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TOXIC SUBSTANCES

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MEMORANDUM

Subject: **Norflurazon. HED Risk Assessment for Tolerance Reassessment Eligibility Decision (TRED).** PC Code 105801. Case 0229. DP Barcode D279777.

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Attached is the Health Effects Division (HED) preliminary human health risk assessment supporting issuance of a Tolerance Reassessment Eligibility Decision (TRED) for the herbicide **Norflurazon**. This assessment will not address the pending uses of norflurazon on Bermudagrass (PP#04621) or caneberries (PP#4E04383). A summary of the findings associated with currently registered uses of norflurazon and an assessment of the resulting human health risk are provided in this document. The supporting documents are included as appendices, as follows:

1. 105801.001.wpd, 9/10/95, O. Odiott (HED chapter of the RED)
2. HED Doc. No. 014286, 8/10/00 (report of the 6/6/00 HIARC meeting)
3. HED Doc. No. 014362, 10/26/00 (report of the 8/14/00 FQPA SFC meeting)
4. D268381, T. Bloem, 8/25/00 (Res. Chem. - field rotational crop study)
5. D268337, T. Bloem, 8/28/00 (MARC decision document for water)
6. D267639, T. Bloem, 8/18/00 (DEEM analysis)
7. D267067, T. Bloem, 7/20/00 (Registrant response to HED deficiencies in 5/14/97 memo)
8. D237815, T. Bloem, 12/5/00 (HED risk assessment)
9. D268075, P. Chin, T. Bloem, and L. Libelo, 8/9/00 (MARC briefing document)
10. D. Donaldson, 8/1/00 (Norflurazon Draft Qualitative Usage Analysis)

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1.0 Executive Summary

Norflurazon is used to control or suppress certain germinating grass and broadleaf weeds and is effective through disruption of carotenoid synthesis (pyridazinone herbicide). Tolerances are established for the combined residues of norflurazon and its desmethyl metabolite (40 CFR 180.356) in/on numerous commodities ranging from 0.05 ppm (asparagus and peanuts) to 5.50 ppm (peanut hay).

Hazard Profile: The toxicity data indicate that norflurazon has low acute oral, dermal, and inhalation toxicity. It is neither a skin sensitizer nor an eye or skin irritant. The subchronic feeding study in rats shows increased liver and kidney weight to body weight ratios and increased incidence of hypertrophic changes in thyroid glands (males only). The chronic feeding studies in rats, mice, and dogs demonstrated that norflurazon induced liver toxicity (increased liver weight) and kidney toxicity (nephritis/pyelonephritis and increased kidney weight). Norflurazon produced developmental toxicity in rabbits but not in rats, and it did not affect reproductive parameters in rats. The carcinogenicity data showed that norflurazon produced a statistically significant increase in incidence of hepatic adenoma/carcinoma in mice (males only) but not in rats. The chemical was classified as a Category C (possible human carcinogen) and does not require a quantitative cancer risk assessment.

The data raised concern for increased susceptibility in offspring. While the results of a developmental toxicity study in rats and a 2-generation reproduction study in rats showed no indication of increased susceptibility in young rats to norflurazon exposure, the data in rabbits provided an indication of increased susceptibility (quantitative) as shown by an increase in the incidence of skeletal variation at a dose lower than the maternal lowest observable adverse effect level (LOAEL). The maternal no-observable adverse effect level (NOAEL) was 30 mg/kg/day while the developmental NOAEL was 10 mg/kg/day. The maternal and developmental LOAELs were 60 and 30 mg/kg/day, respectively. Therefore, an FQPA safety factor of 3x was applied to the females 13 - 50 subgroup during acute exposure.

Dose Response Assessment: The HED Hazard Identification Assessment Review Committee (HIARC) met on July 6, 2000, to select endpoints for risk assessment and to evaluate the potential for increased susceptibility of infants and children from exposure to norflurazon. The FQPA Safety Factor Committee met on August 14, 2000 to evaluate the hazard and exposure data for norflurazon and recommended the FQPA Safety Factor to be used in assessing the risk posed by this chemical.

acute: The acute reference dose (aRfD) (for females aged 13 - 50 only) of 0.10 mg/kg/day was based on a statistical increase in skeletal variations in rabbit offspring. (NOAEL and LOAEL = 10 and 30 mg/kg/day, respectively) The FQPA Safety Factor Committee determined that the FQPA safety factor of 3x is applicable for acute dietary risk assessment. Therefore, the acute population adjusted dose (aPAD) is 0.03 mg/kg/day (aRfD divided by 3x) for females 13 - 50 only. Acute doses and endpoints that were attributable to a single exposure or dose were not selected for the general U.S. population (including infants and children).

chronic: The chronic reference dose (cRfD) of 0.015 mg/kg/day was based on increased absolute and relative liver weight and increased cholesterol values in dogs (NOAEL and LOAEL = 1.5 and 4.77 mg/kg/day respectively, in females). The FQPA Safety Factor Committee determined that the FQPA safety factor of 1x is applicable for chronic dietary risk assessment. Therefore,

the chronic population adjusted dose (cPAD) is also 0.015 mg/kg/day (cRfD divided by 1x).

carcinogenicity: The HED Cancer Peer Review Committee (HED Doc. No. 008487, 18-Jul-1990) evaluated the carcinogenicity studies in the rat and the mouse, along with the relevant toxicity studies and concluded that the high dose levels tested in both rats and mice were considered to be adequate for carcinogenicity testing. Treatment did not alter the spontaneous tumor profile in rats. However, carcinogenic potential was evidenced by an increased incidence of hepatic adenoma and combined adenoma/carcinoma in high dose male mice. The chemical norflurazon was classified as a Category C (possible human carcinogen) and does not require a quantitative cancer risk assessment.

