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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

TXR NO. 0052611

DATE: June 15, 2004

MEMORANDUM

SUBJECT: **Fluazifop-butyl/Fluazifop-P-butyl** - Report of the Hazard Identification Assessment Review Committee.

FROM: David G Anderson
Reregistration Branch 2
Health Effects Division (7509C)

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

TO: Diane Locke, Risk Assessor
Reregistration Branch
Health Effects Division (7509C)

PC Code: 122805/122809

On May 6, 2004, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for Fluazifop-butyl and Fluazifop-P-butyl 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 potential for increased susceptibility of infants and children from exposure to Fluazifop-butyl and Fluazifop-P-butyl was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The conclusions drawn at this meeting are presented in this report.

Committee Members in Attendance

Members present were: Ayaad Assaad, William Burnam, Ray Kent, Jessica Kidwell (Executive Secretary), John Liccione, Brenda May, Susan Makris, Elizabeth Mendez, Jess Rowland (Co-Chair), P.V. Shah, and Karen Whitby (Co-Chair)

Member(s) in absentia: Johnathan Chen and William Dykstra

Data evaluation prepared by: David G. Anderson

Also in attendance were: Diana Locke, Al Nielsen (HED/RRB2), Carmen Rodia (SRRD), James Parker (HED/RRB2), Pauline Wagner and Margaretta Collantes (HED/RAB2)

Data Evaluation / Report Presentation

David G. Anderson
Toxicologist

INTRODUCTION

On May 6, 2004, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for Fluazifop-butyl and Fluazifop-P-butyl 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 potential for increased susceptibility of infants and children from exposure to Fluazifop-butyl and Fluazifop-P-butyl was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996.

Fluazifop-P-butyl is a selective herbicide used in the post-emergent control of grasses in various broad leafed crops including various vegetables, bearing nut and fruit trees and ornamentals. It is especially important in the control of grass weeds after development of resistance to other herbicides. It is believed to act through inhibition of protein synthesis. It is a arylphenoxy ether ester, but appears to be less toxic than other arylphenoxy ether esters.

The purified fluazifop-P-butyl [R] isomer is supported for re-registration and the toxicity data base is sufficient for consideration for re-registration. The previously registered fluazifop-butyl [RS] isomeric mixture is not supported for re-registration.

I. FQPA HAZARD CONSIDERATIONS

1. Adequacy of the Toxicity Data Base

The HIARC concluded that the toxicology database for fluazifop-butyl and fluazifop-P-butyl is complete for FQPA evaluation. Acceptable developmental toxicity studies in rats and rabbits on fluazifop-butyl and fluazifop-P-butyl are available in addition to an acceptable 2-generation reproduction study in rats. Studies on fluazifop-butyl may be used to support fluazifop-P-butyl due to equivalency in toxicity.

2. Evidence of Neurotoxicity

The HIARC concluded that there was not a concern for neurotoxicity resulting from exposure to fluazifop-P-butyl at relevant exposure levels.

There was no evidence of clinical signs indicative of neurotoxicity or neuropathology in the available studies. Marginal increases in brain weights at termination were seen in a subchronic toxicity study in rats and a carcinogenicity study in hamsters but only at high doses.

3. Developmental Toxicity Study Conclusions

The data base included 7 developmental toxicity studies: 2 with fluazifop-butyl in Sprague-Dawley rats; 3 with fluazifop-P-butyl in Wistar rats; 1 with fluazifop-butyl in New Zealand rabbits; and 1 with fluazifop-P-butyl in New Zealand rabbits. These studies are summarized below:

3.1 Developmental Toxicity Studies in Rats:

3.1.1 . Fluazifop-butyl - Sprague Dawley Rats,

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 00088857, 92067047 and 92067019), fluazifop-butyl, [PP009 (94.8% a.i., batch/lot # P14)] was administered to 22 female CD Sprague Dawley strain rats/group in a corn oil (2 ml/kg) gavage at dose levels of 0, 10, 50 or 200 mg/kg bw/day from days 6 through 20 of gestation. Animals were killed on day 21 and uterine contents examined. Maternal body weights, food consumption and liver weights were collected. Ovaries were examined for corpora lutea and uteri were examined for implantation sites. Fetuses were weighed and examined externally and viscerally by free serial sectioning by Wilson's method and approximately half of the fetuses were examined skeletally by the method of Dawson.

No maternal toxicity was seen at any dose level. **For maternal toxicity, the NOAEL was 200 mg/kg/day (HDT); a LOAEL was not established.**

Delayed fetal growth occurred in the form of fetal weight decrement (12%) at 200 mg/kg/day and delayed ossification was seen at all dose levels.

Various parameters significant to development were affected relative to concurrent and/or historical controls. Post implantation loss was increased (125%) at 200 mg/kg/day. Examination of the heads of fetuses showed increased large fontanelles at 200 and 50 mg/kg/day (45.9% and 11.9%, respectively, versus 3.4% in concurrent controls. Increased incomplete and/or irregular ossification of cranial sutures at 200 and 50 mg/kg/day (58.9% and 43.7%, respectively, versus 14.3% in concurrent controls. The incidence of fissures into the interparietal bone was increased at 200 mg/kg/day (2.2% versus 0% in concurrent and historical controls. Only the percentages of fetal anomalies were presented with no litter incidence. No statistical analysis was presented for the fetal anomalies.

Increased incidence of incomplete ossification of thoracic vertebral centra at 200, 50 and 10 mg/kg/day (75.5%, 58.7, 48.4, respectively, versus 38.5% in concurrent controls, with a historical control range of 0-70.3%) appeared to be test material related. Increased incidence of absent hyoid bone at 200 and 50 mg/kg/day (23.0% and 17.2% versus 10.8% in concurrent controls. Increased incidence of incomplete ossification of one or more pelvic bones at 200 and 50 mg/kg/day (7.4% and 2.3%, respectively, versus 1.4% in concurrent control. Absent hyoid bone and incomplete and/or irregular ossification of the cranial bones and incomplete

ossification of one or more pelvic bones may have been increased at 50 mg/kg/day, but since concurrent controls were higher than the mean historical control, these effects may have been incidental. The incidence of bilateral hydronephrosis at 200 mg/kg/day exceeded the historical control mean but not the range. The incidence of bilateral hydroureter at 200 mg/kg/day exceeded the historical control range and mean. No hydronephrosis nor hydroureter was seen in concurrent controls. In addition, subcutaneous edema (17.7 at 200 mg/kg/day versus 3.4 in concurrent controls) exceeded the mean of 8.9% in historical controls (the upper range was unreadable). The concurrent controls also were less than the mean of historical controls.

Diaphragmatic hernia was seen in 1 fetus at 10 mg/kg/day none at 50 mg/kg/day and in 3 fetuses at 200 mg/kg/day with no incidences in 2970 historical control fetuses. However in a subsequent much larger study (MRID# 00088858) with 160 litter/group, showed an incidence of diaphragmatic hernias of 3/1113 in control fetuses, 1/1081 fetuses at 1 mg/kg/day, 3/1073 fetuses at 5 mg/kg/day, 2/1064 fetuses at 10 mg/kg/day and statistically significantly increased incidence in 59/1064 fetuses and 45/159 litters at 200 mg/kg/day. Since this anomaly was seen at a higher incidence (3 fetuses) in the controls in this study and was not replicated at the same dose in the second study, the single incidence of diaphragmatic hernia at 10 mg/kg/day was considered to be an aberration and not attributable to treatment.

For developmental toxicity, the LOAEL is 10 mg/kg/day based on incomplete and/or irregular ossification of the cranial bones and incomplete ossification of thoracic vertebral centra; a NOAEL was not established.

The developmental toxicity study in the rat is classified, **ACCEPTABLE (GUIDELINE)** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat.

3.1.2 Fuazifop-butyl - Sprague Dawley Rats

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 00088858, 92067048 and 92967020)[fluazifop-butyl, PP009 (94.8% a.i., batch/lot # P14)] was administered to 159 or 160 female CD Sprague Dawley strain rats/group in a corn oil (2 ml/kg) gavage at dose levels of 0, 1.0, 5.0, 10 or 200 mg/kg bw/day from day 6 through 20 of gestation. Animals were killed on day 21 and uterine contents examined. Maternal body weights, food consumption and uterine weights were collected. Ovaries were examined for corpora lutea and uteri were examined for implantation sites. Fetuses were weighed and examined externally and viscerally at post mortem and by Wilson's free serial sectioning method and approximately half of the fetuses were skeletal examined by the method of Dawson.

Maternal body weight during gestation was slightly, but statistically significantly reduced (2%, $p < 0.01$) at day 21 at 200 mg/kg/day; dose related decrease gravid uterine weight at all dose levels accounted for all the decrease (4% at 1.0 mg/kg/day to 14% at 200 mg/kg/day). The gravid uterine weight that was reduced at all dose levels may be partly due to incidental reductions in amnionic fluid weight (mean number of implants and number of viable fetuses were not reduced

at 1.0 or 5.0 mg/kg/day, placental weight was not reduced at 1.0, 5.0 or 10 mg/kg/day, and fetal weight was not reduced at 1.0 mg/kg/day. When corrected for gravid uterine weights, the body weights were comparable between treated and control groups. **For maternal toxicity, the NOAEL was 200 mg/kg/day (HDT); a LOAEL was established.**

There were no differences in the number of corpora lutea, but implantations decreased (3% to 4%, $p<0.5$ to $p<0.01$) at 10 mg/kg/day and above. Viable young, resorptions, pre- and post implantation loss were all comparable with concurrent control and within historical control ranges. Fetal weight showed a dose related decrease at 5 mg/kg/day and greater (3% to 13%, $p<0.001$ to $p<0.001$). The incidence of small fetuses less than 3.00 g in weight (mean control fetal weight was 3.60g±0.07) showed an increase at 200, 10 and 5 mg/kg/day (31.8%, 7.3%, 5.5%, respectively, versus 4.5% in concurrent control with a historical control mean of 3.7% and a range of 0-12.0%).

The delays in skeletal ossification such as incomplete ossification of thoracic and/or lumbar centra at ≥5 mg/kg/day are consistent with fetal weight decrement. Dose related incomplete ossification of one or more thoracic vertebral centra (54.5% versus 41.55 in control with a mean of 39.6% and a range of 15-70% in historical controls) and a dose related absent hyoid bone (15% versus 10% in controls with a mean of 7% and range of 0-23% in historical controls) were seen at ≥5 mg/kg/day. The absent hyoid bone may represent unossified hyoid or may have been miss-classified. Some of these delays in ossification were considered biologically significant at 10 mg/kg/day and 200 mg/kg/day, only.

