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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Date: July 12, 2005

Subject: Aminopyralid: Aggregate Human Health Risk Assessment for the Proposed Uses on Wheat, Grasses, Non-cropland Areas, and Natural Areas.

DP No. 301689 Decision No. 341121
PC Code: 005100 Type: Herbicide
Petition No. 4F6827 Reg. No. 62719-LRI
40 CFR 180.new

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JUL 19 2005

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1.0 Executive Summary

Aminopyralid [4-amino-3,6-dichloro-2-pyridinecarboxylic acid] is the proposed common name of XDE-750, a new active ingredient developed by Dow AgroSciences, and the subject of a joint review between EPA, the Pest Management Regulatory Agency (PMRA) of Canada, and the Comisión Intersecretarial para el Control del Proceso y Uso de Plaguicidas y Sustancias Tóxicas (CICOPLAFEST) of Mexico. The petitioner, Dow AgroSciences, is currently proposing food/feed uses on grasses grown in rangelands and permanent pastures and on wheat for the selective control of invasive and noxious broadleaf weeds. It is also proposed for weed control in sites such as parks, campgrounds, electric utility rights-of way, forestry, woodlands, and wildlife openings, with smaller amounts used around railroads, utility substations, pipelines, and pumping stations.

The Health Effects Division (HED) of the EPA's Office of Pesticide Programs has evaluated the toxicity data submitted by the petitioner and has found it to be of sufficient scope and quality to assess the human health hazards associated with aminopyralid, including potential developmental, reproductive and neurotoxic effects. Acute toxicity data indicate that aminopyralid has low toxicity via oral, dermal, and inhalation routes of exposure. The free acid form of the molecule produced severe eye irritation. The stomach, ileum and cecum appear to be targets for this chemical. At mid- and high-level doses, ulcers and erosion of the mucosal lining were noted in the stomach. At high level doses, effects on the mucosal lining of the ileum and cecum were observed. Developmental and reproduction studies show that there is no evidence of increased qualitative or quantitative susceptibility of the fetuses to aminopyralid. Dermal studies indicate that aminopyralid does not have any significant toxicity via the dermal route of exposure. Aminopyralid has been classified as "not likely" to be carcinogenic to humans and there is no evidence that aminopyralid is an endocrine disruptor. Based on the available data, HED has determined that there is no appropriate endpoint to support acute exposure assessment for aminopyralid; therefore such assessments have not been conducted for this chemical. The toxicological data support assessment of short-, intermediate-, and long-term (chronic) durations of exposure based on the results of the developmental toxicity and chronic/cancer toxicity studies. There are no data gaps associated with the toxicology database.

In addition to the toxicology data, HED has also evaluated the residue chemistry database for aminopyralid. The residue chemistry data are fairly complete and are sufficient to evaluate the nature and magnitude of residues in crops and livestock. HED conducted a chronic dietary assessment that likely overestimates potential dietary exposure due to its assumption of 100% crop treated and tolerance-level residues. Even with the highly conservative assumptions used in that assessment, dietary risk estimates are well below HED's level of concern for human health. There are minor data gaps associated with the residue chemistry database for aminopyralid.

Based on the proposed use of aminopyralid in parks and campgrounds, there is the potential for post-application dermal and oral exposures to aminopyralid. As noted above, HED is generally not concerned with dermal exposure to aminopyralid. Oral exposure may occur for children due to the incidental ingestion of treated grass and soil, and via hand-to-mouth activities. HED has evaluated this potential exposure and determined that the human health risks are well

below our level of concern.

HED has also completed an aggregate assessment that takes into account dietary and non-dietary exposure to aminopyralid. As with the path-specific risk estimates, the risk estimates that combine dietary and potential incidental oral exposures are well below HED's level of concern.

HED has evaluated risks to workers applying aminopyralid and those involved in post-application activities. Based on mid- to high-end assumptions of exposure, risk estimates for all of these activities are below HED's level of concern. Due to the eye irritation finding for aminopyralid free acid, HED is recommending that the restricted-entry interval on the label be revised from 12 hours to 48 hours. There are no data gaps associated with residential or occupational exposure information for aminopyralid.

Based on our analysis of the available data and on estimates of risk, HED is recommending that a conditional registration for aminopyralid be granted and that permanent tolerances be established as follows:

Tolerances for free and conjugated residues of aminopyralid:

Grass, forage	25	ppm
Grass, hay	50	ppm
Wheat, forage	2.0	ppm
Wheat, hay	4.0	ppm
Wheat, grain	0.04	ppm
Wheat, straw	0.25	ppm
Wheat, bran	0.1	ppm
Aspirated grain fractions	0.2	ppm

Tolerances for aminopyralid *per se*:

Milk	0.03	ppm
Cattle, meat	0.02	ppm
Goat, meat	0.02	ppm
Horse, meat	0.02	ppm
Sheep, meat	0.02	ppm
Cattle, fat	0.02	ppm
Goat, fat	0.02	ppm
Horse, fat	0.02	ppm
Sheep, fat	0.02	ppm
Cattle, meat byproducts, except kidney	0.02	ppm
Goat, meat byproducts, except kidney	0.02	ppm
Horse, meat byproducts, except kidney	0.02	ppm
Sheep, meat byproducts, except kidney	0.02	ppm
Cattle, kidney	0.3	ppm
Goat, kidney	0.3	ppm
Horse, kidney	0.3	ppm
Sheep, kidney	0.3	ppm.