dermal and inhalation: The short-term dermal and inhalation endpoints were selected from a developmental toxicity study in rabbits. The NOAEL of 10 mg/kg/day was based on a statistical increase in skeletal variation at the LOAEL of 30 mg/kg/day. The intermediate-term dermal and inhalation endpoints were selected from a six-month oral study in dogs. The NOAEL of 1.5 mg/kg/day was based on increased absolute and relative liver weight and increased cholesterol values at the LOAEL of 4.77 mg/kg/day. The long-term dermal and inhalation endpoints were also selected from the six-month oral study in dogs, where the NOAEL of 1.5 mg/kg/day was based on increased absolute and relative liver weight and increased cholesterol values at the LOAEL of 4.77 mg/kg/day. Since an oral endpoint was used in all cases, a dermal absorption factor of 6%, and an inhalation absorption factor of 100% were used for risk assessment.

Estimated Environmental Concentration (Ground and Surface Water): The residues of concern in drinking water are norflurazon and desmethyl norflurazon. Norflurazon has been detected in the ground water in Florida and North Carloina (6(a)2 reports submitted by the registrant). The ground water estimated environmental concentration (EEC) for norflurazon is based on the peak ground water concentration reported in the 1995 EFGWB Science Chapter (64 ppb; Polk County, FL). Tier II surface water EECs for norflurazon were generated using the PRIZM-EXAMS model (acute - 396 ppb; chronic - 40 ppb). The registrant has submitted limited data concerning the persistence and mobility of desmethyl norflurazon. Therefore, EFED was unable to generate an EEC for the degradate in ground water and was only able to generate a Tier I surface water EEC using the GENEEC model (acute and chronic - 169 ppb). EFED stated that the desmethyl norflurazon EECs are uncertain and the actual environmental concentration could be significantly higher. All models were run assuming an application rate of 8 lbs ai/acre (maximum proposed and registered rate).

Residential Exposure and Risk Estimates: At this time, there are no registered products containing norflurazon that are intended for homeowner use. Use on field-grown nursery stock is permitted by the current label, with application prior to emergence of weeds. For this use, only one application per year is permitted. Thus, exposure from registered uses via the residential pathway is negligible.

Aggregate Exposure and Risk Estimates: Aggregate exposures are calculated by summing dietary (food and water) and residential exposures. Residential exposure to norflurazon is expected to be negligible and norflurzon has been classified a Group C carcinogen (possible human carcinogen; does not require a quantitative risk assessment). Therefore, only acute and chronic aggregate exposure assessments are necessary and these will only be concerned with exposure from food and water.

Since HED does not have ground and surface water monitoring data to calculate a quantitative aggregate exposure, drinking water levels of comparison (DWLOC) were calculated (ground water monitoring data reflect only a few data points resulting from 6(a)2 reports and are not appropriate for quantitative assessment). The DWLOC is the theoretical upper limit of a chemical's concentration in drinking water that will result in an aggregate exposure less than a specified PAD. The DWLOC is used as a point of comparison against estimates of a pesticide's concentration in water. DWLOC values are not regulatory standards for drinking water.

Acute: The acute dietary exposure analysis for females 13-50 years old (no acute dietary endpoint was identified for the general US population including infants and children) assumed tolerance level residues, default processing factors, and 100% crop treated for all registered and proposed commodities (Tier 1 analysis). At the 95th percentile, the acute dietary exposure estimate for females 13-50 years old accounted for 10% of the aPAD. The estimated combined norflurazon and desmethyl norflurazon concentration in surface water and the estimated concentration of norflurazon in ground water are less than HED's DWLOC.

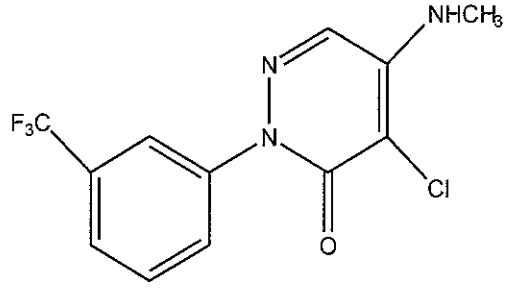
Chronic: The chronic dietary exposure analysis assumed tolerance level residues and default processing factors for all registered and proposed commodities. The weighted average percent crop treated was incorporated into the exposure analysis for the majority of the registered crops (proposed commodities were maintained at 100% crop treated). The chronic dietary food exposure estimates to norflurazon for all population subgroups were less than HED's level of concern (<100% cPAD). The most highly exposed population subgroup was children 1-6 years old at 11% of the cPAD. For all population subgroups, the estimated combined norflurazon and desmethyl norflurazon concentration in surface water and the estimated concentration of norflurazon in ground water are less than HED's DWLOCs (see Table 6 page 17).

The residues of concern in drinking water are norflurazon and desmethyl norflurazon. The registrant has submitted limited data concerning the persistence and mobility of desmethyl norflurazon. Therefore, EFED was unable to generate an EEC for desmethyl norflurazon in ground water and stated that the surface water EECs for desmethyl norflurazon are uncertain and the actual environmental concentration could be significantly higher. If the registrant submits information which allows for the generation of reliable EECs and these EECs (combined norflurazon and desmethyl norflurazon EEC) are less than the calculated DWLOCs, then aggregate acute exposure would be below HED's level of concern.