Total hydroureter (free hand sectioning and post mortem) was significantly increased in litters at 5 mg/kg/day and greater (56%-81% versus 40.0% in concurrent controls) and in fetuses (8.2 - 19% versus 4.5% in concurrent controls with 5.9% in historical controls).

Diaphragmatic hernia (free hand sectioning and post mortem) showed an increased incidence in fetuses (5% versus 0.13% in control) and litters (43.4% versus 1.9%) at 200 mg/kg/day. In addition to the diaphragmatic hernias other anomalies were seen at 200 mg/kg/day, such as kidney and ureter anomalies, ectopic testes, head anomalies, incomplete and reduced ossification.

No statistical analysis was conducted on fetal anomalies other than hydroureter and diaphragmatic hernia. However, the study authors acknowledged the incidence of delayed ossification in the hyoid bone, thoracic and vertebral centra were decreased at 5 and 10 mg/kg/day as well as 200 mg/kg/day.

For developmental toxicity, the NOAEL is 1 mg/kg/day and the LOAEL is 5 mg/kg/day based on delays in skeletal ossifications such as incomplete ossification of thoracic and/or lumbar centra and fetal weight decrements.

The developmental toxicity study in the rat is classified **ACCEPTABLE (GUIDELINE)**; and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD

414) in the rat.

3.1.3 Fluazifop-P-butyl - Wistar Rats

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 46028903)[Fluazifop-p-butyl, calculated as 90.9% a.i.; batch/lot# BX 247T A10209)] was administered to [(24 females) Alderly Park strain of Wistar rats] rats/dose by gavage at dose levels of 0, 2, 5 or 100 mg a.i./kg bw/day from days 7 through 21 of gestation.

No maternal toxicity was seen. The statistically significant decrement in food consumption seen between gestational days 16 and 19 was not treatment related. Food efficiency and clinical observations showed no were treatment related response. **For maternal toxicity, the NOAEL is 100 mg/kg/day (HDT); a LOAEL is not established.**

Delayed ossification was seen in skull bones. The incidence of the partially ossified occipital (3.3% to 7.1% versus 0% in control), interparietals (9.5% to 29.5% versus 0.4% in control, historical controls), and in parietal bones (14.2% to 38.2% versus 0.4% in control) were dose related and statistically significant in fetuses and litters at 5.0 mg/kg/day and above. [In this study, historical control data are useful but limited because it was collected on studies with dosing gestational day 7 - 16.]

The mean manus [10% to 30% of control] and pes scores [4% to 14% of control] showed a statistically significant dose related increase delayed ossification, starting at 5 mg/kg/day. [Manus and pes scores (1-6) were a subjective index of delayed ossification (1-6) in the fore paws and hind paws of each fetus.]

Other indications of delayed ossification were seen at the highest dose tested for cervical vertebral arches and centrum (not ossified) and sternebrae 5 and 6. In addition, the odontoid [tooth related] and calcaneum [heel bone] were not ossified at 100 mg/kg/day.

Fetal weight was significantly decreased 7% at 100 mg/kg/day only. Increased incidence of dilated ureter was seen only in litters at 100 mg/kg/day and kinked ureter in was dose related and statistically significant at all doses in fetuses, but not in litters at any dose level. There were no incidences of diaphragmatic hernias seen in this study.

For developmental toxicity, the NOAEL is 2.0 mg/kg/day and the LOAEL is 5.0 mg/kg/day based on dose related delayed ossification in skull bones [occipital and parietal] in fetuses and litters.

The developmental toxicity study in the rat is classified **ACCEPTABLE [guideline]**; and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat.

3.1.4 Fluazifop-P-butyl - Wistar Rats.

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 46082913; referred to

as RR0491; 25/41 Part II, page 112/181 to 181/181)[Fluazifop-p-butyl, calculated as 90.3% a.i.; batch/lot# P12; CTL Ref.# Y02746/021] was administered to [(24 females) Alderly Park strain of Wistar rats (Alpk:APfSD)] rats/dose level by gavage at dose levels of 0, 2.0, 5.0 or 100 mg a.i./kg bw/day from days 7 through 16 of gestation.
No evidence of maternal toxicity was seen at any dose level. **For maternal toxicity, the NOAEL is 100 mg/kg bw/day (HDT); a LOAEL is not established.**

Delayed ossification was seen at 100 mg/kg/day in skull bones, which may have been dose related at 5 mg/kg/day. The parietal bones showed dose related statistically significant increased incidence of partial ossification in fetuses at 5.0 mg/kg/day and above [5.0% versus control 0%]. Partially ossified interparietals were nominally elevated at all dose levels, but showed a statistically significant dose related increased incidence at 100 mg/kg/day. At 5 and 100 mg/kg/day, partial ossification of skull bones exceeded the historical controls.

The mean manus score showed a statistically significant dose related increase (8%), starting at 5 mg/kg/day. Pes score were increased at 100 mg/kg/day. [Manus and pes scores (1-6) were a subjective index of delayed ossification (1-6) in the fore paws and hind paws of each fetus.]

Other delayed ossifications of concern were sternebrae bipartite and sternebrae partially ossified and calcaneum not ossified. The combination of sternebrae 5 bipartite and partially ossified showed a apparent increased incidence in fetuses at all dose levels, but an increased litter incidence at 5 mg/kg/day and above. The calcaneum not ossified showed a dose related and statistically significant increase in fetuses and litters at 5 mg/kg/day and above. Other indications of delayed ossification were seen at the highest dose tested for cervical vertebral arches and centrum (not ossified).

Fetal weight was significantly decreased 7% at 100 mg/kg/day only. Increased incidence of dilated ureter was seen only in litters at 100 mg/kg/day and kinked ureter in was treatment related and statistically significant in fetuses and litters at 100 mg/kg/day. There were no incidences of diaphragmatic hernias seen in this study.

For developmental toxicity, the NOAEL is 2.0 mg/kg/day and the LOAEL is 5.0 mg/kg/day , based on dose related delayed ossification in skull bones [parietal], sternebrae bipartite, sternebrae partially ossified and calcaneum not ossified in fetuses and litters.

The developmental toxicity study in the rat is classified **ACCEPTABLE [guideline]**; and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat.

3.1.5 Fluazifop-P-butyl - Wistar Rats.

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 46158401)[Fluazifop-p-butyl, calculated as 90.1% a.i.; batch/lot# P12; CTL Ref.# Y02746/021/003] was administered to [(24 females) Alderly Park strain of Wistar rats] rats/dose by gavage at dose levels of 0, 0.5, 1.0, 20, or 300 mg a.i./kg bw/day from days 7 through 16 of gestation.

Maternal toxicity at 300 mg/kg/day was indicated by a body weight gain decrement of 19% during the dosing period, GD 7-16. Food consumption was decreased statistically significantly at the same dose and food efficiency decreased 13%. **For maternal toxicity, the NOAEL is 20 mg/kg/day and the LOAEL is 300 mg/kg/day based on decreases in body weight gain maternal animals.**

Developmental effects were shown by delayed ossification in many parameters at ≥20 mg/kg/day. The incidence of parietals partially ossified were statistically significant and dose related in fetuses and litters at 20 mg/kg/day. The statistically significant increase in interparietals partially ossified in fetuses at 20 mg/kg/day exceeded historical controls and support the delayed ossification of the parietal bones. Cervical vertebral arches 4 and 5 partially ossified and centrum (4^{th} not ossified) at 20 mg/kg/day showed statistically significantly increased incidence in fetuses and litters. Manus Scores were statistically significantly increased at 1.0, 20, and 300 mg/kg/day. Pes score were statistically significantly increased at 20 and 300 mg/kg/day.

The other delayed development at 1.0 and 0.5 mg/kg/day either were not dose related, were less than historical controls or showed no treatment related effects in litters. The slightly increased manus scores at 1.0 mg/kg/day were not supported by the previous 0-100 mg/kg/day (dose GD 6-16; MRID# 46082913) study nor by another study dosed 0-100 mg/kg/day on gestational day 7-21 (MRID# 46082903). Neither study showed statistically significant manus scores at 2.0 mg/kg/day. [Manus and pes scores (1-6) were a subjective mean index of delayed ossification (1-6) in the fore paws and hind paws of each fetus.] Other indications of delayed ossification were seen in fetuses and litters at 300 mg/kg/day, the highest dose tested.
Fetal weight was significantly decreased 14% at 300 mg/kg/day and 2% at 20 mg/kg/day.
Increased incidence of kinked ureter was seen at all doses, but reached statistically significance at 300 mg/kg/day. There were no incidences of diaphragmatic hernias seen in this study.

For developmental toxicity, the NOAEL is 1.0 mg/kg/day and the LOAEL is 20 mg/kg/day based on dose related delayed ossification in skull bones [parietal], delayed ossification of the cervical arches and centrum (not ossified) in fetuses and litters and delayed ossification of the manus and pes.

The developmental toxicity study in the rat is classified **ACCEPTABLE [guideline]**; and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat.

3.2 Developmental Toxicity in the Rabbit

3.2.1. Fluazifop-butyl.

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 00088856, 92067049 and 92067021) [fluazifop-butyl, PP009 (94.8% a.i., batch/lot #) P14] was administered to 20-24 New Zealand White female rabbits/dose in a corn oil gavage at dose levels of 0, 10, 30 or 90 mg PP009/kg bw/day from day 6 through 28 of gestation. Maternal weight data, implantations, and fetal data were evaluated.

Clinical observations revealed no consistent differences between treated animals and control animals, other than abortions and possibly gastro-intestinal distress and respiratory distress at 90 mg/kg/day. At 90 mg/kg/day, 2 had respiratory distress and 4 had gastro-intestinal distress. These deaths occurred from day 2 to day 28 (1 at day 2 and 1 day 8, the remaining after day 14). At 90 mg/kg/day of the animals that died or were killed, 4 animal showed gastro-intestinal tract disorders from intestinal gas to stomach ulceration and 2 showed respiratory distress. This reviewer believes that the test material exacerbated the severity of the respiratory distress as well as the gastro intestinal tract disorders, resulting in death in the 90 mg/kg/day group, but the authors did not believe the deaths were test material related.
Body weight was comparable with control values through out the study. Food and water consumption in treated groups was comparable with control values. A nominal absolute liver (13%) and relative liver weight (9%) increase was seen at 90 mg/kg/day.

