Dermal Absorption in the Rat	85-3 (870.7600)
	(3) Dermal Absorption in the Pregnant Rat	85-3 (870.7600)

MRID Nos.: (1) 42684944
(2) 42684932
(3) 42684931

Executive Summaries:

(1) [Phenyl-U-14C]S-53482; Radiopurity > 99%; Chemical purity > 99%; S-53482, lot C-91019A; 50 WDG lot LE9302. Twenty-four male Sprague-Dawley (CD) rats/dose

group received [phenyl-U-^{14}C]S53482 by the dermal route at levels of 0.02, 0.20, or 1.0 mg/rat (0.002, 0.020 and 0.100 mg/cm^2) as a suspension of 50 WDG formulation in water. Four rats/dose level were sacrificed for assessment of dermal absorption after 0.5, 1, 2, 4, 10 or 24 hours of exposure. At 0.02 mg/rat absorption ranged from 0.48% of the dose at 0.5 hours to 5.46% (and up to 18.5% including excised skin residue) by 24 hours. At 0.2 mg/rat (0.02 mg/cm^2), absorption ranged from 0.007% of the dose at 0.5 hours to 0.74% (and up to 2.3% including excised skin residues) at 24 hours. At 1.0 mg/rat (0.02 mg/cm^2), absorption ranged from 0.004% of the dose at 0.5 hours to 0.47% (and up to 2.4% including excised skin residue) at 24 hours.

(2) [Phenyl-U-^{14}C]S-53482; Radiopurity > 99%; Chemical purity > 99% [Lot No. C-88-084]. Two groups of 15 female rats/group were dosed dermally with [phenyl-U-^{14}C]S--53482 in corn oil at 200 or 800 mg/kg body weight (approximately 2.7 and 11.8 mg/cm^2, respectively). Three rats/dose group were sacrificed at 0, 2, and 6 hours after initiation of exposure. For the remaining 6 rats/dose group, exposure was terminated at 6 hours followed by sacrifice of 3 rats/dose group at 24 and 48 hours after the initiation of dosing. In addition, two groups of 12 rats/group were dosed by oral gavage at doses of 1 or 30 mg/kg. Three rats/dose group were sacrificed at 2, 6, 24 and 48 hours after dosing.

Dermal absorption values for the 200 and 800 mg/kg doses amounted to 3.9 and 8.0% of the dose by 48 hours after the initiation of treatment for a 6-hour exposure. Blood levels of radioactivity at 6-24 hours after dermal dosing (0.24-0.48 ppm) with 200 mg/kg were similar to those obtained at 2-6 hours after oral dosing (0.24-0.15 ppm) with 1 mg/kg. Blood levels of radioactivity at 6-24 hours after dermal dosing (1.53-1.96 ppm) with 800 mg/kg were similar to those obtained at 2-6 hours after oral dosing (1.87-1.59 ppm) with the 30 mg/kg.

Comments about Dermal Absorption: In study (1), by 24 hours, the percent absorption (0.02, 0.20 and 1.0 mg/rat or 0.002, 0.020 and 0.100 mg/cm^2) was up to: 5.46% (and up to 18.5%) including excised skin residue; 0.74% (and up to 2.3% including excised skin residue); and 0.47% (and up to 2.4% including excised skin residue). In study (2), 200 and 800 mg/kg doses resulted in 3.9 and 8.0 % absorption of the dose by 48 hours after the initiation of treatment for a 6-hour exposure.

(3) In a dermal absorption study, 12 Scl:SD pregnant rats (gestation day 13) were dosed dermally with [phenyl-U-^{14}C]S-53482 in corn oil at a level of 100 mg/kg (approximately 1.9 mg/cm^2). Groups of 3 rats were sacrificed at 2 and 6 hours after initiation of exposure. For the remaining 6 rats, exposure was terminated at 6 hours followed by sacrifice of groups of 3 rats at 24 and 48 hours after the initiation of dosing.

Dermal absorption values amounted to 4.3 and 5.8% of the dose by 24 and 48 hours, respectively, after the initiation of treatment for a 6 hour exposure. Radioactivity was evident in blood (0.14 ppm equivalents) as early as 2 hours after the initiation of

exposure. Blood levels of radioactivity 24 hours after initiation of dermal dosing for 6 hours amounted to 0.06 and 0.04 ppm equivalents at the 24- and 48-hour sacrifices, respectively. These results indicate that dermal application of [phenyl-U-^{14}C]S-53482 to pregnant rats results in exposure of the fetuses to radioactivity from the test material.