The recommendation for a conditional registration is due to the interim status of the available storage stability data and confirmation of the ability of the analytical method to differentiate between aminopyralid, picloram, and clopyralid (i.e., interference study). Prior to registration, the analytical method must be successfully validated by the Agency (validation is currently underway), and HED requests revisions to the label and submission of a revised Section F for the petition.

2.0 Ingredient Profile

Aminopyralid [4-amino-3,6-dichloro-2-pyridinecarboxylic acid] is the proposed common name of XDE-750, a new active ingredient developed by Dow AgroSciences. Aminopyralid is a systemic postemergence herbicide which belongs to the pyridine carboxylic acid class of herbicides. HED notes that aminopyralid differs from the active ingredient picloram by the elimination of one chlorine atom from the 5 position on the pyridine ring (i.e., picloram is 4-amino-3,5,6-trichloro-2-pyridinecarboxylic acid) and from the active ingredient clopyralid by the addition of an amino group (clopyralid is 3,6-dichloro-2-pyridinecarboxylic acid). As with other chemicals in this class, aminopyralid's mode of action toward target weeds is not completely understood. The principle action of these compounds appears to affect cell wall plasticity and nucleic acid metabolism. The petitioner is currently proposing food/feed uses on grasses grown in rangelands and permanent pastures and on wheat for the selective control of invasive and noxious broadleaf weeds. It is also proposed for weed control in sites such as parks, campgrounds, electric utility rights-of way, forestry, woodlands, and wildlife openings, with smaller amounts used in railroads, utility substations, pipelines, and pumping stations.

END-USE PRODUCTS:

Table 2.1. Summary of Proposed Aminopyralid End-Use Products.

Trade Name	Reg. No.	ai (% of formulation)	Formulation Type	Target Crops	Target Pests	Label Date
GF-871	62719-LRI	40.6% triisopropanol-ammonium (TIPA) salt of aminopyralid 21.1% acid equivalent (ae) aminopyralid; 2 lb ae/gal	Soluble concentrate liquid (SC/L)	Rangeland, permanent grass pastures, Conservation Reserve Program (CRP) acres, noncropland areas (such as rights-of-way, roadsides and non-irrigation ditch banks), natural areas (such as wildlife trails), and grazed areas in and around these sites; Wheat (including spring wheat, winter wheat, and durum)	Annual and perennial broadleaf weeds	3/4/04

Table 2.2. Summary of Proposed Directions for Use of Aminopyralid.						
Trade Name	Applic. Timing, Type, and Equip.	Applic. Rate (lb ae/A) [g ae/ha]	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ae/A) [g ae/ha]	PHI (days)	Use Directions and Limitations
Rangeland and Permanent Grass Pastures						
GF-871	Broadcast foliar spray or spot treatment; Ground or aerial	0.11]120]	Not specified (NS)	0.11]120]	None proposed	Applications may be made alone or as a tank mix with other herbicides. Applications may be made in a minimum of 2 gal/A by air and 10 gal/A by ground. Application through any type of irrigation system is prohibited.
Wheat, Including Durum (not underseeded with a legume)						
GF-871	Broadcast foliar spray or spot treatment; Ground or aerial	0.009]10]	NS	0.009 [10]	50 (grain and straw) 0 (hay and forage)	Broadcast applications may be made to actively growing wheat from the 3-leaf crop growth stage up to early jointing stage (Zadoks scale 30). Application to a cereal crop underseeded with a legume is prohibited. Applications may be made alone or as a tank mix with other herbicides such as fluroxypyr 1-methylheptyl ester (Starane), 2,4-D ester or amine, MCPA ester or amine, thifensulfuron-methyl (Harmony GT), tribenuron-methyl (Express XP), and metsulfuron-methyl (Ally XP).

The product label for GF-871 additionally specifies that an approved agricultural surfactant may be used and that any tank mixes should be pre-tested to determine physical compatibility between formulations and to confirm safety to the target crop. A re-entry interval of 12 hours is proposed.

The following rotational crop restrictions are proposed: (i) 0 months for wheat (including durum); (ii) 3 months for barley, canola (rapeseed), flax, grasses, field corn, grain sorghum, oats, mustard, popcorn, sweet corn; (iii) 9 months for safflower; and (iv) 18 months for all other crops.

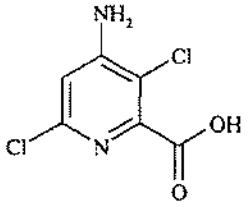
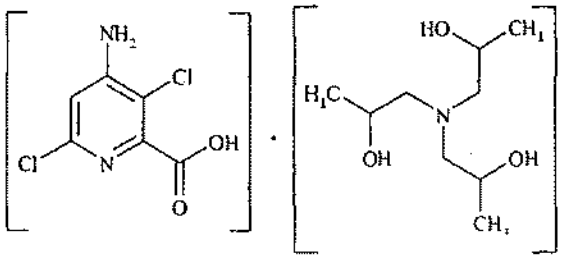
Table 2.3. Aminopyralid Nomenclature.	
Chemical structure	
Common name	Aminopyralid
Company experimental name	XDE-750
IUPAC name	4-amino-3,6-dichloropyridine-2-carboxylic acid
CAS name	4-amino-3,6-dichloro-2-pyridinecarboxylic acid
CAS registry number	150114-71-9
End-use product (EP)	2 lb ae/gal TIPA salt SC/L formulation (GF-871 Herbicide; EPA Reg. No. 62719-LRI)
Chemical structure	
Common name	Aminopyralid, triisopropanolamammonium (TIPA) salt
Company experimental name	XDE-750 TIPA salt
IUPAC name	Not provided
CAS name	Not provided
CAS registry number	Not provided
End-use product (EP)	2 lb ae/gal TIPA salt SC/L formulation (GF-871 Herbicide; EPA Reg. No. 62719-LRI)