A treatment related increase in abortions was seen in the study. From control to 90 mg/kg/day, 3, 1, 2 and 7, respectively, abortions occurred from day 21 through day 29. The dams with abortions showed no decrease in corpora lutea or implantation sites. Five of the 7 dams aborting had all of their implants resorbing, suggesting that death of the fetus may have been implicated in the abortion. One totally resorbed litter was seen in 1 control animal not aborting.

For maternal toxicity, the NOAEL is 30 mg/kg/day and the LOAEL is 90 mg/kg/day based on abortions.

No statistically significant fetal effects were shown in the study, however, several nominally increased fetal effects were noted at 90 mg/kg/day. A weight of evidence analysis shows that the fetus was affected at 90 mg/kg/day. Abortion with total litter loss was increased (43.8% versus 25.0% in control) at 90 mg/kg/day. Cloudy eyes were seen in the 90 mg/kg/day group (12.7% verus 0 in control). Although one fetus from1 litter showed cloudy eye(s) (0.9%) with 0% in concurrent control, subsequent historical control data showed 2.2% incidence of cloudy eye(s). Gall bladder variants (not otherwise specified) were increased at 90 mg/kg/day (43.7% versus 34.4% in control with 42.7% maximum in historical controls). The incidence of small fetuses less the 32 g were nominally increased in the 90 mg/kg/day group (22.5% versus 12.9% in controls with a mean of 14.5% and a range of 0 to 30.4% in historical controls). Incompletely ossified hind limb long bone was increased (38% versus 9.7% in control with a maximum of 45.6% in historical controls) at 90 mg/kg/day. Absent tarsals and pubic bones were increased at 90 mg/kg/day (1.4% versus 0 in control with none seen in historical control data). Incompletely

ossified hyoid bone was increased (16.9% versus 2.2% in control with a mean of 3.5% and a maximum historical control of 20.7%).

Other skeletal variations were increased over control, but control was either increased over the historical control range or increased over the mean of the historical control range, such as enlarged cranial sutures, enlarged posterior fontanelles, reduced/ misshappened/irregularly ossified interparietal bones.

Contributing to the weight of evidence for fetal effects at 90 mg/kg/day is an apparent treatment relationship with various anomalies and that the increased level in concurrent controls over historical controls is always accompanied by even higher levels of the anomaly at 90 mg/kg/day than in concurrent controls. Even though, none of the fetal effects were statistically significant, the weight of evidence would suggest that the fetus was affected at 90 mg/kg/day. Post implantation loss was increased (16.5% versus 5.1% in control with a mean of 11.1% and a maximum historical control range of 27.2%) at 90 mg/kg/day.

For developmental toxicity, the NOAEL is 30 mg/kg/day and the developmental LOAEL is 90 mg/kg bw/day based on a weight of the evidence including nominal increases in delayed ossification, total litter loss through death and abortions with total litter loss, small fetuses, cloudy eyes and possible post implantation loss, all of which were above the mean and/or the range in historical control data.

The developmental NOAEL/LOAEL indicated above differs from the values established in the original DER (TXR No.001852) since the the effects seen at the 30 mg/kg/day (nominal increase in small fetuses of 15.7%) was not considered to be adverse since the small fetuses were not significantly increased (22.5%) even at 90 mg/kg/day; the incidences were 12.5% in the concurrent controls and ranged from 1 to 30.5% among historical controls (MRID# 00088856, 92067049).

The developmental toxicity study in the rabbit is classified **ACCEPTABLE (GUIDELINE)**; and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rabbit.

3.2.2 Fluazifop-P-butyl

EXECUTIVE SUMMARY: In a developmental toxicity study [MRID 46082904] [fluazifop-p-butyl (90.1% a.i., batch/lot # P12)] was administered to [(20 females) New Zealand White] rabbits/group by gavage in corn oil vehicle [1 ml/kg] at dose levels of 0, 2, 10 or 50 mg a.i./kg bw/day from days 8 through 20 of gestation. Day sperm was found was designated as day 1. On day 30 of gestation, dams were killed and the uterine contents examined for live and dead fetuses. Fetuses were weighed, examined for external and visceral abnormalities, sexed, eviscerated and stained for skeletal examination.
Minimal maternal toxicity was shown by body weight loss and inappetance at 50 mg/kg/day among 3/4 dams that aborted and one dam that showed extreme body weight loss and

inappetance and was killed on day 14. The aborted fetuses were alive. The abortions were uniformly distributed among groups and were not dose related, however, the abortion occurring at lower doses and in the control group were not preceded by body weight loss. No difference for controls in body weight or weight gain were seen among the surviving rabbits in the study.

For maternal toxicity, the NOAEL is 10 mg/kg/day and the LOAEL is 50 mg/kg/day based on death, abortions and body weight loss in dams.

Treatment related effects on development were seen in the 50 mg/kg/day group only. Statistically significant extra 13th rib and delayed ossification was seen in sternebrae 2 and 5. An increase in partially ossified 5 sternebrae was seen at 10 mg/kg/day, but the litter incidence was not increased. A nominal increase in malformations were seen at 50 mg/kg/day, such as acephaly [1 fetus/1 litter], cebocephaly [1 fetus/1 litter], cleft patate [1 fetus/1 litter], microphthalmia [1 fetus/1 litter], gastroschisis [1 fetus/1 litter], and multiple anomalies in 1 fetus/1 litter. None were duplicated and all could have occurred 1 to 3 times in the same litter, with 0 in control. Since individual animal data was not submitted, this incidence in litters could not be verified.

For developmental toxicity, the NOAEL is 10 mg/kg/day and the LOAEL is 50 mg/kg/day based on increased 13th rib and increased incidence of delayed ossification of sternebrae 2 and 5.

The developmental toxicity study in the rabbit is classified **ACCEPTABLE** (guideline) and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rabbit.

4. <u>Reproductive Toxicity Study Conclusions</u>

<u>EXECUTIVE SUMMARY</u>: In a 2-generation reproduction study (MRID 92067050, update of 00088859) [fluazifop-butyl, 94.8% a.i., batch/lot P14] was administered to 15 male Wistar rats and 30 female Wistar rats per group in the diet at dose levels of 0, 10, 80, 250 ppm (equivalent to a chemical consumption of 0, 0.74, 5.8, 17.5 mg/kg bw/day for males and 0, 0.88, 7.1, 21.7 mg/kg-bw/day for females) for 2 generations. Dosing was continuous for the P0 (100 days) generation and F1 (120 days) generation and to weaning of the F2 generation. Mating was 1 male to 2 females. Each female of the P0 and F1 generations was allowed to produce one litter. Estrous cycles were determined prior to the P0 and F1 matings. Pre-coital interval, mating index, pregnancy index, fertility index and gestation index were determined. All live pups were allowed survive to the end of lactation, i.e., no pup reduction to 8/litter at lactational day 4. P0 animals were subjected to gross necropsy, but only the male reproductive organs were weighed and subjected to histological examination. P0 females were examined for implantation sites and discarded. Ten F1 adults per sex per group were subjected to gross necropsy and complete histological examination. Five f1 and f2 weanlings per sex per group were subjected to gross necropsy and complete histological examination.
Clinical observations were unremarkable. Body weight of P0 and F1 adult males were unaffected by treatment at any dose. However, a nominal body weight increase was noted in

both generations of males at 250 ppm during treatment. Body weight of P0 and F1 adult females were significantly increased (7% and 10%, respectively) only just prior to sacrifice, week 14 and week 17, respectively. No significant dose related changes in food consumption or efficiency were noted during the study. Water intake was not affected in either generation. The length of gestation was slightly, but significantly increased from 22.8 to 23.2 days for the P0 and from 22.6 to 23.1 days for the F1 parturition at 250 ppm. The F1 gestation length was also statistically significantly increased at 80 ppm (from 22.6 to 22.8 days), but the increase may not have been biologically significant. Estrous cycles were similar in all groups of P0 and F1 females and showed normal 4-5 day cycles.

The body weight increases in females may have been incidental or related to the significant absolute and relative increased kidney weight and slight increase in geriatric nephropathy found at termination at 250 ppm.

Signs of systemic toxicity were seen in organ weight changes in F1 adult males and females at the top dose and less frequently at the 2 top doses. In F1 adult males, absolute (18%) and relative (17%) liver weights were statistically significantly increased at 250 ppm and absolute (17%-18%) and relative (17.6%-17.6%) spleen weight were decreased at 80-250 ppm, respectively. Absolute (21%) and relative (13%) liver weights and absolute (15%) and relative (7%) kidney weights were also significantly increased in F1 adult females at 250 ppm. In F1 adult females, absolute and relative spleen weights were nominally decreased at 80 and 250 ppm, but neither were considered to be biologically significant. Spleen, liver, kidney, pituitary, uterine, ovarian weights were not measure in P0 males or females.

For parental/systemic toxicity, the NOAEL is 0.74 mg/kg/day in males and 7.1 mg/kg/day in females. The LOAEL is 5.8 mg/kg/day in males based on based on decreased spleen weight and 21.7 mg/kg/day in females based on increase absolute and relative liver and kidney weights and geriatric nephropathy.

The number of live f1 (16% to 28%) and f2 pups (18 to 27%) were significantly decreased at day 1, 4, 11, 18 and 25 of lactation at 250 ppm. Implantation sites were significantly decreased in P0 females (8%) and nominally in F1 females (4.6%) at 250 ppm, only. F1 pup weights were not significantly affected at any dose level, but f2 pups (19%) showed significantly reduced weight at 250 ppm on lactational day 25, only. Hydronephrosis was increased in f1and f2 pups at 250 ppm. Pinnea unfolding, hair growth, eye opening, auditory response and visual response were comparable in all groups of f1 offspring, the only groups tested. Tooth eruption may have been marginally delayed.

For offspring toxicity, the NOAEL is 7.1 mg/kg/day and the LOAEL is 21.7 mg/bw/day based on decreased viability of F1 and F2 pups during lactational day 1, 4, 11, 18 and 25 and decreases in F2 pup weight on lactational day 25.