2.0 Physical/Chemical Properties

Norflurazon is noncorrosive and stable under alkaline and acidic conditions. It is an odorless white crystalline solid with a melting point of 177 C (Registration Eligibility Document (RED), O. Odiott *et. al.,* 10-Sep-1995).

Chemical Name:	4-chloro-5-(methylamino)-2-(α,α,α-trifluoro-m-tolyl)-3-(2H)-pyridazinon
Common Name:	norflurazon
Chemical Type:	pyridazinone herbicide
PC Code Number:	105801
CAS Registry No.:	27314-13-2
Empirical Formula:	$C_{12}H_9ClF_3N_3O$
Molecular Weight:	303.7
Vapor Pressure:	$<1 \times 10^{-5}$ torr at 25 C
Partition Coefficient (n-Octanol/Water):	2.3
Water Solubility:	<40 mg/l



norflurazon

3.0 Hazard Characterization

3.1 Hazard Profile (Tables 1 and 2)

The toxicity data indicate that norflurazon has low acute oral, dermal, and inhalation toxicity. It is neither a skin sensitizer nor an eye or skin irritant. The subchronic feeding study in rats shows an increased liver and kidney weight to body weight ratios and increased incidence of hypertrophic changes in thyroid glands (males only).

The chronic feeding toxicity study in rats, mice and dogs demonstrated that norflurazon induced liver toxicity (increased liver weight) and kidney toxicity (nephritis/pyelonephritis and increased kidney weight). Norflurazon produced developmental toxicity in rabbits but not in rats, and it did not affect reproductive parameters in rats.

The carcinogenicity data showed that norflurazon produced a statistically significant increase in incidence of hepatic adenoma/carcinoma in mice (males only) but not in rats. The chemical norflurazon was classified as a Category C (possible human carcinogen) and does not require a quantitative cancer risk assessment.

Norflurazon was negative for inducing mutations in all acceptable guideline studies of the standard battery of mutagenicity tests.

Norflurazon was rapidly absorbed orally and eliminated mainly in the urine (18.5-28.4% of the dose) and feces (65.3-79.5% of the dose). There appear to be four pathways for norflurazon metabolism: N-demethylation; displacement of the chlorine atom by glutathione; glutathione attack on the aromatic ring; and replacement of the chlorine atom by hydrogen. No tissue accumulation was observed.

Table 1: Acute Toxicity Data on Norflurazon Technical

Guideline No./Study Type	MRID No.	Results	Toxicity Category
870.1100 Acute Oral Toxicity-Rat	00111612	LD 50 = 9.3 g/kg (males)	IV
870.1200 Acute Dermal Toxicity - Rabbit	00090786	LD50 > 20 g/kg	IV
870.1300 Acute Inhalation Toxicity -Rat	00112980	LC5 > 200 mg/L (1-hour)	IV
870.2400 Acute Eye Irritation- Rabbit	00111612	No eye irritation	IV
870.2500 Acute Dermal Irritation-Rabbit	00111612	No dermal irritation	IV
870.2600 Skin sensitization - Guinea pig	00111615	acceptable study unavailable	N/A

Table 2: Toxicity Profile of Norflurazon Technical

Guideline No. Study Type	MRID No. (year) Classification Dose Levels	Results
870.3200b 21-day Dermal Toxicity, rabbit	00063617 (1972) Acceptable/Guideline dermal doses of 150 mg 80% w.p./ml and 400 mg 80% w.p./ml, 5 days per week, 6-8 hours per day, for 21 days	**NOAEL**:375 mg/kd/day **LOAEL**: 1000 mg/kg/day, based on increased alkaline phosphatase, increased liver weight and increased liver to body weight ratio
870.3700a Developmental Toxicity in rodents (rat)	00063621 (1972) Acceptable/Guideline 0, 100, 200, or 400 mg/kg/day (20 rats/dose) by oral gavage on gestation days 6 through 15 inclusive.	**NOAEL:** ***Maternal:*** <100 mg/kg/day ***Developmental:*** ≥ 400 mg/kg/day **LOAEL:** ***Maternal:*** ≤100 mg/kg/day, based on decreased body weight gain. ***Developmental:*** >400 mg/kg/day.
870.3700b Developmental Toxicity in non-rodents (rabbit)	00131152 (1983) Acceptable/Guideline 0, 10, 30, or 60 mg/kg/day norflurazon technical by oral gavage on gestation days 7 through 19 inclusive.	**NOAEL:** ***Maternal:*** 30 mg/kg/day ***Developmental:*** 10 mg/kg/day **LOAEL:** ***Maternal:*** 60 mg/kg/day, based on clinical toxicity and reduced body weight gain. ***Developmental:*** 30 mg/kg/day based on the statistical increase in skeletal variations (see comments) observed.
870.3800 Reproduction and fertility effects in rats (two generation)	43522301 (1991) Acceptable/Guideline dietary dose levels of 0, 150, 750, 1500 ppm over 2 generations (10.2, 50.8, and 102.5 mg/kg/day for F_o males; 12.1, 62.0, and 129.7 mg/kg/day for F_o females; 13.2, 67.8, and 138.6 mg/kg/day for F_1 males; 17.1, 81.7, and 173.0 mg/kg/day for F_1 females).	**NOAELs:** ***Parental toxicity:*** 150 ppm ***Reproductive toxicity:*** 750 ppm ***Offspring toxicity:*** 150 ppm **LOAELs** ***Parental toxicity:*** 750 ppm based upon the significant increases in liver and kidney weights observed in both generations of parental rats and the increased incidence of hepatocellular hypertrophy in both generations of parental rats. ***Reproductive toxicity:*** 1500 ppm based on a decreased lactation index in the F_2b litter and decreased mean pre-coital interval for the first litter of the F_o parental generation, and for both litters of the F_1 parental generation. In addition, there were decreased weight gain in F_2b litter pups (18%) vs control for days 4-21 post-partum. ***Offspring toxicity:*** 750 ppm based on decreased weight gain in F_2b litter pups (18%) vs control for days 4-21 post-partum and statistically significant increases in relative weight of the liver for male and female pups.