Table 2.4. Physicochemical Properties of the Technical-Grade Aminopyralid.		
Parameter	Value	Reference
Melting point	163.5 °C	MRID 46235703
pH	2.31 at 23.4 °C (1% solution in water)	MRID 46235703
	7.33 at 19.8 °C (TIPA salt)	MRID
Density	1.72 g/mL at 20 °C	MRID 46235703
	1.14 g/mL at 20 °C (TIPA salt)	MRID 46235704

Table 2.4. Physicochemical Properties of the Technical-Grade Aminopyralid.			
Parameter	Value		Reference
Water solubility	2.48 g/L unbuffered water at 18 °C 212 g/L pH 5 buffer at 20 °C 205 g/L pH 7 buffer at 20 °C 203 g/L pH 9 Buffer at 20 °C		MRID 46235703
Solvent solubility at 20 °C	methanol acetone n-octanol ethyl acetate 1,2-dichloroethane xylene heptane	52.2 g/L 29.2 g/L 3.9 g/L 3.9 g/L 0.2 g/L 0.04 g/L <10 µg/mL	MRID 46235703
Vapor pressure	2.59×10^{-8} Pa at 25 °C; 9.52×10^{-9} Pa at 20 °C		MRID 46235703
Dissociation constant, pK_a	2.56		MRID 46235703
Octanol/water partition coefficient, $Log(K_{ow})$	0.201 unbuffered water at 19 °C; -1.76 at pH 5; -2.87 at pH 7; -2.96 at pH 9		MRID 46235703
UV/visible absorption spectrum	Solution	Wavelength λ max, nm	Extinction coefficient ε, L/(mol*cm)	MRID 46235703
	Neutral	217	29100	
	Basic	220	26100	
	(pH 12.6)	245	10150	
	Acidic	217	22800	
	(pH 1.4)	270	9140	

Based on the properties of technical-grade aminopyralid, exposure to this herbicide in the vapor phase is highly unlikely. Furthermore, the octanol-water partitioning coefficient indicates that this material is unlikely to sequester in fatty tissues and is unlikely to bioaccumulate.

3.0 Metabolism Assessment

3.1 Comparative Metabolic Profile

The Agency has received studies depicting the metabolic fate of aminopyralid in pasture grasses, wheat, lactating goat, laying hen, rat, and various environmental settings. In wheat and grasses as target crops, the major residues, totaling approximately 90% of the TRR in each matrix, were parent aminopyralid and glucose conjugates of aminopyralid (Table 3.1). In lettuce, sorghum, and turnips planted as rotated crops, aminopyralid and its glucose conjugates accounted for 88 to 97% of the TRR. In goats, hens, and rats, the majority of the dose was excreted as parent aminopyralid and, with the exception of goat kidney, radioactivity in animal tissues was too low for compound identification. In goat kidney, 80% of the TRR was parent aminopyralid.

Table 3.1. Identification of Compounds from Aminopyralid Metabolism Studies

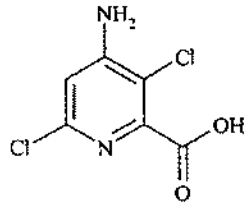
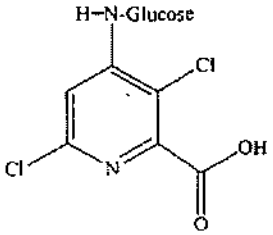
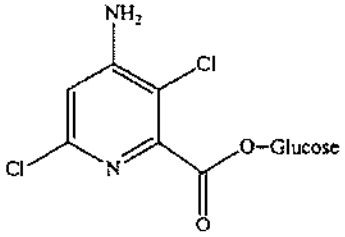
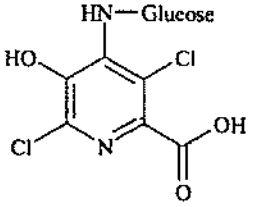
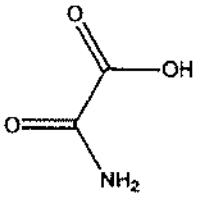
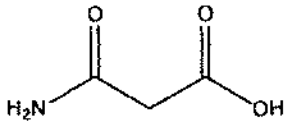
Common name/code	Chemical name	Chemical structure
Major Residues (> 10% TRR)		
Aminopyralid/XDE-750 Grass 25-35% TRR in forage Wheat ~60% TRR in grain ~15% TRR in hay ~90% TRR in forage (Day-0) ~40% TRR in forage (Day-14) ~80% TRR in straw Rotational Crops (lettuce, sorghum, turnips) 17-44% TRR Goat ~80% TRR in kidney TRR too low in other tissues and milk >94% TRR in urine and feces Poultry TRR too low in tissues and eggs ~93% TRR in excreta Rat Essentially 100% TRR	4-amino-3,6-dichloro-2-pyridinecarboxylic acid	
Glucose conjugates of aminopyralid Grass 61-66% TRR in forage Wheat ~75% TRR in hay Rotational Crops (lettuce, sorghum, turnips) 43-81% TRR Livestock/Rat Not Found	glucose conjugates of 4-amino-3,6-dichloro-2-pyridinecarboxylic acid	 
Minor Residues (< 10% TRR)		