Most of the absolute and relative testes and epididymal weight decreases were significant in the P0 and F1 adults. In P0 adults these organ were decreased (testes weights; abs. 7.7-8.3% and rel.13%-13% and abs. epididymal weights; 9%-10% and rel.12%-12%). Absolute and relative

testes weights were decreased in F1 adults at 80 ppm and 250 ppm (abs. 14%-14% and rel. 18%-16%). Absolute (8%-12%) and relative (9%-14%) epididymal weights were decreased in the F1 generation at 80-250 ppm, respectively. Slight pathology was shown in the testes of F1 adults. Slight atrophy of the germinal epithelium and/or seminiferous tubules were seen at histological examination in the P0 generation 2/13 and in the F1 adults 5/15 at 250 ppm, respectively. Correlated with these findings were decreased female pregnancy and fertility index in the F1 generation, but not in the male fertility index or male or female fertility index in the P0 generation.

Although some of the depressions in testes and epididymal weights in P0 and F1 males did not show a good dose related response, the consistency between generations and dose groups and the statistically significant tends show a treatment relationship.

F1 adult females showed an absolute (28%) and relative (18%) statistically significant increase in ovarian weight at 250 ppm. In F1 adult females, absolute pituitary weights (13%-20%) and uterine weights (18%-25%) were statistically significantly reduced at 80-250 ppm. Relative pituitary weights (18%-27%) and uterine weights (19%-29%) were reduced in F1 adult females at 80-250 ppm.

For reproductive toxicity, the NOAEL is 0.74 mg/kg/day in males and 0.88 mg/kg/day in females. The LOAEL is 5.8 mg/bw/day in males based on decreases in absolute and relative testes and epididymal weights and 7.1 mg/kg/day in females based on decreases in absolute and relative pituitary and uterine weights.

The NOAEL/LOAEL indicated above differs from the values established in the DER (TXR# 0001852) and reviewed by the RfD Committee in 1996 (TXR# 011840). The difference is due to the re-evaluation and interpretation of the study results.

This study is **ACCEPTABLE (GUIDELINE)**; and satisfies the guideline requirement for a 2-generation reproductive study (OPPTS 870.3800); OECD 416 in rats.

5. <u>Additional Information from Literature Sources</u>

A literature search found several studies related to fluazifop toxicity. Several were combinations of studies submitted in greater detail to the Agency, including human excretion studies and studies on peroxasome proliferation in the rat, mouse and hamster (Kemal & Casida, 1992)(Kostka et al, 2002)(O'Brien et al, 2001). *In vitro* and *in vivo* skin permeability studies in the rat, human and pig were found, which yield some information about the low skin permeability of fluazifop-butyl (Dick & Scott, 1992)(Ramsey et al, 1992 and 1994). However, the published data included only summary data and lacked experimental detail and individual animal data to verify the summary data.

6. <u>Pre-and/or Postnatal Toxicity</u>

The HIARC concluded that there is concern for pre/post-natal toxicity resulting from exposure to

fluazifop-butyl and fluazifop-P-butyl.

A. Determination of Susceptibility

There was quantitative evidence of increased susceptibility in the fetuses of rats exposed *in utero* to fluazifop-butyl and fluazifop-P-butyl. Developmental toxicity characterized as delays in skeletal ossifications were seen in the absence of maternal toxicity consistently in two strains of rats.
There was no evidence (quantiative or qualitative) of increased susceptibility following *in utero* exposures to rabbits or following pre-and/or post-natal toxicity in the two generation reproduction toxicity study in rats.

B. Degree of Concern Analysis and Residual Uncertainties

The degree of concern in low for the increased susceptibility seen in the rats based on the following considerations: the endpoint of concern (delayed ossifications) is considered to be a development delay as opposed to a malformation or variation which is considered to be more serious in nature; there was considerable variations in the incidences among the five studies; the NOAELs/LOAELs for this effect were well defined and consistent across these studies; and a developmental endpoint of concern (diaphragmatic hernia) is used for assessing acute dietary risk. Therefore, there is no residual uncertainty for pre and/or post natal toxicity.

C. Special FQPA Safety Factor(s):

Based on the above-discussed data, there is no need for a special FQPA safety factor (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 there is not a concern for developmental neurotoxicity resulting from exposure to fluazifop-butyl or fluazifop-P-butyl.

A. Evidence that suggest requiring a Developmental Neurotoxicity study:

- Slight increases in absolute and relative brain weights (2.5% in males and 1.6% in females) were seen at 3000 ppm (approximately 194 mg/kg/day) at termination in the carcinogenicity study in hamsters.

- Slight increases in brain weights were seen in female rats (2.9%) at 100

mg/kg/day and at 120 mg/kg/day in male hamsters (4%) after subchronic exposures with fluazifop-P-butyl.

B. Evidence That Support Not requiring a Developmental Neurotoxicity Study:

- No developmental or central nervous system malformations were seen in any of the developmental toxicity studies with rats or rabbits.
- No evidence of neurotoxicity or neuropathology in adult animals in the available studies.
- The toxicological significance of the marginal increases in brain weights at high doses is unknown in the absence of corroborative histopathological lesions.

II. HAZARD IDENTIFICATION

1. Acute Reference Dose (aRfD) - (Females13 to 49)

Study Selected: Developmental Toxicity - Spargue Dawley Rats Guideline# 870.3700

MRID No.: 00088857 & 00088858

Executive Summary : These two studies are described in detail in Section I.3.1. A brief summary relevant to the endpoint selected is presented below:

In a developmental toxicity study (MRID 00088857), fluazifop-butyl was administered to 22 female CD Sprague Dawley strain rats/group in a corn oil (2 ml/kg) gavage at dose levels of 0, 10, 50 or 200 mg/kg bw/day from days 6 through 20 of gestation. Diaphragmatic hernia was seen in 1 fetus at 10 mg/kg/day, none at 50 mg/kg/day and in 3 fetuses at 200 mg/kg/day. No diaphragmatic hernia was seen in 2970 historical control fetuses. In a subsequent study (discussed below) with a larger number of litters (160 litter/group) diaphragmatic hernias were seen in 3 of 1113 control fetuses, 1 of 1081 fetuses at 1 mg/kg/day, 3 of 1073 fetuses at 5 mg/kg/day, 2 of 1064 fetuses at 10 mg/kg/day and in 59 of 1064 fetuses (and 45/159 litters)at 200 mg/kg/day. Since this anomaly was seen at a higher incidence (3 fetuses) in the controls in this study and was not replicated at the same dose in the second study, the single incidence of diaphragmatic hernia at 10 mg/kg/day was considered to be an aberration and not attributable to treatment.

In an another developmental toxicity study (MRID 00088858) fluazifop-butyl was administered to 159 or 160 female CD Sprague Dawley strain rats/group in a corn oil (2 ml/kg) gavage at dose levels of 0, 1.0, 5.0, 10 or 200 mg/kg bw/day from day 6 through 20 of gestation. There was an increased incidence of diaphragmatic hernia were seen in fetuses (5% versus 0.13% in control) and litters (43.4% versus 1.9%) at 200 mg/kg/day.

Dose and Endpoint for Establishing aRfD: NOAEL is 50 mg/kg/day based on the increased incidence of diaphragmatic hernia at 200 mg/kg/day.

Uncertainty Factor (UF): 100. This includes 10X for inter-species extrapolation and 10X for intra-species variation.

Comments about Study/Endpoint/Uncertainty Factor: The NOAEL selected is based on the combined results of the two studies. In the two studies conducted in the same strain of rats with an identical dosing regimen, diaphragmatic hernias were seen at 200 mg/kg/day in both studies; none were seen at 50 mg/kg/day in the second study (MRID 00088858); and a single incidence was seen at 10 mg/kg/day in the first study (MRID 00088857). The single incidence in the first study was not considered to be treatment-related since the incidence was lower than that seen in the control fetuses in the second study and was not replicated at the same dose in the later study. Therefore, based on the combined doses tested, 0, 1, 5, 10, 50, or 200 mg/kg/day, for this effect, the NOAEL is 50 mg/kg/day and the LOAEL is 200 mg/kg/day. These values differ from the study NOAEL/LOAEL. This particular developmental effect is presumed to occur after a single exposure and thus is appropriate for this population subgroup (Females 13-49).

Acute RfD (Female 13- 49) = $\frac{\text{50 mg/kg (NOAEL)}}{\text{100 (UF)}}$ = **0.50 mg/kg**

2. Acute Reference Dose (aRfD) - General population Including Infants and Children

An appropriate endpoint attributable to a single dose was not available in the database including the developmental toxicity studies.

3. Chronic Reference Dose (cRfD)

Study Selected: Two-Generation Reproduction Study in rats. Guideline# 870.3800

MRID No.: 00008859, 92067022 & 92067050

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

Dose and Endpoint for Establishing cRfD: NOAEL is 0.74 mg/kg/day based on decreases in absolute and relative testes and epididymal weights in males at 5.8 mg/kg/day (LOAEL).

Uncertainty Factor(s): 100X (10X for inter species extrapolation and 10X for intra species variation.

Comments about Study/Endpoint/Uncertainty Factor: The study/dose/endpoint is appropriate for the route (oral) and duration (chronic) of concern. Although the endpoint of concern in based on male reproductive effects, decreases in pituitary and uterine weights were seen in females at a comparable NOAEL (0.88 mg/kg/day) and LOAEL (7.1 mg/kg/day).

Chronic RfD = $\frac{0.74 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}}$ = **0.0074 mg/kg/day**

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

Study Selected: Developmental Toxicity Studies in the Rat. § 870.3700

MRID No.: 46082913, 46158401, 46082903

Executive Summary: These three studies are described in detail in Section I.3.1. A brief summary relevant to the endpoint selected is presented below:

In a developmental toxicity study (MRID 46082913) Fluazifop-p-butyl was administered to Aderly Park strain of Wistar rats by gavage at dose levels of 0, 2.0, 5.0 or 100 mg a.i./kgday from days 7 through 16 of gestation. No evidence of maternal toxicity was seen at any dose level. **For maternal toxicity, the NOAEL is 100 mg/kg/day (HDT); a LOAEL is not established**

In another developmental toxicity study (MRID 46158401) fluazifop-P-butyl was administered to Alderly Park strain of Wistar rats rats by gavage at dose levels of 0, 0.5, 1.0, 20, or 300 mg/kg /day from days 7 through 16 of gestation. Maternal toxicity at 300 mg/kg/day was indicated by a body weight gain decrement of 19% during the dosing period, GD 7-16. Food consumption was decreased statistically significantly at the same dose and food efficiency decreased 13%. **For maternal toxicity, the NOAEL is 20 mg/kg/day and the LOAEL is 300 mg/kg/day based on decreases in body weight gain maternal animals.**

In yet another developmental toxicity study (MRID 46028903) fluazifop-P-butyl was administered to Alderly Park strain of Wistar rats by gavage at dose levels of 0, 2, 5 or 100 mg a.i./kgday from days 7 through 21 of gestation. No maternal toxicity was seen. **For maternal toxicity, the NOAEL is 100 mg/kg/day (HDT); a LOAEL is not established.**

Dose and Endpoint for Risk Assessment: Maternal NOAEL of 100 mg/kg/day based on decreases in body weight gain in maternal animals during the dosing period (GD 7-16) at 300 mg/kg/day (LOAEL).