There is already a Core minimum rat dermal absorption study with [phenyl-U-^{14}C]S--53482 (N. Isobe, 3/31/92, study No. 2326, MRID 42684944) which satisfies EPA Guideline 85-2. The present study provides acceptable information on the dermal absorption of S-53482 by pregnant rats and is intended by the authors to be a supplement to the data presented in oral and dermal rat teratology studies.

7. Dermal Exposure (All Durations)

Study: Developmental Dermal Study in Rats (870.3700; 83-3)

MRID No.: 42684929 (pilot); 42684926 (main study)

Executive Summary: See Section I.3, Developmental Toxicity Study Conclusions

Dose and Endpoint for Developmental Risk Assessment: NOAEL = 30 mg/kg/day based on a biologically significant increase in cardiovascular abnormalities, particularly ventricular septal defect, at 100 mg/kg/day (LOAEL)

Comments about Study/Endpoint:

This dose/endpoint is appropriate since the study (dermal) simulates the exposure scenario (dermal) of concern and addresses the concern for developmental toxicity seen via this route. The Committee concluded that this study is appropriate for all durations because of the developmental toxicity concerns which were not measured in the 21-day dermal study. The HIARC usually recommends the oral NOAEL selected for chronic dietary risk assessment to assess long-term dermal risk. In this case, the developmental NOAEL was selected for all time periods including long-term since the use of the oral NOAEL of 2.0 mg/kg/day (chronic RfD) with a 8% dermal absorption factor yielded a dermal equivalent dose of 25 mg/kg/day (2.0 ÷ 0.08 = 25) which is comparable to the selected dermal NOAEL of 30 mg/kg/day.

8. Inhalation Exposure (Short-Term)

Study: The HIARC selected the oral NOAELs for inhalation exposure risk exposure.

Short-Term: Developmental (oral) Toxicity Study in Rats 83-3 (870.3700)
MRID No.: 42684930 (pilot); 42684925 (main study)

Executive Summary: See Section I.3, Developmental Toxicity Study Conclusions

Dose and Endpoint for Risk Assessment:

Developmental oral NOAEL = 3.0 mg/kg/day

Comments about Study/Endpoints: In the absence of repeated inhalation toxicity studies, oral doses were selected. Absorption via the inhalation route is presumed to be equivalent to oral absorption.

9. Inhalation Exposure (Intermediate- and Long-term)

Study: The HIARC selected the oral NOAELs for inhalation exposure risk exposure.

Combined Chronic/Carcinogenicity Study in Rats 83-3(870.3700)
MRID No.: 44295028

Executive Summary: See Section II.3, Chronic Reference Dose

Dose and Endpoint for Risk Assessment:

Oral NOAEL = 2.0 mg/kg/day

Comments about Study/Endpoints: In the absence of repeated inhalation toxicity studies, oral doses were selected. Absorption via the inhalation route is presumed to be equivalent to oral absorption.

10. Margins of Exposure

Summary of target Margins of Exposure (MOEs) for risk assessment.

Route / Duration	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	100	100	100
Inhalation	100	100	100
Residential (Non-Dietary) Exposure			
Oral	100	100	N/A

Route / Duration	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Dermal	100	100	100
Inhalation	100	100	100

For Occupational Exposure: A MOE of 100 is required. This is based on the conventional uncertainty factor of 100X (10X for intraspecies extrapolation and 10X for interspecies variation).

For Residential Exposure: A MOE of 100 is required. This is based on the conventional uncertainty factor of 100X (10X for intraspecies extrapolation and 10X for interspecies variation).

11. Recommendation for Aggregate Exposure Risk Assessments

For short- and intermediate-term aggregate exposure risk assessment, the incidental oral exposure cannot be combined with dermal or inhalation exposure due to differences in the toxicity end points via the oral (body weight and testicular atrophy), dermal (cardiovascular defects) and inhalation (cardiovascular defects) routes. For long-term aggregate exposure risk assessments, the dermal (cardiovascular) and inhalation (nephrotoxicity) pathways cannot be combined.

III CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No.: 44295028

Executive Summary: See Section II.3, Chronic Reference Dose

Discussion of Tumor Data: Flumioxazin did not increase the incidence of tumors over concurrent control and/or historical control values.