Table 3.1. Identification of Compounds from Aminopyralid Metabolism Studies

Common name/code	Chemical name	Chemical structure
Glucose conjugate of hydroxylated aminopyralid Grass < 1% TRR in forage Wheat < 5% TRR in forage Rotational Crops Not Found Livestock/Rat Not Found	glucose conjugate of 4-amino-3,6-dichloro-5-hydroxypyridine -2-carboxylic acid	
Oxamic acid Aqueous photolysis only	Oxamic acid	
Malonamic acid Aqueous photolysis only	Malonamic acid	

Grass Metabolism: MRID 46235710. Single, foliar application of [2,6-^{14}C]aminopyralid, formulated as a potassium salt, made to pasture grasses at 0.321 lb ai/A and harvested 0, 7, 14, 21, or 42 days after treatment.

Wheat Metabolism: MRID 46235709. Single, foliar application of [2,6-^{14}C]aminopyralid, formulated as a potassium salt, made to wheat at 0 036 lb ai/A (40.1 g ai/ha, low rate] or 0.072 lb ai/A (80.3 g ai/ha, high rate) and harvested 0, 14, 35, or 86 days after treatment, depending on the commodity.

Goat Metabolism: MRID 46235708. Oral dosing of [2,6-^{14}C]aminopyralid at 13.31-14.79 ppm (average 13.96 ppm) in the diet for 6 consecutive days. Milk was collected twice daily. Urine and feces were collected daily. Animals were sacrificed and tissues were harvested ca. 24 hours after the last dose. With the exception of kidney, TRR were too low to allow residue identification.

Poultry Metabolism: MRID 46235711. Oral dosing of [2,6-^{14}C]aminopyralid at 11.56 ppm in the diet for 7 consecutive days. Eggs were collected twice daily. Excreta was collected daily. Animals were sacrificed and tissues were harvested ca. 24 hours after the last dose. TRR were too low to allow residue identification.

Rat Metabolism: MRIDs 46235807, 46235833. Oral gavage dosing of [2,6-^{14}C]aminopyralid at a single low dose (50 mg/kg bw), a single high dose (1000 mg/kg bw, or repeated low doses (50 mg/kg bw) for 14 days.

In all of the environmental fate studies except aqueous photolysis, residues were identified as aminpyralid, CO_2, or "bound.". In the aqueous photolysis study, residues of oxamic acid (CAS#471-47-6) and malonamic acid (CAS# 2345-56-4) were identified.

3.2 Residues of Concern

Overall, it appears that aminopyralid is not extensively metabolized in plants or animals. Grasses and wheat are able to conjugate significant amounts of the aminopyralid with glucose. These conjugates are readily convertible back to free aminopyralid by acid and/or base hydrolysis. The proposed plant analytical method includes both base and acid hydrolysis as an integral step in the extraction process. Based on the available metabolic data, HED has determined that the residues of concern for purposes of human health risk assessment and for

expression of tolerances are equivalent (Table 3.2). For plant commodities, this should be the combined free and conjugated aminopyralid, calculated as parent aminopyralid; for livestock commodities, this should be aminopyralid *per se*. The residue of concern in drinking water is also aminopyralid *per se*. HED has very low concern regarding the hazard associated with the environmental metabolites oxamic acid and malonamic acid. Searches of various hazard databases (e.g., TOXNET, MEDLINE, and others) did not reveal any cause for concern for either chemical. Both chemicals are small amino acid analogs. Following uptake, they are expected to be readily metabolized and/or rapidly excreted without any significant biological effects. Based on the available information, HED does not believe that it is appropriate to include residues of either oxamic acid or malonamic acid in dietary risk assessments; therefore, these compounds should not be included as residues of concern in drinking water.

Table 3.2. Residues of Concern for Human Health Risk Assesment and Residue Tolerance Expressions

Matrix		Risk Assessment	Residue Tolerance Expression
Plants	Primary Crop	Aminopyralid, free and conjugated	Aminopyralid, free and conjugated; expressed as aminopyralid
	Rotational Crop	Aminopyralid, free and conjugated	Aminopyralid, free and conjugated; expressed as aminopyralid
Livestock	Ruminant	Aminopyralid	Aminopyralid
	Poultry	Aminopyralid	Aminopyralid
Drinking Water		Aminopyralid	Not Applicable

4.0 Hazard Characterization/Assessment

4.1 Hazard Characterization

The toxicology database for aminopyralid is complete and there are no data gaps. The scientific quality of the database for aminopyralid is relatively high and the toxicity profile can be characterized for all effects, including potential developmental, reproductive and neurotoxic effects.

The acute toxicity data indicate that aminopyralid (XDE-750) has low toxicity (Category IV) via oral, dermal, and inhalation routes of exposure. It is not irritating to the skin: however, it is severely irritating to the eye. An acute eye irritation study in rabbits demonstrated corneal opacity (1/3) that was unresolved through day 35. Aminopyralid is not a sensitizer in a guinea pig skin sensitization study. Aminopyralid Triisopropanolamine salt (GF-871) is not toxic via oral, dermal, and inhalation routes of exposure. It is not irritating to the eye but is mildly irritating to the skin. An acute dermal irritation study in rabbits demonstrated slight erythema at 25 and 72 hours, resolving by day 7. It is not a sensitizer in a guinea pig skin sensitization study.