Guideline No. Study Type	MRID No. (year) Classification Dose Levels	Results
870.3800 Reproduction and fertility effects in rats (three generation)	00080750 (1971) Acceptable (Guideline) Sprague-Dawley rats (40 rats/dose) received Norflurazon technical (98.8% a.i.) in the diet at nominal doses of 0, 125, 375, and 1025 ppm (0, 6.25, 18.75, and 51.25 mg/kg/day).	**NOAELs:** ***Parental toxicity:*** 18.75 mg/kg/day (based on effects observed in the 9-month and 3-month rat toxicity studies) ***Reproductive toxicity:*** $\geq$ 51.25 mg/kg/day ***Offspring toxicity:*** $\geq$ 51.25 mg/kg/day **LOAELs:** ***Parental toxicity:*** 51.25 mg/kg/day (based on effects observed in the 9-month and 3-month rat toxicity studies) ***Reproductive toxicity:*** not established. ***Offspring toxicity:*** not established.
870.4100 Chronic toxicity in dogs	00111618 (1973) Acceptable/Guideline 0, 50, 150, and 450 ppm (1.53, 5.02, and 14.27 mg/kg for males; 1.58, 4.77, and 17.75 mg/kg for females) in the diet for 6 months	**NOAEL:** 50 ppm (1.53 mg/kg/day *males*; 1.58 mg/kg/day *females*) **LOAEL:** 150 ppm (5.02 mg/kg/day *males*; 4.77 mg/kg/day *females*) based on increased absolute and relative liver weight and increased cholesterol in both sexes.
870.4300 Chronic toxicity in rodents (rat)	00091056 (1971) Acceptable/Non-guideline Sprague-Dawley rats (80 rats/dose) 0ppm, 125ppm, 250ppm, and 500ppm (0, 6.25, 12.50, and 25.00 mg/kg/day) for 39 weeks in the diet	**NOAEL:** 250 ppm (12.50 mg/kg/day) **LOAEL:** 500 ppm (25.00 mg/kg/day) based on the dose-related increase in liver weight in male and female rats at 39 weeks, the increase in gonad weight of females, and the microscopic changes observed in kidneys of both sexes.
870.4300 Chronic toxicity/ carcinogenicity in rodents (rat)	00082019 (1971) Acceptable/Guideline O, 125, 375, and 1025ppm (0, 6.25, 18.75, and 51.25 mg/kg/day) for 104 weeks in the diet.	**NOAEL:** 375 ppm (18.75 mg/kg/day) **LOAEL:** 1025 ppm (51.25 mg/kg/day) Based on increased kidney weight and accompanying microscopic pathologic changes, as well as increased liver weight in male and female rats and the increase in thyroid weight in males. **Treatment related increase in tumor incidence was not found.**
870.4200 Carcinogenicity study in mice	00111649 (1971) Acceptable/Guideline 0, 85, 340, or 1360 ppm (0, 12.8, 58.7, or 218.8 mg/kg/day) for 100-104 weeks in the diet.	**NOAEL:** ***males:*** 85 ppm (12.8 mg/kg/day) ***females:*** 340 ppm (58.7 mg/kg/day) **LOAEL:** ***males:*** 340 ppm (58.7 mg/kg/day) based on the increased incidence of enlarged spleen, increased absolute and relative liver weight, and increased incidence of nephritis. ***females:*** 1360 ppm (218.8 mg/kg/day) based on the increased incidence of enlarged liver and cystic ovaries, the increased absolute and relative liver weight, and the increased incidence of pyelonephritis.
870.5300 Mutagenicity: chromosomal aberration	00155734 (1994) Acceptable/Guideline 63 - 1000 μg/ml	No evidence of a clastogenic response at any of the dose levels tested (with or without S9 activation)

Guideline No. Study Type	MRID No. (year) Classification Dose Levels	Results
870.5300 Mutagenicity: Unscheduled DNA synthesis	00155375 (1988) Acceptable/Guideline 1 - 333 μg/ml	No evidence of unscheduled DNA synthesis in rat hepatocytes at any of the dose levels tested.
870.7485 Metabolism	43081501 (1993) Acceptable/Non Guideline ^{14}C-Norflurazon was administered orally in ethanol : Emulphor EL-620 (2:3.2, v/v) to groups (5 sex/dose) of rats at a single low oral dose (1 mg/kg; Group A) and a single high oral dose (100 mg/kg; Group B).	In urine, the sulfone metabolite accounted for 0.03% of urinary radioactivity in Group A, and 0.2% in Group B. The sulfone metabolite accounted for 0.3% of fecal radioactivity in Group A, and 0.1% of fecal radioactivity in Group B.
870.7485 Metabolism	260490 (1985) Acceptable/Non Guideline Single oral doses of 2 or 110 mg/kg; single i.v. dose of 2 mg/kg; single oral dose 2 mg/kg following administration of 2 ppm in animal diet for 14 days.	norflurazon is rapidly and almost completely absorbed into the systemic circulation and excreted in female rats within 4 days after dosing. The radioactivity recovered in the urine and feces was 18.5-28.4% and 65.3-79.5% of the dose, respectively. There was no indication of bioaccumulation in any tissue or organ after administration of norflurazon.