Adequacy of Dose Levels Tested: The animals were administered flumioxazin at doses up to 1000 ppm (36.5 mg/kg/day in males and 43.6 mg/kg/day in females). At a LOAEL of 18.0 mg/kg/day, there was decreased hemoglobin, MCV, MCH and MCHC in females and increased chronic nephropathy in males. Because of these effects, it was considered that the dose levels tested were adequate.

2. Carcinogenicity Study in Mice

MRID No.: 44295018

Executive Summary: In a mouse oncogenicity study (MRID 44295018), flumioxazin technical, 94.8% a.i. (S-53482) was administered in the diet for 78 weeks to 51 CD-1 mice/sex/dose at levels of 0, 300, 3000 or 7000 ppm which is equivalent to dietary levels of 0, 31.1, 314.9 or 754.1 mg/kg/day in males and 0, 36.6, 346.4,or 859.1 mg/kg/day in females, respectively. An additional 15 mice/sex/dose were used to provide samples for hematological examination, pathology and histopathology. These animals were terminated at 53 weeks. All remaining animals were sacrificed at 79 weeks of the study.

Survival rates, clinical observations, body weights, feed consumption, organ weights, gross pathology and hematological parameters were unaffected by treatment with S-53482. No clinical chemistry was performed.

There were statistically significant increases in malignant lymphoma/leukemia in mid-dose males (6/15 treated; 1/14 controls, $p<0.05$) and increases in pulmonary adenoma in mid-dose females (5/51 treated; 0/50 control, $p<0.05$), these tumor incidences were comparable to historical controls and did not exhibit dose-dependency.

The LOAEL was not observed. The chronic NOAEL is $\geq$ 7000 ppm which is equivalent to 754.1 and 859.1 mg/kg/day in male and female mice, respectively.

Under the conditions of this study, there was no evidence of carcinogenic potential.

Dosing was considered adequate because the highest dose of 7000 ppm represented a "limit dose".

This study is classified as **acceptable/guideline (§83-2b; 870.4200)** and satisfies the guideline requirements for a carcinogenicity study in mice.

Discussion of Tumor Data: Flumioxazin did not increase the incidence of tumors over concurrent control and/or historical control values.

Adequacy of the Dose Levels Tested: The animals were administered flumioxazin at the limit dose (7000 ppm).

3. Classification of Carcinogenic Potential

In accordance with the draft 1999 "Proposed Guidelines for Carcinogen Risk Assessment", the HIARC Committee determined that the chemical was **"not likely to be**

carcinogenic to humans." Flumioxazin did not induce significant increases in any tumor type in either rats or mice under the conditions of the studies.

IV MUTAGENICITY

The HIARC concluded that the submitted mutagenicity studies are adequate and flumioxazin is not mutagenic in various *in vivo* and *in vitro* mutagenic assays.

In Vitro Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells

MRID No.: 42684939

Positive in the Chinese hamster ovary in vitro cytogenetics assay at S9-activated concentrations ≥ 100 µM (35 µg/mL). S-53482 (98.2% purity) was negative at all nonactivated levels, 30, 100, 200, and 500 µM (11, 35, 70, and 177 µg/mL, respectively), and at S9-activated 30 µM. The test material precipitated at 200 and 500 µM -S9 and at 100, 200, and 500 µM +S9, and was cytotoxic at 500 µM ±S9. The predominant forms of aberrations were chromatid breaks and chromatid exchanges. An acceptable in vivo chromosome aberration assay showing that S-53482 was negative in rat bone marrow was also submitted (see DER for MRID No. 42684940).

This study is Acceptable and satisfies the data Guideline requirement 84-2 for genetic effects Category 11, Structural Chromosomal Aberrations.

In Vivo Chromosome Aberration in Rat Bone Marrow Cells

MRID No:. 42684940

Negative in the rat bone marrow in vivo cytogenetics assay in male and female rats orally administered 1250, 2500, or 5000 mg/kg (94.8% purity) using a 24-hour harvest. Also negative at oral gavage doses of 5000 mg/kg (males) or 4400 mg/kg (females) with harvests at 6, 12, 24, and 48 hours. Levels that were systemically toxic and cytotoxic to the target tissue were attained. Body weight was significantly ($p<0.05$) reduced in the high-dose males and in the mid- and high-dose females. The ratio of PCEs was significantly ($p<0.01$) decreased in males at all dose levels, and in low- and high-dose females ($p<0.05$). An acceptable in vitro chromosome aberration assay showing that S-9 activated S-53482 was clastogenic in Chinese hamster ovary (CHO) cells was also submitted (see DER for MRID No. 42684939).