Comments about Study/Endpoint: The maternal NOAEL is selected based on the combined results of the two studies with support from the third study. The first two studies were conducted in the same strain of rats (Wistar) with identical dosing regimen (dosing during GD 7-16) in the same laboratory. The lower NOAEL (20 mg/kg/day) in

the second study (46158401) is an artifact of dose selection. Additionally, the NOAEL is supported by another study conducted in the same strain of rats with a slightly longer dosing period (GD 7-21) where no maternal toxicity was seen at 100 mg/kg/day, the highest dose tested (MRID# 46082903). This 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 Selected: Two-Generation Reproduction Study in Rats § 870.3800

MRID No.: 0008859, 92067022 and 92067050

Executive Summary: See Section I. 4. Reproductive Toxicity

Dose and Endpoint for Risk Assessment: NOAEL is 0.74 mg/kg/day based on decreases in absolute and relative testes and epididymal weights in males at 5.8 mg/kg/day (LOAEL).

Comments about Study/Endpoint: The endpoint of concern was seen after approximately 13-16 weeks of exposure and thus is appropriate for the duration (1-6 months) of concern. Although the endpoint of concern in based on male reproductive effects, decreases in pituitary and uterine weights were seen in females at a comparable NOAEL (0.88 mg/kg/day) and LOAEL (7.1 mg/kg/day). These endpoints are appropriate for the population (infants and children) of concern.

6. Dermal Absorption

Dermal Absorption Factor: 9% to assess risks from high exposure and 2% to assess risks from low exposure.

Selected Study: Dermal Absorption Study - in humans § Nonguideline

MRID#: 46082918

Executive summary: In a dermal absorption and pharmacokinetic study (MRID# 46082918), six men (age 18-45; weight 60-90 kg)/dose were dosed dermally with 2 mg or 200 mg of 0.05% or a 5.0% (w/v) solution of fluazifop-butyl in a formulation. Four ml of each solution was spread over 800 cm^2 of the backs of 6 men/dose level, allowed to dry and left unoccluded for 8 hours. Plasma and urine was collected in multiple samples over a 264 hour period. Plasma was collected hourly for 4 hours, every 2 hours for 12 hours and every 24 hours to the end. Urines were collected every 4 hours for 12 hours and then every 24 hours to the end. The application site was washed with water using cotton swabs and 3%Teepol and covered with a T-shirt over the application site until morning. At 24 hours after application the site was again washed with a 3% solution of Teepol. The washes, T-shirts, plasma and urine samples were analyzed for fluazifop-butyl or fluazifop acid.

Most of the applied dose appeared to be in the stratum corneum and easily removed. Recovery of test material was good, a mean of 93.4% ± a standard deviation of 13% at the 2 mg dose and mean of 83.2% ± a standard deviation of 21% at the 200 mg dose. Peak plasma levels were shown to occur 24 to 31 hours after application in these men. The one half life for excretion was about 18 hours. In arriving at these percentages of recovery, the study author's added a correction to the amount excreted in the urine up to 120 hours, i.e., to the amount excreted up to 120 hours was added the amount excreted after 120 hours through a 2 compartment pharmacokinetic model. However, this latter correction was insignificantly small amounting about 0.008% of the 200 mg applied to the skin. In arriving at the dermal absorption percentage, the study author's corrected the recovery by three factors, 1.17 [the ratio of the mole weight fluazifop-butyl and fluazifop acid], 100/91 [the amount of recovery from thawed frozen urine (no supporting data was presented)] and 100/90 [the recovered urinary fluazifop acid from a oral study in humans (supported by MRID 00131464)]. This later factor was used to correct for residual material in organs and tissue, which would require similar test subjects in both studies for which there is not evidence. The study author's calculated the percentage absorption to be 8% at the 2 mg dose and 1.6% at the 200 mg dose.

The current reviewer modified the study author's percentage absorption. The modified dermal absorption was calculated by two methods; (1) Unrecovered added to absorbed material, and (2) Scaling recovered material to100%. Method (1) yielded absorption factors of 18.4% and 14.6% at the 2 mg dose and 200 mg dose, respectively. Method (2) yielded absorption factors of 8.6% and 1.9% at the 2 mg dose and 200 mg dose, respectively. Method (2) appeared to be more reasonable because residual material (unrecovered) may have been relatively immobile. The unrecovered test material was speculated to be in the outer layers of the skin and appeared to be easily removed.

Human oral studies with fluazifop-butyl show rapid excretion of fluazifop acid in the urine and almost no excretion in the feces of humans (MRID# 00131464). Oral dog and female rat studies show similar results, which were similar to human oral studies. Male rats show similar fluazifop acid excretion to the female, but excretion is slower because fluazifop is excreted in the bile, resulting in a higher % in the feces of males rats. Residual fluazifop acid appears to be retained in the body fat (<1% to 8% in the rat) and

speculated to be esterified to mono or diglycerides. This small amount of residual material if released, was too low to be accurately detectable in the urine. Since multiple dosing studies show that fluazifop-butyl does not accumulated in the body and is not a carcinogen. This residual material is relatively immobile and may be toxicologically insignificant. Thus, the scaling of the recovered material to100% or method (2) may supply an appropriate dermal absorption factor. In conclusion, the dermal absorption factors are 8.6% and 1.9% for the dermal dose of 2 mg and 200 mg, respectively.

7. Dermal Exposure: Short-Term (1- 30 days) Exposure (Females 13-49)

Study Selected: Developmental Toxicity Studies in Rats § 870.3700

MRID No.: 00088858, 46082903, 46082913, 46158401

Executive Summary: See Section I.3.1.2 thru I. 3.1.5

Dose and Endpoint for Risk Assessment: Developmental NOAEL is 2.0 mg/kg/day based on fetal weight decrement, increased incidence of hydroureter and delayed ossification at 5.0 mg/kg/day (LOAEL)

Comments about Study/Endpoint: The *in utero* effects are appropriate to assess dermal risks for the population subgroup, Females 13-49 from exposure to fluazifop-butyl. This endpoint was selected because of the developmental toxicity concerns seen consistently in rats and rabbits via the oral route. The Committee did not select the 21-day dermal toxicity study in rabbits due to the concern for developmental toxicity which is not evaluated in the dermal study. In addition, dermal study would not address the developmental concerns since the NOAEL (100 mg/kg/day) in that study is considerably higher than the dermal equivalent dose (22 mg/kg/day) obtained using the oral dose (2.0 mg/kg/day) with a 9% dermal absorption factor (2.0 ÷ 0.09 = 22).

Since an oral NOAEL was selected an appropriate dermal absorption factor (i.e., 2% or 9%, exposure depended) should be used for route-to-route extrapolation.

8. Dermal Exposure: Short-Term (1- 30 days) Exposure (General Population including Infants and children)

Study Selected: Developmental toxicity Study in Rats § 870.3700

MRID No.: 46158401, 46082913 and 46082903

Executive Summary: These three studies are described in detail in Section I..3.1. A brief summary relevant to the endpoint selected is presented in Section II. 4. Incidental Oral Exposure - Short Term.

Dose and Endpoint for Risk Assessment: Maternal NOAEL of 100 mg/kg/day based on decreases in body weight gain in maternal animals during the dosing period (GD 7-16) at 300 mg/kg/day (LOAEL).

Comments about Study/Endpoint: This endpoint is appropriate for the population subgroup (general population including infants and children) and duration (1-30 days) of concern. The maternal NOAEL is selected based on the combined results of the two studies with support from the third study. The first two studies were conducted in the same strain of rats (Wistar) with an identical dosing regimen (dosing during GD 7-16) in the same laboratory. The lower NOAEL (20 mg/kg/day) in the second study (46158401) is an artifact of dose selection. Additionally, the NOAEL is supported by another study conducted in the same strain of rats with a slightly longer dosing period (GD 7-21) where no maternal toxicity was seen at 100 mg/kg/day, the highest dose tested (MRID# 46082903).

Since an oral NOAEL was selected an appropriate dermal absorption factor (i.e., 2% or 9%, exposure depended) should be used for route-to-route extrapolation.

9. Dermal Exposure: Intermediate-Term and Long-Term (1 - 6 Months and > 6 Months)

Study Selected: The Two-Generation Reproduction Study in Rats § 870.3800

MRID No.: 00088858, 92067022 and 92067050

Executive Summary: See Section I. 4. Reproductive Toxicity

Dose and Endpoint for Risk Assessment: NOAEL is 0.74 mg/kg/day based on decreases in absolute and relative testes and epididymal weights in males at 5.8 mg/kg/day (LOAEL).

Comments about Study/Endpoint: The endpoint of concern was seen after approximately 13-16 weeks of exposure and thus is appropriate for the duration (1-6 months) of concern. Although the endpoint of concern in based on male reproductive effects, decreases in pituitary and uterine weights were seen in females at a comparable NOAEL (0.88 mg/kg/day) and LOAEL (7.1 mg/kg/day). These endpoints are appropriate for the general population including infants and children. Since an oral NOAEL was selected an appropriate dermal absorption factor (i.e., 2% or 9%, exposure depended) should be used for route-to-route extrapolation.

10. Inhalation Exposure: Short -Term (1- 30 days) (Females 13-49)

Study Selected: Developmental Toxicity Studies in Rats § 870.3700

MRID No.: 00088858, 46082903, 46082913, 46158401

Executive Summary: See Section I. 3.1.2 thru I. 3.1.5

Dose and Endpoint for Risk Assessment: Developmental NOAEL is 2.0 mg/kg/day based on fetal weight decrement, increased incidence of hydroureter and delayed ossification at 5.0 mg/kg/day (LOAEL)

Comments about Study/Endpoint: The *in utero* effects are appropriate to assess inhalation risks for the population subgroup, Females 13-49 from exposure to fluazifop-butyl. This endpoint was selected because of the developmental toxicity concerns seen consistently in rats and rabbits via the oral route. The Committee noted the absence of a repeated exposure inhalation toxicity study. For route-to-route extrapolation, absorption via the inhalation route is assumed to be equivalent to oral absorption.