3.2 FQPA Considerations

The HED Hazard Identification Assessment Review Committee (HIARC) met on June 6, 2000, to select endpoints for risk assessment and to evaluate the potential for increased susceptibility of infants and children from exposure to norflurazon (HED Doc. No. 014286). The FQPA Safety Factor Committee met on August 14, 2000, to evaluate the hazard and exposure data for norflurazon and recommend the FQPA Safety Factor to be used in assessing the risk posed by this chemical. The summary conclusions/recommendations of these committees are as follows:

The toxicology database for norflurazon is adequate according to the Subdivision F Guideline requirements for a food-use chemical. Acceptable developmental toxicity studies in the rat and rabbit are available, as is an acceptable multi-generation study. A developmental neurotoxicity study with norflurazon is not required.

Based on the results of developmental toxicity study in rats and 2-generation reproduction study in rats, there was no indication of increased susceptibility in young rats to norflurazon exposure. However, the data provided an indication of increased susceptibility (quantitative) of rabbits following *in utero* exposure to norflurazon as shown by an increased incidence of skeletal variations at a dose lower than the maternal LOAEL. The maternal NOAEL was 30 mg/kg/day while the developmental NOAEL was 10 mg/kg/day. The maternal and

developmental LOAELs were 60 and 30 mg/kg/day, respectively (HED Doc. No. 014286). It was recommended that the FQPA safety factor for protection of infants and children (as required by FQPA) should be **reduced to 3x** for norflurazon. A safety factor greater than 1x is required for norflurazon since there is evidence of quantitative increased susceptibility of the young demonstrated in the prenatal developmental study in rabbits. The FQPA safety factor is applicable to **only Females 13-50 Population Subgroup** for **Acute Dietary Risk Assessment** (there are currently no residential scenarios).

Cumulative Risk: EPA does not have, at this time, available data to determine whether norflurazon has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. Therefore, for the purposes of this risk assessment, EPA has not assumed that norflurazon has a common mechanism of toxicity with other substances.

Endocrine Disruption: The Food Quality Protection Act (FQPA; 1996) requires that EPA develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect...." EPA has been working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists to develop a screening and testing program as well as a priority setting scheme to implement this program. The Agency's proposed Endocrine Disrupter Screening Program was published in the Federal Register of December 28, 1998 (63 FR71541). The Program uses a tiered approach and anticipates issuing a Priority List of chemicals and mixtures for Tier 1 screening in the year 2000. As the Agency proceeds with implementation of this program, further testing of norflurazon and its end-use products for endocrine effects may be required.

3.3 Dose Response Assessment

Acute Dietary Endpoint: A developmental toxicity study in the rabbit was used to select the endpoint for establishing the Acute Reference Dose (RfD). The acute RfD (for females 13 - 50 only) of 0.10 mg/kg/day was based on a statistical increase in skeletal variations in rat offspring. (NOAEL and LOAEL = 10 and 30 mg/kg/day, respectively) The FQPA Safety Factor Committee determined that the FQPA safety factor of 3x is applicable for acute dietary risk assessment. Therefore, the **acute population adjusted dose (aPAD) is 0.03 mg/kg/day (aRfD divided by 3x) for females 13 - 50 only**.

An acute dose and endpoint were not selected for the general U.S. population (including infants and children) because there were no effects observed in oral toxicology studies, including maternal toxicity in the developmental toxicity studies in rats and rabbits, that were attributable to a single exposure or dose.

Chronic Dietary Endpoint: The six-month chronic/feeding study in the dog was used to select the endpoint for establishing the chronic reference dose (cRfD). The chronic RfD of

0.015 mg/kg/day was based on increased absolute and relative liver weight and increased cholesterol values at 4.77 mg/kg/day (LOAEL in females). The FQPA Safety Factor Committee determined that the FQPA safety factor of 1x is applicable for chronic dietary risk assessment. Therefore, **the chronic population adjusted dose (cPAD) is 0.015 mg/kg/day (cRfD divided by 1x).**

Carcinogenicity: The HED Cancer Peer Review Committee (HED Doc. No. 008487, 18-Jul-1990) evaluated the carcinogenicity studies in the rat and the mouse, along with the relevant toxicity studies and concluded that the high dose levels tested in both rats and mice were considered to be adequate for carcinogenicity testing. Treatment did not alter the spontaneous tumor profile in rats. However, carcinogenic potential was evidenced by an increased incidence of hepatic adenoma and combined adenoma/carcinoma in high dose male mice. The chemical norflurazon was classified as a Category C (possible human carcinogen) and does not require a quantitative cancer risk assessment.

Mutagenicity: Norflurazon was negative for inducing mutations in a standard battery of 3 mutagenicity studies. The database for mutagenicity is considered inadequate based on pre-1991 mutagenicity guidelines because 2 studies (chromosome aberration assay and unscheduled DNA synthesis assay) were acceptable and one study (Ames assay) was unacceptable. Although the Ames tests had technical difficulties which rendered them unacceptable under guideline requirements, another study may not provide us with substantial information concerning the mutagenicity of norflurazon based on the analysis of mutagenicity database for this chemical.