The database on aminopyralid indicates that the stomach, ileum and cecum are targets for this chemical. In a developmental toxicity study in rabbits with aminopyralid (XDE-750), there were ulcers and erosions observed in the glandular mucosa of the stomach in the mid- and high-

dose groups. Sub-chronic and chronic toxicity studies in dogs demonstrated slight diffuse hyperplasia and hypertrophy of the mucosal epithelium of the stomach at the highest dose tested. In addition, the chronic toxicity study demonstrated thickening of the stomach, slight lymphoid hyperplasia of the gastric mucosa, and slight chronic mucosal inflammation. Ileum and cecum toxicity was observed in a sub-chronic toxicity study in rats. Males of the high-dose group displayed hyperplasia of the mucosal epithelium of the ileum and the cecum. High-dose females displayed increased cecal weights without corresponding histopathology.

In a developmental toxicity study in rabbits with aminopyralid XDE-750, maternal toxicity was observed in the mid- and high-dose groups in the form of decreased body weights and incoordinated gait. Similar toxic effects were also observed in a developmental toxicity study in rabbits with aminopyralid GF-871. Developmental toxicity could not be determined in XDE-750 since the high-dose group was removed from the study due to the severity of clinical signs (body weight changes, decreased food consumption and a decreased amount of feces). However, in the developmental study with GF-871, developmental toxicity was demonstrated by a decrease in fetal body weights. In a 2-generation reproduction study in rats, there was no evidence of parental, reproductive, or offspring toxicity observed after exposure to aminopyralid. The developmental toxicity studies and the 2-generation reproduction study did not exhibit quantitative or qualitative susceptibility.

There were no systemic toxic effects observed in a 28-day dermal toxicity study in rats with aminopyralid. However, dermal toxicity was indicated by slight epidermal hyperplasia in males of the high-dose group.

Aminopyralid has been classified as "not likely" to be carcinogenic to humans. No increase in any tumors were found in carcinogenicity studies in rats and mice.

In an acute neurotoxicity study in rats with XDE-750, there were no treatment-related effects on Functional Observation Battery (FOB), motor activity, or neuropathological observations. Clinical observations of rats in the 2000 mg/kg/day group revealed a higher incidence of fecal soiling in males and urine soiling in females compared to the controls. However, these effects were transient (most resolving within 3-4 days of treatment) and without gross or neuropathologic changes. A chronic neurotoxicity study in rats did not demonstrate effects that would suggest neurotoxicity. Incoordinated gait was observed in developmental toxicity studies in rabbits with aminopyralid (XDE-750 and GF-871). This effect was transient (resolved 2 hours post-dosing) and not observed in any other toxicity study reviewed.

There is no evidence that aminopyralid is an endocrine disruptor.

The mutagenicity studies submitted for aminopyralid satisfy the mutagenicity test battery. Aminopyralid was negative in all mutagenicity studies, except for an *in vitro* chromosome aberration assay in Sprague Dawley rats. In this assay, XDE-750 induced chromosome aberrations, but only at cytotoxic concentrations. The clastogenic response was induced secondary to toxicity.

In a metabolism study in rats, aminopyralid was rapidly absorbed, distributed, and excreted following oral administration. Tissue distribution and bioaccumulation were minimal; <0.73% of administered dose (AD) was recovered in tissues after 7 days for all dosing groups. The highest levels of radioactivity were found in the skin and carcass. Aminopyralid was excreted unchanged indicating an absence of metabolism. The AD was recovered as parent compound in 100% of the feces and ≥ 96% of the urine. Three unknown components found in urine (≤ 4 %) were also detected in similar quantities in dose formulations, suggesting that they were trace impurities.

Results of the toxicity studies conducted with aminopyralid are summarized in Tables 4.1a and 4.1b.

Table 4.1a Acute Toxicity Profile - Aminopyralid Technical (XDE-750)				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute oral-rat	46235603	LD_{50} = >5000 mg/kg/bw (both sexes)	IV
870.1200	Acute dermal-rabbit	46235605	LD_{50} = >5000 mg/kg/bw (both sexes)	IV
870.1300	Acute inhalation-rat	46235607	LC_{50} = >5.5 mg/L (both sexes)	IV
870.2400	Acute eye irritation-rabbit	46235609	Corneal opacity in 1/3 unresolved through day 35	I
870.2500	Acute dermal irritation -rabbit	46235611	non-irritant	IV
870.2600	Skin sensitization-guinea pig	46235613	Not a sensitizer	N/A
Acute Toxicity Profile - Aminopyralid Triisopropanolamine salt (GF-871)				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute oral-rat	46235604	LD_{50} = >5000 mg/kg/bw (both sexes)	IV
870.1200	Acute dermal-rabbit	46235606	LD_{50} = >5000 mg/kg/bw (both sexes)	IV
870.1300	Acute inhalation-rat	46235608	LC_{50} = >5.79 mg/L (both sexes)	IV
870.2400	Acute eye irritation-rabbit	46235610	No positive signs of corneal opacity, iritis or conjunctivitis observed	IV
870.2500	Acute dermal irritation -rabbit	46235612	Slight erythema observed at 24 hours and 72 hours, resolving by study day 7	IV

870.2600	Skin sensitization-guinea pig	46235614	Not a sensitizer	N/A

Table 4.1b. Subchronic, Chronic and Other Toxicity Profile.