This study is Acceptable and satisfies the data Guideline requirement (84-2) for genetic effects Category II, Structural Chromosomal Aberrations.

In Vivo Unscheduled DNA Synthesis Assay in Rat Hepatocytes

MRID No.: 42684941

Negative for inducing unscheduled DNA synthesis (UDS) in hepatocytes recovered from male Sprague-Dawley rats 3, 12, or 24 hours post exposure by oral gavage to 5000 mg/kg S-53482 (94.8% purity) or 12 hours post exposure to 1250 or 2500 mg/kg S-53482. No signs of overt toxicity were reported; however, possible interaction with the target organ, suggested by a decrease in hepatocyte viability, was observed in the 5000 mg/kg treatment groups at the 3- and 12-hour harvest times.

This study is Acceptable and satisfies the requirements for Guideline 84-4 for in vivo UDS mutagenicity study.

In Vivo Micronucleus Assay with Mice

MRID No.: 42684942

No conclusions can be reached from the micronucleus assay conducted with male mice (4/group) exposed to 300, 1000, or 5000 mg/kg S-53482 or S-23031 by intraperitoneal injection with a cell harvest only at 24 hours posttreatment. Numerous technical and reporting deficiencies (see Section D, Reviewers' Discussion/Conclusions) preclude acceptance of the study results as valid.

This study is classified as **Unacceptable** and does not satisfy the guideline requirements for a micronucleus assay (84-2).

Microbial/Mammalian Microsome Preincubation Mutagenicity Assay

MRID No.: 42684938

In two independently performed microbial mammalian microsome preincubation assays, Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, or TA100 and Escherichia coli strain WP2uvrA were exposed with or without metabolic activation to 0, 50, 100, 200, 500, 1000, or 2000 µg/plate S-53482. Preparations for metabolic activation were made from induced rat livers. S-53482 was delivered in dimethyl sulfoxide.

The test material was neither cytotoxic nor mutagenic in S. typhimurium strains TA1535, TA1537, or TA100 or in E. coli WP2uvrA. However, reproducible increases in revertant colonies of S. Typhimurium strains TA1538 and TA98 occurred in the S9--activated phases of the preliminary cytotoxicity and both mutation assays. The responses

were not clearly dose related, were seen at insoluble (>100 µg/plate) and soluble (≤1000 µg/plate) levels, and did not achieve a doubling over background at any concentration. We, therefore, consider the results to be equivocal. We assess, however, that since the study was properly conducted and the study author utilized the more sensitive preincubation modification to the standard plate incorporation assay, it is not likely that the findings would be substantively altered by repeating the test.

This study is classified as Acceptable and satisfies the guideline requirements for a gene mutation study (84-2).

V HAZARD CHARACTERIZATION

Flumioxazin (V-53482 WP) is a herbicide for control of broadleaf weeds in soybeans and peanuts. It is a low use rate preemergence herbicide which will be packaged as a 51% wettable powder in water soluble bags to minimize exposure to mixers/loaders. The product controls susceptible weeds as a preemergence treatment in conventional, minimum or no-tillage soybeans and preemergence treatment in peanuts. The chemical name is 7-fluoro-6-[(3,4,5,6-tetrahydro)phthalimido]-4-(2-propynyl)– 1,4-benzoxazin-3(2H)-one. The CAS number is 103361-09-7. It has a molecular weight of 354.

Flumioxazin has mild or no acute toxicity (categories III or IV) when administered orally or dermally. It has little or no toxicity (categories III or IV) regarding eye irritation or skin irritation. The acute inhalation study with the technical material was not acceptable (need data on particle size). The acute inhalation study with the use-formulation (flumioxazin 50 WDG) resulted in the classification of category I based on focal degeneration of the larynx cartilage. The chemical was not a dermal sensitizer.

Hematologic (hematopoietic) effects of anemia were noted in rats (alterations in hemoglobin, MCV, MCH and MCHC parameters). Increased absolute and relative liver weights and/or increased alkaline phosphatase values (>300%) were observed in dogs.