11. Inhalation Exposure: Short -Term (1- 30 days) (General Population including Infants and Children)

Study Selected: Developmental toxicity Study in Rats § 870.3700

MRID No.: 46158401, 46082913 and 46082903

Executive Summary: These three studies are described in detail in Section I..3.1. A brief summary relevant to the endpoint selected is presented in Section II. 4. Incidental Oral Exposure - Short Term.

Dose and Endpoint for Risk Assessment: Maternal NOAEL of 100 mg/kg/day based on decreases in body weight gain in maternal animals during the dosing period (GD 7-16) at 300 mg/kg/day (LOAEL).

Comments about Study/Endpoint: This endpoint is appropriate for the population subgroup (general population including infants and children) and duration (1-30 days) of concern. The maternal NOAEL is selected based on the combined results of the two studies with support from the third study. The first two studies were conducted in the same strain of rats (Wistar) with an identical dosing regimen (dosing during GD 7-16) in the same laboratory. The lower NOAEL (20 mg/kg/day) in the second study (46158401) is an artifact of dose selection. Additionally, the NOAEL is supported by another study conducted in the same strain of rats with a slightly longer dosing period (GD 7-21) where no maternal toxicity was seen at 100 mg/kg/day, the highest dose tested (MRID# 46082903). The Committee noted the absence of a repeated exposure inhalation toxicity study. For route-to-route extrapolation, absorption via the inhalation route is assumed to be equivalent to oral absorption.

12. Inhalation Exposure: Intermediate-Term and Long-Term (1- 6 Months and >6 Months)

Study Selected: The Two-Generation Reproduction Study in Rats § 870.3800

MRID No.: 00088859 and 92067050

Executive Summary: See Section I. 4. Reproductive Toxicity

Dose and Endpoint for Risk Assessment: NOAEL is 0.74 mg/kg/day based on decreases in absolute and relative testes and epididymal weights in males at 5.8 mg/kg/day (LOAEL).

Comments about Study/Endpoint: The endpoint of concern was seen after approximately 13-16 weeks of exposure and thus is appropriate for the duration (1-6 months) of concern. Although the endpoint of concern is based on male reproductive effects, decreases in pituitary and uterine weights were seen in females at a comparable NOAEL (0.88 mg/kg/day) and LOAEL (7.1 mg/kg/day). These endpoints are appropriate for the general population including infants and children. The Committee noted the absence of a repeated exposure inhalation toxicity study. For route-to-route extrapolation, absorption via the inhalation route is assumed to be equivalent to oral absorption.

13. 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
Dermal (All Populations)	100	100	100
Inhalation (All Populations)	100	100	100

For Occupational exposure: This is based on the conventional uncertainty factor of 100X (10X for interspecies extrapolation and 10X for intraspecies variation)

For Residential exposure: This is based on the conventional uncertainty factor of 100X (1X for FQPA, 10X for interspecies extrapolation and 10X for intraspecies variation).

14. Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. The toxicity endpoints selected for these routes of exposure may be aggregated as follows:

The oral, dermal and inhalation routes of exposure can be combined to assess aggregate risks because of the selection of a common toxicity endpoint for short-term (decrease in maternal body weight gain) and intermediate-term (decreases in testicular and ovarian weights) via the oral, dermal (oral equivalent) and inhalation (oral equivalent) routes.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats §870. 4300

MRID No. 41563703

Executive summary: In a combined chronic/carcinogenicity study fluazifop-butyl (94.8% a.i.) was administered to [(60 Wistar rats/sex/group in the diet at dose levels of 0, 2, 10, 80 or 250 ppm (equivalent to 0, 0.10, 0.51, 4.15 or 12.29 mg/kg bw/day for males and 0.127, 0.65, 5.20 or 16.0 for females) for 106 or 107 days, respectively. Additional groups of 10 rats/sex/group were administered test material in an analogous manner for 52 weeks prior to an interim sacrifice. Clinical signs in the rats were characteristic of rats, except respiratory distress, nasal and ocular discharge were seen among some males at 80 and among some males and females 250 ppm from week 29 to 55. These signs were accompanied by body weight loss and death in the seriously affected males at 80 and 250 ppm and in the seriously affected females at 250 ppm.

Body weight gain of males and females, not dying, were increased significantly up to week 28 at 80 (14% in males and 19% in females) and 250 ppm (10% in males and 20% in females) and in males week 29-44 at 250 ppm (26%), thereafter body weight gain was nominally increased in males at 10, 80 and 250 ppm and nominally increased in females from week 29-108 at 2, 10, 80 and 250 ppm. There was an overall nominal body weight gain increase in males and females at the three top dose levels for the 106 weeks of the study. However, male (-79 g to -123g versus 101 in control males) and female (-9 g to -24 g versus -24g in control females) rats lost body weight between week 81-85 and the end of the study.

No differences from control were seen in food consumption, food efficiency, water consumption or urinalysis among the groups.

There appeared to be a dose related increased mortality among males at 80 and 250 ppm (33% at 80 ppm and 34% at 250 ppm versus 14% in control) and among females (21% at 250 ppm versus 4% in control) during the first 52 weeks of the study. Overall mortality at cumulative termination appeared to be increased in males at 80 and 250 ppm (88%-86% versus 68% in control) and in females at 250 ppm (65% versus 45% in controls).

The report stated that the death occurring up to week 52 was cause by respiratory problems exacerbated by test material related nephropathy (all grades) in nearly 100% of the affected males dying at 80 and 250 ppm and 87% of the affected females dying at 250 ppm. No dose related mortality was seen from week 52 to termination.

Dose related nephropathology, slight, moderate and marked, but not otherwise specified was seen in the animals dying or killed in extremis during the first 52 weeks of the study. This nephropathy was seen in control, 2, 10, 80 and 250 ppm group animals; 9/10, 9/9, 6/6, 22/23, and 24/24, respectively in males and 0/3, 0/1, 1/6, 1/ 2 and 13/15, respectively in females dying or killed in extremis. Treatment may have exacerbated the nephropathy. In animals sacrificed at termination, geriatric nephropathy was seen in nearly all surviving animals [23/24 (96%) HDT versus 30/31 (97%) in control males] and [20/24 (83%) HDT versus 19/24 (79%) control females]. Gasto-intestinal tract lesions appeared to be increased slightly at 250 ppm in males and females.

At ophthalmological examination, increased keratitis was seen in males (5/20) at 250 ppm. Since this observation was not seen in females and did not appear to be dose related at lower dose levels, the study authors questioned the toxicological significance of the finding.

Hematological parameters showed slight changes in males at 80 and 250 ppm. Decreased hematocrit (6-8%), hemoglobin concentration (3-4%) and erythrocyte count (6-8%) were slightly but statistically significant at week 12 and 25 and nominally decreased at week 78 at 80 ppm and 250 ppm. Hemosiderosis was found only in the spleens of one female each in control, 2 , 80 and 250 ppm groups. Blood chemistries showed increased cholesterol (about 85% to 107%) at various times of analyses up to 78 weeks in males and females, but not after 100 weeks in females at 250 ppm; males showed a nominal decrease in cholesterol after 100 weeks at the same dose. Albumin showed statistically significantly decreases of about 24% in males and females at 250 ppm. Bone smears on males and female rats were similar to controls at week 52 or 106, but many smears in all groups could not be evaluated. Decreased absolute (16%) and relative (17%) liver weights were statistically significant in males at 250 ppm at terminal sacrifice, and increased absolute (40%) and relative (37%) ovarian weights were significant at termination at 250 ppm; animals with ovarian cysts and masses were excluded from these calculations. Testes and seminal vesicle weight did not differ from control weight at terminal sacrifice, but were nominally decreased at 250 ppm. At the 52 week interim sacrifice, absolute and relative kidney (Abs. 29%), thyroid (Abs. 33%) and were significantly increased in males, but not in females at 250 ppm. Absolute (31%) and relative (24%) testes weight showed a treatment related decrease at 250 ppm at the 52 week sacrifice. Ovarian weights were nominally increased at 250 ppm and 52 weeks. Ovaries, possibly enlarged by cysts, appeared to have an increased incidence in the 250 ppm group than in control.

The LOAEL in males is 80 ppm (4.15 mg/kg/day) based on increased mortality and nephropathy from start to week 52 of the study. The NOAEL is 10 ppm (0.51 mg/kg/day in males). The LOAEL in females is 250 ppm (16.0 mg/kg/day) based on increased morality and nephropathy during the first 52 weeks of the study and increased ovarian weight and ovarian cysts at termination. The NOAEL is 80 ppm

(5.2 mg/kg/day) for females.

This chronic/carcinogenicity study in the rat is ACCEPTABLE (GUIDELINE) and satisfies the guideline requirement for a chronic/carcinogenicity study OPPTS 870.4300); OECD 453] in the rat.

Discussion of Tumor Data At the doses tested, there was no treatment related increase in tumor incidence when compared to controls. The only statistically significant neoplasia seen in the study was an increase in male adrenal phaeochromocytomas at 80 ppm, but not at 250 ppm. The incidence of adrenal phaeochromocytoma bearing males in control, 2, 10, 80 or 250 ppm were, respectively, 5/70, 3/70, 2/70, 11*/70 and 7/70 for males that died, were killed or sacrificed. [* Significant at $p < 0.019$ by a Peto analysis, when the 80 ppm group was compared with control]. None of these adrenal tumors were seen at the interim sacrifice.

Adequacy of the Dose Levels Tested: The doses tested were judged to be adequate to assess the carcinogenic potential of fluazifop-butyl based on increased mortality and nephropathy in both sexes and increased ovarian weights and the presence of ovarian cysts.

2. Carcinogenicity Study in Mice § 870.4200

A carcinogenicity study in mice was not conducted. Peroxasome proliferation in the mouse was at levels much higher than in the hamster at comparable dose levels. Therefore, a carcinogenicity study in hamsters was conducted. The hamster was chosen because peroxasome proliferation *in vivo* and *in vitro* was more comparable to that found in human cell culture.

3. Carcinogenicity Study in Hamsters §870. 4300

MRID No. 46082905

Executive summary: In a carcinogenicity study, fluazifop-P-butyl (91.6%) was administered to 63 Golden Syrian hamsters/sex/dose in the diet at dose levels of 0, 0, 200, 750 or 3000 ppm (mean of measured test material consumption equivalent to 0, 0, 12.5, 47.4 or 193.6 mg/kg bw/day for males and 0, 0, 12.1, 45.5 or 181.4 mg/kgbw/day for females, page 25 of 45345401) for 80 weeks. Of these animals, 12/sex/group were designated for interim sacrifice on week 53. Two control groups were included.