GDLN	Study Type	Dose Levels	MRID	Results
870.3100	2001-13 WEEK FEEDING-RAT (XDE-750) with 4 week recovery period	• mg/kg/day = 0, 10, 100, 500, 1000 Acceptable/Guideline	46235621	NOAEL (mg/kg/day): M=500, F= 1000 LOAEL (mg/kg/day): M=1000 based on hyperplasia of the mucosal epithelium of the ileum and cecum. F=not determined
870.3100	2004-13 WEEK FEEDING-RAT (GF-871)[‡]	XDE-750 TIPA* • mg/kg/day= 0, 192, 500, 1000 [¶] ACID EQUIVALENT (ac) mg ae/kg/day= 0, 100, 260, 520 Acceptable/Guideline	46235622	NOAEL (mg/kg/day): 520 LOAEL (mg/kg/day): not determined
870.3100	2001-13 WEEK FEEDING-MOUSE (XDE-750)	• mg/kg/day = 0, 10, 100, 500, 1000 Acceptable/Guideline	46235618	NOAEL (mg/kg/day): 1000 LOAEL (mg/kg/day): not determined
870.3150	2002-13 WEEK FEEDING-DOG (XDE-750)	%=0, 0.15, 0.75, 3.0 [§] ppm= 0, 1500, 7500, 30000 mg/kg/day = M: 0, 55, 282, 1070 F: 0, 53, 232, 929 Acceptable/Guideline	46235623	NOAEL (mg/kg/day): M=282, F= 232 LOAEL (mg/kg/day): M=1070, F=929 based on stomach histopathology (slight diffuse hyperplasia and hypertrophy of the mucosal epithelium).

870.3200	2002-28 DAY DERMAL-RAT (XDE-750)	mg/kg/day = 0, 100, 500, 1000 Acceptable/Guideline	46235626	Systemic: NOAEL (mg/kg/day): 1000 LOAEL: (mg/kg/day) not determined Dermal: NOAEL (mg/kg/day): M=100, F=1000 LOAEL (mg/kg/day): M=500, based on histopathological changes (slight epidermal hyperplasia). F=not determined
870.3700	2001-DEVELOPMENTAL TOX-RAT (XDE-750)	mg/kg/day = 0, 100, 300, 1000 Acceptable/Guideline	46235629	Maternal: NOAEL (mg/kg/day): 1000 LOAEL (mg/kg/day): not determined Developmental: NOAEL (mg/kg/day): 1000 LOAEL (mg/kg/day): not determined
870.3700	2004-DEVELOPMENTAL TOX-RAT (GF-871)[1]	XDE-750 TIPA* mg/kg/day= 0, 200, 500, 1000 *ACID EQUIVALENT (ae) mg ae/kg/day= 0, 104, 260, 520 Acceptable/Guideline	46235631	Maternal: NOAEL (mg/kg/day): 520 LOAEL (mg/kg/day): not determined Developmental: NOAEL (mg/kg/day): 520 LOAEL (mg/kg/day): not determined
870.3700	2002-DEVELOPMENTAL TOX-RABBIT (XDE-750)	mg/kg/day = 0, 25, 100, 250 (phase 1) mg/kg/day = 0, 500, 750 (phase 2) Acceptable/Guideline	46235630	Maternal: NOAEL (mg/kg/day): 250 LOAEL (mg/kg/day): 500 based on decrease in body weight (GD 7-10), decreased food consumption, incoordinated gait (23/26), and ulcers and erosions of the stomach. Developmental: NOAEL (mg/kg/day): 500 LOAEL (mg/kg/day): not determined

870.3700	2004-DEVELOPMENTAL TOX-RABBIT (GF-871)[f]	XDE-750 TIPA* mg/kg/day= 0, 200, 500, 1000 [f] ACID EQUIVALENT (ae) mg ae/kg/day= 0, 104, 260, 520 Acceptable/Guideline	46235632	Maternal: NOAEL (mg/kg/day): 104 LOAEL (mg/kg/day): 260 based on severe inanition and body weight loss, decreased fecal output, and mild incoordinated gait. Developmental: NOAEL (mg/kg/day): 260 LOAEL (mg/kg/day): 520 based on decreased fetal body weights.
870.3800	2003-2-GENERATION REPRODUCTION-RAT (XDE-750)	• mg/kg/day = 0, 50, 250, 1000 Acceptable/Guideline	46235635	Parental: NOAEL (mg/kg/day): 1000 LOAEL (mg/kg/day): not determined Reproductive: NOAEL (mg/kg/day): 1000 LOAEL (mg/kg/day): not determined Offspring: NOAEL (mg/kg/day): 1000 LOAEL (mg/kg/day): not determined
870.4100	2003-1 YEAR FEEDING-DOGS (XDE-750)	% =0, 0.03, 0.30, 3.0 [f] ppm= 0, 300, 3000, 30000 mg/kg/day = M: 0, 10, 99, 967 F: 0, 9, 93, 1038 Acceptable/Guideline	46235627	NOAEL (mg/kg/day): M=99, F= 93 LOAEL (mg/kg/day): M=967, F=1038 based on thickening of stomach mucosa (females), and stomach histopathology in all animals (slight diffuse hyperplasia and hypertrophy of the mucosal epithelium, slight lymphoid hyperplasia of the gastric mucosa and very slight/slight chronic mucosal inflammation).
870.4200	2003-18 MONTH CARCINOGENICITY-MICE (XDE-750)	• mg/kg/day = 0, 50, 250, 1000 Acceptable/Guideline	46235628	NOAEL (mg/kg/day): M=1000 LOAEL (mg/kg/day): not determined.