Dermal Penetration: The norflurazon dermal absorption factor is estimated by the HIARC to be 6% based on the comparison of the LOAELs in a 21-day rabbit dermal toxicity study (1000 mg/kg/day) and a rabbit developmental toxicity study (60 mg/kg/day) (memo, BH Chin, 10-AUG-2000). The estimate is considered to represent a worst-case scenario.

Short-term Dermal Endpoint: The short-term dermal endpoint was selected from a developmental toxicity study in rabbits. The NOAEL of 10 mg/kg/day was based on a statistical increase in skeletal variation at the LOAEL of 30 mg/kg/day. A dermal absorption factor of 6% was used for the extrapolation of an oral endpoint to a dermal exposure scenario.

Intermediate-term Dermal Endpoint: The intermediate-term dermal endpoint was selected from a six-month oral study in dogs. The NOAEL of 1.5 mg/kg/day was based on increased absolute and relative liver weight and increased cholesterol values at the LOAEL of 4.77 mg/kg/day. A dermal absorption factor of 6% was used for the extrapolation of an oral endpoint to a dermal exposure scenario.

Long-term Dermal Endpoint: The long-term dermal endpoint were also selected from the six-month oral study in dogs, where the NOAEL of 1.5 mg/kg/day was based on increased absolute and relative liver weight and increased cholesterol values at the LOAEL of 4.77 mg/kg/day. A dermal absorption factor of 6% was used for the extrapolation of

an oral endpoint to a dermal exposure scenario.

Short-term Inhalation Endpoint: The short-term inhalation endpoint was selected from a developmental toxicity study in rabbits. The NOAEL of 10 mg/kg/day was based on a statistical increase in skeletal variation at the LOAEL of 30 mg/kg/day. An inhalation absorption factor of 100% was used for the extrapolation of an oral endpoint to an inhalation exposure scenario.

Intermediate-term Inhalation Endpoint: The intermediate-term inhalation endpoint was selected from a six-month oral study in dogs. The NOAEL of 1.5 mg/kg/day was based on increased absolute and relative liver weight and increased cholesterol values at the LOAEL of 4.77 mg/kg/day. An inhalation absorption factor of 100% was used for the extrapolation of an oral endpoint to an inhalation exposure scenario.

Long-term Inhalation Endpoint: The long-term inhalation endpoint were also selected from the six-month oral study in dogs, where the NOAEL of 1.5 mg/kg/day was based on increased absolute and relative liver weight and increased cholesterol values at the LOAEL of 4.77 mg/kg/day. An inhalation absorption factor of 100% was used for the extrapolation of an oral endpoint to an inhalation exposure scenario.

The doses and toxicological endpoints selected for various exposure scenarios are summarized in Table 3.

Table 3: Norflurazon Technical: Summary of Toxicological Endpoints and Factors for Use in Human Risk Assessment

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA Safety Factor and LOC for Risk Assessment	Study and Toxicological Endpoints
Acute Dietary (Females 13 - 50)	NOAEL = 10 mg/kg/day UF = 100	FQPA SF = 3x **aPAD = 0.03 mg/kg/day**	Developmental Toxicity Study in Rabbits LOAEL = 30 mg/kg/day, based on increased incidence in skeletal variations observed.
Acute Dietary (General population)	n/a	n/a	No endpoint established.
Chronic Dietary (all populations)	NOAEL = 1.5 mg/kg/day UF = 100	FQPA SF = 1x **cPAD = 0.015 mg/kg/day**	6-Month Feeding Study in Dogs LOAEL = 4.77 mg/kg/day, based on increased absolute and relative liver weight and increased cholesterol in both sexes.
Incidental Oral, Short-Term	Maternal NOAEL= 30 mg/kg/day	LOC for MOE < 100 (occupational)	Developmental Toxicity Study in Rabbits LOAEL = 60 mg/kg/day, Based on reduced body weight gain during gestation days 7-19.
Incidental Oral, Intermediate-Term	Oral NOAEL = 1.5 mg/kg/day	LOC for MOE < 100 (occupational)	6-Month Feeding Study in Dogs LOAEL = 4.77 mg/kg/day Based on increased absolute and relative liver weight in both sexes.
Short-Term Dermal [a] and Inhalation [b]	Developmental NOAEL = 10 mg/kg/day[a, b]	LOC for MOE < 100 (occupational)	Developmental Toxicity Study in Rabbits LOAEL = 30 mg/kg/day, based on increased incidence in skeletal variations observed.
Intermediate- and Long-Term Dermal [a] and Inhalation [b]	Oral NOAEL = 1.5 mg/kg/day[a, b]	LOC for MOE < 100 (occupational)	6-Month Feeding Study in Dogs LOAEL = 4.77 mg/kg/day Based on increased absolute and relative liver weight in both sexes.

[a] Since an oral NOAEL was selected, a dermal absorption factor of 6% should be used in route-to-route extrapolation.

[b] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) should be used in route-to-route extrapolation.

legend: UF = uncertainty factor, FQPA SF = 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; LOC = level of concern; MOE = margin of exposure; CARC = Cancer Assessment Review Committee.

4.0 Exposure Assessment

4.1 Dietary (food) Risk Analyses

Acute and chronic dietary exposure analyses were conducted using DEEM™ (ver 7.075) and consumption data from the USDA 1989-92 CSFII (D267639, 18-Aug-2000, T. Bloem). The acute dietary exposure estimates used the entire distribution of single day food consumption while the chronic dietary exposure estimates used the three day average consumption for each population subgroup.