Flumioxazin administered orally and dermally to rats in developmental studies, resulted in cardiovascular anomalies (the most serious being ventricular septal defects). The same effects occurred by both routes with the oral being observed at 10 and the dermal at 100 mg/kg/day. A mechanistic oral developmental study in rats indicated that a single dose of 400 mg/kg caused the ventricular septal defects when administered on gestation day 12, but not when given on days 11 or 13 or 14 or 15. In the 2-generation reproduction study, systemic effects (clinical signs and mortality as well as a decrease in body weight/gain and food consumption) were noted at about 19 and 23 mg/kg/day in males and females, respectively; whereas, effects on the offspring (decrease in the number of liveborn and pup body weights) occurred at lower doses (about 13 and 15 mg/kg/day). Based on the lack of evidence of carcinogenicity in mice and rats, flumioxazin is classified as "not likely to be carcinogenic to humans".

VI DATA GAPS/Requirements

28-Day Inhalation Study in the Rat

VII. ACUTE TOXICITY

Acute Toxicity of FLUMIOXAZIN TECHNICAL

Guideline No.	Study Type	MRID #	Results	Toxicity Category
81-1	Acute Oral	42684911	LD_{50}>5000 mg/kg M & F	IV
81-2	Acute Dermal	42684913	LD_{50}>2000 mg/kg	III
81-3	Acute Inhalation	42684915	LC_{50} =3.93 mg/L	IV
81-4	Primary Eye Irritation	42684917	Not an ocular irritant	III
81-5	Primary Skin Irritation	42684917	Non-irritating	IV
81-6	Dermal Sensitization	42684921	Non-sensitizer	N/A
81-8	Acute Neurotoxicity	—	NOT AVAILABLE	---

VIII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

Summary of Toxicological Dose and Endpoints for Flumioxazin

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-49 years of age)	NOAEL = **3.0** mg/kg/day UF = **100** **Acute RfD = 0.03** mg/kg/day	FQPA SF = **1** **aPAD** = acute RfD / FQPA SF = **0.03** mg/kg/day	**Oral developmental and supplemental prenatal studies in rats** LOAEL = **10.0** mg/kg/day based on **cardiac effects (interventricular septal defects)**
Acute Dietary (General population including infants and children)	An endpoint attributable to a single dose (exposure) was not identified from the available studies, including the developmental toxicity studies in rats and rabbits.		
Chronic Dietary (All populations)	NOAEL= **2.0** mg/kg/day UF = **100** **Chronic RfD** = **0.02** mg/kg/day	FQPA SF = **1** **cPAD** = chronic RfD / FQPA SF = **0.02** mg/kg/day	**Two-year toxicity study in rats.** LOAEL = **18** mg/kg/day based on **decreased hemoglobin, MCV, MCH and MCHC in females and increased incidence of chronic nephropathy in males**
Short- and Intermediate-Term Incidental Oral (1-30 days)	NOAEL= **6.3** mg/kg/day	**Residential** LOC for MOE = **100** **Occupational** = NA	**Two-generation reproduction study in rats** LOAEL = **12.7** mg/kg/day based on **decreased pup body weight and testicular atrophy in F1 males**
Short-Intermediate- and Long-Term Dermal (1 to 30 days; 1 to 6 months; >6 months)	Dermal study NOAEL= **30** mg/kg/day	**Residential** LOC for MOE = **100** **Occupational** LOC for MOE = **100**	**Dermal Developmental Study in Rats** LOAEL = **100** mg/kg/day based on **cardiac effects (intraventricular septal defects)**

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Short-Term Inhalation (1 to 30 days)	Oral study NOAEL= **3.0** mg/kg/day (inhalation absorption rate = 100%)	**Residential** LOC for MOE = **100** **Occupational** LOC for MOE = **100**	**Oral Developmental Study in Rats** LOAEL = **10** mg/kg/day based on **cardiac effects (interventricular septal defects)**
Intermediate- and Long-Term Inhalation (1 to 6 months; >6 months)	Oral study NOAEL = **2.0** mg/kg/day (inhalation absorption rate = 100%)	**Residential** LOC for MOE = **100** **Occupational** LOC for MOE = **100**	**Two-year Toxicity** Study in Rats LOAEL = **18.0** mg/kg/day based on **decreased hemoglobin, MCV, MCH and MCHC in females and increased incidence of chronic nephropathy in males**
Cancer (oral, dermal, inhalation)	2.0 mg/kg/day UF = 100	SF = 1 0.02 mg/kg/day	Chronic Toxicity/Carcinogenicity Study in Rats LOAEL = 18.0 mg/kg/day based on decreased hemoglobin, MCV, MCH and MCHC in females and increased incidence of chronic nephropathy in males

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

NOTE: The Special FQPA Safety Factor recommended by the HIARC **assumes** that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

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PC Code:	**129034**
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