870.4300	2004-2 YEAR TOXICITY/ CARCINOGENICITY-RAT (XDE-750)	• mg/kg/day = 0, 50, 500, 1000 Acceptable/Guideline	46235615	NOAEL (mg/kg/day):50 LOAEL (mg/kg/day): 500 based on cecal enlargement, slight mucosal hyperplasia (males) and slightly decreased body weights.
870.5100	2004-BACTERIAL REVERSE MUTATION ASSAY (XDE-750)	0, 100, 333, 1000, 3300 or 5000 µg/plate (*Salmanella-Escherichia cali*) in the presence and absence of metabolic activation (± S9). Acceptable/Guideline	46235636	Negative
870.5100	2004-BACTERIAL REVERSE MUTATION ASSAY (GF-871)	XDE TIPA * 33, 100, 333, 1000, 3330, 5000 µg/plate (*Salmonella-Escherichia coh*) in the preseoce and absence of metabolic activation (± S9). Acceptable/Guideline	46235637	Negative
870.5300	2004-*IN VITRO* MAMMALIAN CELL GENE MUTATION TEST	0, 31, 63, 125, 250, 500, 1000, 1500, 2070 µg/mL (1st assay); 250, 500, 1000, 2000, 4000 µg/mL (2nd assay), both in the presence and absence of metabolic activation (± S9). Acceptable/Guideline	46235801	Negative
870.5300	2004-*IN VITRO* MAMMALIAN CELL GENE MUTATION TEST (GF-871)	XDE TIPA * 250, 500, 1000, 2000, 4000 µg/mL in the presence and absence of metabolic activation (± S9). Acceptable/Guideline	46235804	Negative

870.5375	2002-*IN VITRO* MAMMALIAN CELL CHROMOSOME ABERRATION TEST (XDE-750)	0, 32, 65, 129, 259, 518, 1035, 2070 µg/mL with and without metabolic activation (1st assay); 0, 125, 250, 500, 750, 1000, 1400, 1700, 2070 µg/mL without metabolic activation and 0, 62.5, 125, 500, 1000 or 2070 µg/mL with metabolic activation (2nd assay); 400, 600, 800, 1000, 1200, 1400, 1600, 1700, 1800, 2070 µg/mL without metabolic activation (3rd assay). Accceptable/Guideline	46235802	XDE induced chromosome aberrations, but only at cytotoxic concentrations; the clastogenic response was induced secondary to toxicity.
870.5375	2004-*IN VITRO* MAMMALIAN CELL CHROMOSOME ABERRATION TEST (GF-871)	XDE TIPA * 1000, 2000, 4000 µg/mL with and without metabolic activation (± S9); 0, 500, 1000, 2000 µg/mL without metabolic activation. Acceptable/Guideline	46235803	Negative
870.5395	2002-MAMMALIAN ERYTHROCYTE MICRONUCLEUS TEST (XDE-750)	mg/kg/day = 0, 500, 1000 or 2000 Acceptable/Guideline	46235805	Negative
870.5395	2004-MAMMALIAN ERYTHROCYTE MICRONUCLEUS TEST (GF-871)	mg/kg/day = 0, 500, 1000, or 2000 Acceptable/Guideline	46235806	Negative
870.6200	ACUTE NEUROTOXICITY-RAT (XDE-750)	• mg/kg/day = 0, 500, 1000, 2000 Acceptable/Guideline	46235616	NOAEL (mg/kg/day): 1000 LOAEL (mg/kg/day): 2000 based on fecal soiling in males and urine soiling in females.
870.6200	CHRONIC NEUROTOXICITY-RAT (XDE-750)	• mg/kg/day = 0, 5, 50, 500, 1000 Acceptable/Guideline	46235617	NOAEL (mg/kg/day): 1000 LOAEL (mg/kg/day): not determined

870.7485	2004-METABOLISM AND PHARMACOKINETICS-RAT (XDE-750)	mg/kg/day = Low dose: 50 High dose: 1000 Repeated low dose: 50 (unlabelled) for 14 days, 50 (labelled) on day 15 Acceptable/Guideline	46235807	Recovery after 168 hrs: 96% in low dose (urine-50%, feces-43%, tissues-0.1%, cage wash-3%), 95% in high dose (urine-41%, feces-43%, tissues-1%, cage wash-10%), and 95% in the repeated low dose (urine-59%, feces-33%, tissues-0.1%, cage wash-3%). XDE -750 represented ≥96% of administered dose (AD) in urine and 100% AD in feces. Three unknown components (≥ 4%) found in urine were also found in dose formulations.
Non-Guideline	XDE-750, Triisopropanolamine salt Dissociation and Metabolism in Male Fischer 344 Rats	mg/kg/day= 50 or 96	46235833	^{14}C-XDE-750 and ^{14}C-XDE-750-TIPA, when administered orally to rats, were bioequivalent in terms of absorption, distribution, metabolism, and excretion of the amino-dichloro-picolinate portion of the molecule(s).

* XDE-750 TIPA (aminopyralid triisopropanolammonium salt)
[1] GF-871 (41.3% TIPA)
[§] ppm calculated by reviewer
[4] dose levels were not given in ppm
[¶] acid equivalents calculated by reviewer

4.2 FQPA Hazard Considerations

4.2.1 Adequacy of the Toxicity Data Base

The toxicology database for aminopyralid is complete and there are no data gaps. Acceptable developmental toxicity studies were submitted for both the rat and the rabbit. There is also an acceptable 2-generation reproduction study, as well as acceptable acute and chronic neurotoxicity studies.