HED notes that there is a degree of uncertainty in extrapolating exposures for certain population subgroups which may not be sufficiently represented in the consumption survey (e.g., nursing infants and nonursing infants). However, risk estimates for these population subgroups are included in representative populations having sufficient numbers of survey respondents (e.g. all infants). The population subgroups listed in the following tables include only those subgroups having a sufficient number of respondents in the USDA 1989-92 CSFII food consumption survey to be considered statistically reliable.

Acute: The acute analysis assumed tolerance level residues, default processing factors, and 100% crop treated for all registered and proposed commodities. The acute dietary food exposure estimates to norflurazon for females 13-50 years old were less than HEDs level of concern (<100% aPAD). No acute endpoint was identified for general US population including infants and children. The following table summarizes the acute dietary exposure estimates.

Table 4: Summary of Norflurazon Acute DEEM™ Analysis

subgroups	exposure[1] (mg/kg/day)	% aPAD[2]
Females (13-50 years old)	0.003424	10

[1] 95th percentile
[2] aPAD = 0.03 mg/kg/day

Chronic: The chronic dietary exposure analysis assumed tolerance level residues for all registered and proposed commodities. The weighted average percent crop treated (Biological Economic Analysis Division, D. Donaldson, 1-Aug-2000) was assumed for all registered crops excluding citrus citron, kumquats, loganberries, raspberries, and pecans which were maintained at 100 % (no data available for these crops). Percent crop treated was maintained at 100% for all proposed commodities. Residues in livestock tissues were assumed to be present 100% of the time. Residues in milk were assumed to be present 32% of the time (highest percent crop treated for all feed items is 32%). The chronic dietary food exposure estimates to norflurazon, for all population subgroups, were less than HED's level of concern (<100% cPAD). The following table summarizes the chronic dietary exposure estimates.

Table 5: Summary of Norflurazon Chronic DEEM™ Analysis

subgroups	exposure (mg/kg/day)	% cPAD[1]
U.S. pop - all seasons	0.000623	4
All Infants (<1 year old)	0.000851	6
Children (1-6 years old)	0.001635	11
Children (7-12 years old)	0.000981	6
Females (13-50 years old)	0.000450	3
Males (13-19 years old)	0.000612	4
Males (20+ years old)	0.000450	3
Seniors (55+ years old)	0.000448	3

[1] cPAD = 0.015 mg/kg/day

4.2 Drinking Water Exposure

Environmental Fate Assessment: Information pertaining to the environmental fate of norflurazon was provided by EFED (D268674, L. Libelo, 8-Sep-2000; OPP RED, June 1996).
Norflurazon is resistant to abiotic hydrolysis and has a relatively low volatilization potential. Norflurazon is relatively resistant to microbial degradation with half lives of 130 days (aerobic soil metabolism study), 6-8 months (aerobic aquatic metabolism study), and 8 months (anaerobic aquatic metabolism study). The relatively low soil/water partitioning of norflurazon indicates that norflurazon can leach to ground water and runoff will generally be via dissolution rather than adsorption to eroding soil. The primary microbial degradate is desmethyl norfluazon. There is little data available on the persistence and mobility of desmethyl norflurazon. Based on the norflurazon degradation studies, it appears that desmethyl norflurazon is stable to hydrolysis, photolysis, and microbial degradation.

In 1992 and 1993, the registrant submitted 6(a)2 reports detailing the detection of norflurazon in ground water wells from Polk County and Highlands County, Florida (maximum of 64 ppb). In 1995, the registrant submitted a 6(a)2 report detailing the detection of norflurazon by the North Carolina Department of Agriculture in two samples taken from a newly installed 18-foot deep monitoring well (1.7 ppb and 5.3 ppb). In response to these detections, the registrant voluntarily commenced work on a prospective ground water monitoring study for the State of Florida. However, preliminary data submitted in quarterly reports suggest that the study is flawed and not likely to provide useful data (EFED, L. Libelo, 1998).

Drinking Water Levels of Comparison: In general, aggregate exposures are calculated by summing dietary (food and water) and residential exposures. Residential exposure to norflurazon is expected to be negligible and norflurzon has been classified a Group C carcinogen (possible human carcinogen; does not require a quantitative risk

assessment). Therefore, only acute and chronic aggregate exposure assessments are necessary and these will only be concerned with exposure from food and water. Since HED does not have ground and surface water monitoring data to calculate a quantitative aggregate exposure, DWLOCs were calculated (ground water monitoring data reflect only a few data points resulting from 6(a)2 reports and are not appropriate for quantitative assessment). The DWLOC is the theoretical upper limit of a chemical's concentration in drinking water that will result in an aggregate exposure less than a specified PAD. The DWLOC is used as a point of comparison against estimates of a pesticide's concentration in water. DWLOC values are not regulatory standards for drinking water.

To calculate the acute and chronic DWLOC, the dietary food exposure estimates were subtracted from the appropriate PAD. A DWLOC is then calculated using the following default body weights and drinking water consumption figures: 70kg/2L (adult male), 60kg/2L (adult female) and 10kg/1L (infant/child). Table 6 summarizes the acute and chronic DWLOCs.