There were no significant definitive body weight changes or meaningful food consumption or food efficiency differences from control in males or females during the study. There was an increased frequency of a clinical observation at 3000 ppm ("thin") (13 versus 5 in control). Survival was unchanged statistically, but females showed a slight nominal decrease at 3000 ppm (70.6% versus 78.5% in pooled control).

Probably no biologically significant hematological effects were seen in the study. Statistically significant decrease in white cell count in interim sacrificed males (22%-23%) at 750 ppm and 3000 ppm and in terminal females (17%) at 3000 ppm. The

remaining statistically significant hematological changes at 3000 ppm were minor and probably not biologically significant. No clinical chemistry analysis were conducted. Testes weights were decreased at 750 and 3000 ppm and liver and kidney weights were increased in males and females at 3000 ppm. In males, absolute and adjusted testes weights were decreased in a dose related manner and statistically significantly reduced ($p < 0.01$) at 750 (abs 8% and adj 10%) and 3000 ppm (abs 20% and adj 19%). In males, adjusted liver weight was statistically significantly elevated at 750 (5%) and 3000 ppm (7%), but the absolute weight was not elevated at any dose level. In males and females, a kidney weight (males 11% and females 9%) and adjusted kidney weights (males 11% and females 9%) were statistically significantly elevated in the 3000 ppm group, only. In females absolute liver weight was statistically significantly elevated at all dose levels (9%-38%), but adjusted liver weights (34%) were significantly elevated only at 3000 ppm. Slight absolute and adjusted brain weight increases (2.5% and 1.6%) respectively in males and females at 3000 ppm are of unknown biologically significance.

Non-neoplastic microscopic histological findings were increased in the epididymis, testes, eyes, livers and gall bladder in males and in females, ovarian stromal cell/sex cord hyperplasia was increased at 750 and 3000 ppm. In males dose related incidences were seen at 750 ppm of reduced spermatozoa in epididymes (24% versus 8% in pooled controls), increased incidences of testicular tubule degeneration (37% versus 7% in pooled controls), increased incidences of eye cataractous changes (31% in males at 750 ppm versus 16% in pooled controls), increased incidences of male liver mononuclear cell infiltration (35% versus 20% in pooled controls) and increased incidences of gall bladder stones (73% versus 31% in pooled controls) in males and in females at 3000 ppm (41% versus 13% in pooled controls). The incidence of chronic nephropathy was nominally increased in males and female at all dose levels. In females dose related increased incidences were seen at 750 ppm in ovarian stromal/sex cord hyperplasia (14%versus 6% in pooled controls).

The LOAEL for systemic effects is 750 ppm (equivalent to 47.4 mg/kg/day in males and 45.5 mg/kg/day in females) based on increased incidence of males with reduced sperm, testicular degeneration, eye cataractous changes, liver inflamation and gall stones and in females increased incidences of ovarian stromal cell/sex cord hyperplasia. The NOAEL is 200 ppm (equivalent to 12.5 mg/kg/day in males and 12.1 mg/kg/day in females.

The carcinogenicity study [n the hamster is ACCEPTABLE (guideline) and does satisfy the guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in hamsters.

Discussion of Tumor Data: No dose related tumors were seen in males. Benign ovarian stromal cell/sex cord tumors were statistically significantly elevated at the 3000 ppm 5/51 (9.8%) versus 3/103 (2.9%) in pooled controls. However, when the incidence of malignant and benign tumors were combined, no significant differences were seen at any dose. It was concluded that fluazifop-butyl, [R] isomer is not carcinogenic at the dose levels studied.

Adequacy of the Dose Levels Tested in the hamster study: Dosing was adequate in males and females as indicated by the kidney weight increase and histological findings in eyes [cataracts], liver [inflammation], gall bladder [gall stones], the testes [tubular degeneration] and epididymes [reduced spermatoza] of males, and in females by the ovarian findings [hyperplasia and adenomas], gall bladder [gall stones] and the severity of progressive chronic nephropathy at 3000 ppm (HDT).

4. Classification of Carcinogenic Potential

The HIARC, in accordance with the 1999 Draft Carcinogen Risk Assessment Guideline (April, 1999) classified fluazifop-butyl and fluazifop-P-butyl as "Not likely to be carcinogenic in humans," based on the lack of evidence of carcinogenicity in rats and hamsters.

IV. MUTAGENICITY

The HIARC concluded that there is not a concern for mutagenicity resulting from exposure to fluazifop-P-butyl.

Adequacy of data base for Mutagenicity: The data base for mutagenicity is considered adequate based on pre-1991 guidelines. No mutagenic potential was seen in adequately conducted pre-1991 guideline mutagenicity studies (*in vivo and in vitro*) on fluazifop-P-butyl [FPB] or fluazifop-butyl [FB]. A structural analogue {haloxyfop-methyl [methyl 2-[4-[[3-chloro-5-(trifluromethyl)-2-pyridinyl] oxy]phenoxy]propinonate]} of fluazifop-P-butyl showed no mutagenic potential.

1. Gene Mutation

Guideline 870.5100, Ames/*Salmonella typhimurium,* reverse mutation MRID 00162443 Acceptable Test material [FB]	In a reverse gene mutation assay in bacteria (MRID 00162443, 92067023), histidine deficient strains TA98, TA100, TA1535, TA1537, TA1538 of *S. typhimurium* were exposed to fluazifop-butyl (96.8% a.i., batch/lot# P25) in the presence and absence of mammalian metabolic activation by plate incorporation. Negative with and without S9 up to the limit dose of 5000 µg/plate.

Guideline 870.5100, Ames/*Salmonella typhimurium,* reverse mutation MRID 00162442 Acceptable Test material [FPB]	In a reverse gene mutation assay in bacteria (MRID 00162443, 92067013), histidine deficient strains TA98, TA100, TA1535, TA1537, TA1538 of *S. typhimurium* were exposed to fluazifop-butyl (93.6% a.i., batch/lot# P8) in the presence and absence of mammalian metabolic activation by plate incorporation. Negative with and without S9 up to the limit dose of 5000 µg/plate (insoluble at 5000µg/plate).
Guideline 870.5300, Mouse lymphoma cell test Acceptable Test material [FB]	In a mammalian cell gene mutation assay (MRID 00116678), heterozygous TK+/- P 388 mouse lymphoma cells cultured *in vitro* were exposed to fluazifop-butyl, (99.6% a.i., batch/lot # ADGM/1021/79) at concentrations of 0, 0.25, 2.5, 25, 250 or 2500 µg/mL in the presence and absence of mammalian metabolic activation, S9, for 30 minutes. Negative with and without S9 up to cytotoxic doses.

2. Cytogenetics

Guideline 870.5375; *In vitro* chromosomal aberrations in human blood lymphocytes. (1985) Acceptable Test material: [FPB]	In independently performed mammalian cell cytogenetic assays (chromosome aberration) (MRID 41555202), lymphocyte cultures prepared from human peripheral blood were exposed to fluazifop-p-butyl (R-enantiomer, 93.8% a.i.; CTL reference # Y02746/001/008) in dimethyl sulfoxide for 4 hours at concentrations of 0, 1, 10, 100, 500, or 1000 µg/mL both in the presence and absence of S9-activation. Cells were harvested at 27 hours after initiation of treatment. The was no evidence of chromosome aberration induced over background in the presence or absence of S9-activation at toxic doses.
Guideline 870.5385, *In vivo* rat mammalian cytogenetics; bone marrow chromosomal aberrrations (1980) Acceptable Test material: [FB]	In independent bone marrow chromosome aberration assays (MRID 00088861), 10 male CD rats/dose were treated via oral gavage (10 mL/kg) either once (acute) or daily for 5 consecutive days (sub-acute) with fluazifop-butyl (94.5% a.i.; Lot/Batch #: CTL Compound code: Y00083/001/006), in corn oil at doses of 0, 21.0, 67.2, or 210.0 mg/kg. Bone marrow cells were harvested at 6 or 24 hours after treatment in the acute study, and at 6 hours after treatment in the sub-acute study. There was no evidence of chromosome aberration induced over background at toxic doses.
Guideline 870.5450, Mouse Dominant lethal test (1980) Unacceptable: Top dose not sufficiently toxic Test material: [FB]	In a dominant lethal assay (MRID 00088862) [PP009, fluazifop-butyl (97.0% a.i., batch/lot # 310M)] was administered to 25 CD-1 male mice/group by corn oil gavage (10 mL /kg) at dose levels of 0, 28.7, 91.8 or 287 mg/kg/day for 5 days for the first mating. Based on the results of the first mating, subsequent matings were based on 15 of the 25 dosed males. These 15 males were mated with 30 females in 8 sets and the females examined for dominant lethal effects (resorptions) at day 15 of pregnancy. The investigators reported that fluazifop-butyl does not cause dominant lethal effects in CD-1 mice up to and including 287 mg/kg/day for 5 days. No toxicity demonstrated.

3. Other Genotoxicity

Guideline 870.5395; *In vivo* mouse micronucleus test (1983) Acceptable Test material: [FB] and [FPB] Acceptable	In an *in vivo* mamalian cell mouse micronucleus assay (MRID# 0016244,92068014), C57BL/6J mice were administered FB or FPB at doses of 250 or 400 mg/kg and bone marrow removed after 24, 48 or 72 hours to determine the frequency of MPCEP. FB and FPB were tested up to 80% and 50% of the LD50 in mice. There were no adequate evidence of a positive response of increased micronuclei over background with either fluazifop-butyl [FB] or fluazifop-P-butyl [FPB] at toxic doses.

V. HAZARD CHARACTERIZATION

Fuazifop-butyl and fluazifop-P-butyl have low acute toxicity by the oral, dermal and inhalation routes (all six acute studies on both isomers are placed in Toxicity Category III). They are mildly irritating to the eye and skin (both are placed in Toxicity Category IV) and are not skin sensitizers.