Table 6: Acute and Chronic DWLOCs

Population Subgroup	PAD mg/kg/day	Dietary Exposure Estimate (mg/kg/day)	Allowable Drinking Water Exposure mg/kg/day	DWLOC[1] (ppb)	EEC (ppb)	
					Surface Water[2]	Ground Water[3]
acute						
Females (13-50 years old)	0.03	0.003424	0.026576	797	565	64
chronic						
U.S. pop - all seasons	0.015	0.000623	0.014377	503	96	64
All Infants (<1 year old)	0.015	0.000851	0.014149	141	96	64
Children (1-6 years old)	0.015	0.001635	0.013365	134	96	64
Children (7-12 years old)	0.015	0.000981	0.014019	140	96	64
Females (13-50 years old)	0.015	0.000450	0.014550	436	96	64
Males (13-19 years old)	0.015	0.000612	0.014388	504	96	64
Males (20+ years old)	0.015	0.000450	0.014550	509	96	64
Seniors (55+ years old)	0.015	0.000448	0.014552	509	96	64

1 $$DWLOC = \frac{(PAD\,(mg/kg/day) - \text{dietary exposure}\,(mg/kg/day))(\text{body weight}\,(kg))}{\text{water consumption}\,(\text{liter}/\text{day})} * 1000\mu g/mg$$

2 combined norflurazon and desmethyl norflurazon concentration; the chronic EEC is the sum of the norflurazon EEC (Tier II estimate) and 1/3 the desmethyl norflurazon EEC (Tier I estimate; HED SOP 99.5)

3 norflurazon concentration only; due to lack of appropriate fate and physical data EFED was unable to generate a ground water EEC for desmethyl norflurazon

4.3 Residential Exposure

At this time, there are no registered products containing norflurazon that are intended for homeowner use. Use on field-grown nursery stock is permitted by the current label, with application prior to emergence of weeds. For this use, only one application per year is permitted. Thus, exposure from registered uses via the residential pathway is negligible.

5.0 Aggregate Exposure and Risk Assessment

Residential exposure to norflurazon is expected to be negligible and norflurzon has been classified a Group C carcinogen (possible human carcinogen; does not require a quantitative risk assessment). Therefore, only acute and chronic aggregate exposure assessments are necessary and these will only be concerned with exposure from food and water.

Acute Aggregate Risk: The acute dietary exposure analysis for females 13-50 years old (no acute dietary endpoint was identified for the general US population including infants and children) assumed tolerance level residues, default processing factors, and 100% crop treated for all registered and proposed commodities (Tier 1 analysis). At the 95th percentile, the acute dietary exposure estimate for females 13-50 years old accounted for 10% of the aPAD. The estimated combined norflurazon and desmethyl norflurazon concentration in surface water and the estimated concentration of norflurazon in ground water are less than HED's DWLOC (see Table 6, page17).

The residues of concern in drinking water are norflurazon and desmethyl norflurazon. The registrant has submitted limited data concerning the persistence and mobility of desmethyl norflurazon. Therefore, EFED was unable to generate an EEC for desmethyl norflurazon in ground water and stated that the surface water EECs for desmethyl norflurazon are uncertain and the actual environmental concentration could be significantly higher. If the registrant submits information which allows for the generation of reliable EECs and these EECs (combined norflurazon and desmethyl norflurazon EEC) are less than the calculated DWLOCs, then aggregate acute exposure would be below HED's level of concern.

Chronic Aggregate Risk: The chronic dietary exposure analysis assumed tolerance level residues for all registered and proposed commodities. The weighted average percent crop treated (Biological Economic Analysis Division, D. Donaldson, 1-Aug-2000) was assumed for all registered crops excluding citrus citron, kumquats, loganberries, raspberries, and pecans which were maintained at 100 % (no data available for these crops). Percent crop treated was maintained at 100% for all proposed commodities. Residues in livestock tissues were assumed to be present 100% of the time. Residues in milk were assumed to be present 32% of the time. This was based on the fact that the highest percent crop treated for all feed items is 32%. The chronic dietary food exposure estimates to norflurazon, for all population subgroups, were less than HED's level of concern (<100% cPAD). The most highly exposed subpopulation was children (1-6 years old) at 11% of cPAD. For all population subgroups, the estimated combined norflurazon and desmethyl norflurazon concentration in surface water and the estimated concentration of norflurazon in ground water are less than HED's DWLOCs (see Table 6 page 17).

The residues of concern in drinking water are norflurazon and desmethyl norflurazon. The registrant has submitted limited data concerning the persistence and mobility of desmethyl norflurazon. Therefore, EFED was unable to generate an EEC for desmethyl norflurazon in ground water and stated that the surface water EECs for desmethyl norflurazon are uncertain and the actual environmental concentration could be significantly higher. If the registrant submits information which allows for the generation of reliable EECs and these EECs (combined norflurazon and desmethyl norflurazon EEC) are less than the calculated DWLOCs, then aggregate chronic exposure would be below HED's level of concern.

References (Attachments)

1: HED Doc. No. 014286, 10-Aug-2000 (HIARC)
2: HED Doc. No. 014362, 26-Oct-2000 (FQPA SFC)
3: D268075, P. Chin, T. Bloem, and L. Libelo, 9-Aug-2000 (Marc Briefing)
4: D268337, T. Bloem, 28-Aug-2000, (MARC briefing document)
5: D267639, T. Bloem, 18-Aug-2000 (DEEM analysis)
6: BEAD, D. Donaldson, 1-Aug-2000 (BEAD Draft Quantitative Usage Analysis
7: D237815, T. Bloem, 5-Dec.2000 (HED risk assessment)
8: D268381, T. Bloem, 25-Aug-2000 (Res. Chem.-field rotational crop study)
9: D267067, T. Bloem, 20-July-2000 (Registrant response to HED deficiencies in 5/14/97 memo)

References (not Attached)

1. 105801.001.wpd, 9/10/95, O. Odiott (HED Chapter of the RED)

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