Subchronic and Chronic toxicity studies with fluazifop-butyl or fluazifop-P-butyl show that the rat is more sensitive to toxic effects than the dog, rabbit or hamster, possibly due to longer retention time of the main metabolite (fluazifop acid) in the rat. The kidney and liver are the target organs and the toxicity is expressed as exacerbation of the age related kidney toxicity and liver toxicity in the presence of peroxasome proliferation. However, the extensive and age related nephopathy in control groups complicate this conclusion with regard to the kidney. At the highest dose in the chronic studies, hematological effects, gastro-intestinal lesions, cataracts were noted in the dog. Less definitive effects were noted with vacuolation of the adrenal glands. Cholesterol depression was noted at the two top doses in the male dog and rat and to a lesser degree in the female? An unusual finding was noted in the older toxicity studies with fluazifop-butyl in the rabbit, rat and dog. Frequently death was seen in some animals at the highest dose levels, but few histological effects being noted on surviving animals. These studies showed an exacerbation of an age related nephropathy which may be related to the deaths..

The data base includes 7 developmental toxicity studies: 2 with fluazifop-butyl in Sprague-Dawley rats; 3 with fluazifop-P-butyl in Wistar rats; 1 with fluazifop-butyl in New Zealand rabbits; and 1 with fluazifop-p-butyl in New Zealand rabbits. There was evidence (quantitative) of increased susceptibility in the fetuses of two strains of rats exposed *in utero* to fluazifop-butyl and fluazifop-P-butyl. Developmental toxicity characterized as delays in skeletal ossifications were seen in the absence of maternal toxicity consistently in all studies. However, the concern is low for the increased susceptibility seen in the rats based on the following considerations: the endpoint of concern (delayed ossifications) is a development delay and not a malformation or a variation which are considered to be of more serious in nature and there was considerable variations in the incidences among the five studies. There was no evidence (quantiative or qualitative) of increased susceptibility following *in utero* exposures to rabbits.

There was no evidence (quantiative or qualitative) increased susceptibility following pre and/or post natal toxicity in the two generation reproduction toxicity study in rats.

Fluazifop-butyl and fluazifop-P-butyl is classified as “not likely to be carcinogenic to humans” based on the lack of evidence of carcinogenicity in rats and hamsters. The hamster (instead of mice) was tested because the increase in peroxasome proliferation in the liver of hamsters *in vitro* and *in vivo* more closely related to that found in *in vitro* studies in human tissue than either the rat or the mouse.

A battery of mutagenicity studies with fluazifop-butyl and fluazifop-P-butyl were

negative.

One structurally related pesticide, haloxyfop, was classified as a Group C Carcinogen based on liver tumors in mice. Peroxasome proliferation was noted in livers of these mice at dose levels where tumors were found.

Potential endocrine related effects were noted in the testes (weight decrement), uteri (weight decrement) and ovaries (weight decrement) of rats and hamsters (sex cord hyperplasia). However, *in vitro* studies failed to find any agonistic or antagonistic activity with recombinant yeast strains sensitive to human estrogen or androgen receptors with either fluazifop-butyl or fluazifop-P-butyl or their acid metabolites. Although these studies do not completely rule out endocrine mediated effects, no estrogen or androgen activity was noted.

Metabolism studies with fluazifop-butyl and fluazifop-P-butyl suggest individual variation in rate of excretion is associated with exposure. This individual variation was noted in the rat, dog and human studies. Male rats were the only sex and species shown to excrete the pesticide in the bile and which resulted in a longer one-half life in male rats. However, variation in one-half lifes or delayed absorption was also noted in humans. This assumed individual variation in rate of absorption and excretion may have been at least partly due to experimental variation. In rats fluazifop acid was the major metabolite excreted in the urine and feces and essentially the only metabolite along with conjugates excreted in the urine of females. Strong binding of fluazifop acid to plasma proteins was found in rat and human blood with approximately 92% being bound. Typically, in females, 90% of the test material administered is excreted in the urine and about 10% in feces, whereas in males 44% is excreted in urine and about 52% in feces in 7 days. The metabolite fluazifop acid and it's conjugates are the major products excreted in the urine a feces of males and females with typically less than 2.6% of the ether cleavage products. Other metabolic products are less than 3%.

VI. DATA GAPS / REQUIREMENTS

The HIARC recommended a 28-Day Inhalation toxicity study to address the concerns for repeated inhalation exposure based on the use profile.

VII. ACUTE TOXICITY

Acute Toxicity Data on FLUAZIFOP-BUTYL & FLUAZIFOP-P-BUTYL.

Fluazifop-butyl (PC 122805)			
Guideline No./ Study Type	**MRID No.**	**Results**	**Toxicity Category**
870.1100 Acute oral toxicity/rats (PP009; 97.2%)	00162439 (1983)	LD50 = 1940 mg/kg (males) ± 1193-2758 mg/kg LD50 = 2653 mg/kg (females) ± 1764-3625 mg/kg	III
870.1200 Acute dermal toxicity/rabbits (PP009; 97.2%)	00162439 (1983)	LD50 > 2mL/kg (males and females) or approximately 2000 mg/kg	III
870.1300 Acute inhalation toxicity/rats (PP009; 97%) 79/ISK034/387	46082901, same as 41563701 (1979)	LC50 > 2.3 mg/L for 43% with a particle size <5 µm LC50 >4.37 mg/L for 83% with a particle size <10 µm	III
870.2400 Acute eye irritation/rabbit (PP009; 93.3%) 79/ILK9/068	00088855 (1979)	Non-irritating	IV
870.2500 Acute dermal irritation/rabbit (PP009; 93.3%) 79ILK8/056	00088853 (1979)	Mild erythema at 72 hours	IV
870.2600 Skin sensitization/GP (PP009; 99.6%) 80/ILK026/349	00088854 (1980)	Not a dermal sensitizer	

Fluazifp-P-butyl (PC 122809)			
Guideline No./ Study Type	**MRID No.**	**Results**	**Toxicity Category**
870.1100 Acute oral toxicity/rats (PP005; 93.7% & 86.3%)	00162440 (1984)	LD50 = 3680 mg/kg for males rats LD50 = 2451 mg/kg for female rats	III III
870.1200 Acute dermal toxicity/rabbits (PP005; 93.7% & 86.3%)	00162440 (1984)	LD50 > 2000 mg/kg or >1.73 mL/kg	III
870.1300 Acute inhalation [a] toxicity/rats (PP005; 24.6%) CTL/P/3331	41917904 (1991)	LC50 > 1.7 mg/L	III
870.2400 Acute eye irritation/rabbit (PP005; 86.3%) CTL/P/856	00162441 (1983)	Mild irritation, cleared within 3 days	IV
870.2500 Acute dermal irritation/rabbit (PP005; 86.3%) CTL/P/856	00162441 (1983)	Slight irritation, cleared within 72 hours	IV
870.2600 Skin sensitization/GP (PP005; 99.6%) 80/ILK026/349	00162441 (1983)	Not a skin sensitizer	

[a] This study was conducted with a mixture of 24.6% fluazifop-p-butyl and 7.0% fenoxyprop-p-ethyl, however, the concentration fluazifop-p-butyl in the inhalation chamber was determined to be 1.7 mg/L. PPOO9 was used to indicate the technical grade of fluazifop-butyl. PPOO5 was used to indicate the technical grade of fluazifop-P-butyl.

VIII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

Summary of Toxicological Dose and Endpoints for Fluazifop-butyl & Fluazifop-P-butyl

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 = **50** mg/kg/day UF = 100 **Acute RfD** = **0.50** mg/kg	FQPA SF = **1X** **aPAD** = acute RfD / FQPA SF = 0.50 mg/kg/	**Developmental Toxicity in rats** LOAEL = 200 mg/kg/day based on diaphragmatic hernia
Acute Dietary (General population including infants and children)	An appropriate endpoint attributable to a single dose was not identified in the available studies including the developmental toxicity studies.		
Chronic Dietary (All populations)	NOAEL= **0.74** mg/kg/day UF = 100 **Chronic RfD** = **0.008** mg/kg/day	FQPA SF = **1X** **cPAD** = chronic RfD / FQPA SF = **0.0074** mg/kg/day	**Two-Generation Reproduction in rats** LOAEL = 5.8 mg/kg/day in males and 7.1 in females based on decreased spleen, testes & epididymal weights in males and uterine & pituitary weights in females
Short-Term Incidental Oral (1-30 days)	Maternal NOAEL = 100 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** = NA	**Developmental Toxicity Study in rats** LOAEL = 300 mg/kg/day based on maternal body weight decrement during GD 7-16.
Intermediate-Term Incidental Oral (1- 6 months)	Parental/ Systemic NOAEL= 0.74 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** = NA	**Two-Generation Reproduction in rats** LOAEL = 5.8 mg/kg/day in males and 7.1 in females based on decreased spleen, testes & epididymal weights in males and uterine & pituitary weights in females
Short-Term Dermal [a] (1 to 30 days) **(Females 13-49)**	Developmental NOAEL= 2.0 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**Developmental Toxicity Study in rats** LOAEL = 5.0 mg/kg/day based on fetal weight, hydroureter and delayed ossification

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Short-Term Dermal [a] (1 to 30 days) **(General Population including Infants & children)**	Maternal NOAEL= 100 mg/kg/day	**Residential** LOC for MOE = **[100]**	**Developmental Toxicity Study in rats** LOAEL = 300 mg/kg/day based on maternal body weight decrements during GD 7-16.
Intermediate & Long-Term Dermal [a] (1 to >6 months)	Parental/ Systemic NOAEL= 0.74 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**Two-Generation Reproduction in rats** LOAEL = 5.8 mg/kg/day in males and 7.1 in females based on decreased spleen, testes & epididymal weights in males and uterine & pituitary weights in females
Short-Term Inhalation [b] 1 to 30 days) **(Females 13-49)**	Developmental NOAEL= 2.0 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**Developmental Toxicity Study in rats** LOAEL = 5.0 mg/kg/day based on fetal weight, hydroureter and delayed ossification
Short-Term Dermal [a] (1 to 30 days) **(General Population including Infants & children)**	Maternal NOAEL= 100 mg/kg/day	**Residential** LOC for MOE = **[100]**	**Developmental Toxicity Study in rats** LOAEL = 300 mg/kg/day based on maternal body weight decrements during GD 7-16.
Intermediate & Long-Term Inhalation [b] (1 to >6 months)	Parental/ Systemic NOAEL= 0.74 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**Two-Generation Reproduction in rats** LOAEL = 5.8 mg/kg/day in males and 7.1 in females based on decreased spleen, testes & epididymal weights in males and uterine & pituitary weights in females
Cancer (oral, dermal, inhalation)	"Not likely to be carcinogenic to humans."		

[a] Use either 9% (low exposure scenario) or 2% (high exposure scenario) for route-to-route extrapolations
[b] Absorption via the inhalation route is presumed to be equivalent to oral absorption.

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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