4.2.2 Evidence of Neurotoxicity

There is no evidence of neurotoxicity.

4.2.3 Developmental Toxicity Studies

Developmental Toxicity Study (XDE-750)-Rat; OPPTS 870.3700a; OECD 414

EXECUTIVE SUMMARY: In a developmental toxicity study (2001, MRID No.: 46235629), XDE-750, 94.5%, in 0.5% Methocel A4M, was administered to pregnant CD rats by gavage at dose levels of 0, 100, 300 or 1000 mg/kg/day on gestation days 6-20.

There were no treatment-related effects on mortality, body weight and body weight gain, food intake, organ weights, gross pathology or reproductive parameters.

The maternal LOAEL could not be determined since there were no treatment-related effects observed at any dose level tested. The NOAEL is 1000 mg/kg/day.

There were no treatment-related developmental nor teratogenic effects noted at any dose level tested.

The developmental LOAEL could not be determined. The developmental NOAEL is 1000 mg/kg/day.

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

Developmental Toxicity Study (GF-871)-Rat; OPPTS 870.3700a; OECD 414

EXECUTIVE SUMMARY: In a developmental toxicity study (2004, MRID No.: 46235631), GF-871 (containing 41.5% XDE-750 triisopropanolammonium, TIPA) in deionized water was administered to pregnant Sprague Dawley rats by gavage at dose levels of 0, 200, 500, or 1000 mg/kg/day in terms of XDE-750 TIPA at a constant volume of 4 mL/kg/bw/day on gestation days 6-19. The acid equivalent doses are 0, 104, 260, and 520 mg ae/kg/day. The animals were sacrificed on gestation day 20.

There were no deaths. There were no toxicologically meaningful clinical observations in any animals. A few clinical signs were observed sporadically throughout the groups; however, the findings were minor and did not follow a consistent pattern or dose response that would indicate a relationship to treatment. There were no statistically significant or toxicologically meaningful differences in mean body weights, body weight changes, mean maternal body weight change or food consumption between the control and test groups. Gross findings at scheduled necropsy were generally unremarkable and there were no statistically significant or toxicologically meaningful differences in absolute liver and kidney weights or organ-to-body weight ratios between the control and test animals. There were no toxicologically meaningful differences in cesarean section parameters between the control and test groups. No statistically significant or toxicologically meaningful differences were noted among the groups with respect to fetal malformations or developmental variations.

The maternal and developmental LOAEL could not be determined. The NOAEL for maternal and developmental toxicity is 520 mg ae/kg/day (1000 mg/kg/day based on XDE-750 TIPA), the highest dose tested. There was no evidence of teratogenicity.

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

Developmental Toxicity Study (XDE-750)-Rabbit; OPPTS 870.3700b; OECD 414

EXECUTIVE SUMMARY: In a developmental toxicity study (2002, MRID No.: 46235630), XDE-750, 94.5%, in 0.5% Methocel A4M, was administered to pregnant New Zealand White rabbits by gavage at dose levels of 0, 25, 100 or 250 mg/kg/day (Phase I) or 0, 500 or 750 mg/kg/day (Phase II), from gestation days 7-27.

Two animals in the 750 mg/kg/day group were sacrificed in a moribund condition (incoordinated gait, significant body weight losses, and decreased food intake), which was considered to be treatment-related. In the 500 and 750 mg/kg/day groups, there was an increased incidence of incoordinated gait, which was more pronounced in the 750 mg/kg/day group. In most cases, the incoordination was transient, with complete reversal within two hours post-dosing, and did not appear to progressively worsen on subsequent days. The only other clinical observation was decreased amounts of feces observed in the 750 mg/kg/day group. There was a net loss in body weight in the 500 and 750 mg/kg/day groups during the first 3 days of the dosing period (days 7 to 10), with a corresponding decrease in food consumption, which was more pronounced in the 750 mg/kg/day group. The 750 mg/kg/day group was removed from the study on day 20 due to decreases in body weight gain on gestation days 7-10 as well as severity of clinical signs. At necropsy, there was an increased incidence of pale kidneys and of ulcers/erosions in the glandular mucosa of the stomach in the 750 mg/kg/day group. The observation of ulcers/erosions in the glandular mucosa of the stomach of a single rabbit in the 500 mg/kg/day group was considered to possibly be related to treatment. There were no treatment-related maternal findings observed in the 25, 100 or 250 mg/kg/day groups.

The maternal LOAEL is 500 mg/kg/day based on clinical signs and body weight changes. The NOAEL is 250 mg/kg/day.

There were no treatment-related developmental nor teratogenic effects noted at any dose level tested.

The developmental LOAEL could not be determined. The developmental NOAEL is 500 mg/kg/day.

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

Developmental Toxicity Study (GF-871)-Rabbit; OPPTS 870.3700b; OECD 414

EXECUTIVE SUMMARY: In a developmental toxicity study (2004, MRID No.: 46235632), GF-871 (41.3 % XDE-750 triisopropanolammonium, TIPA) in deionized water was administered to pregnant New Zealand White rabbits by gavage at dose levels of 0, 200, 500, or 1000 mg/kg/day in terms of terms of TIPA at a constant volume of 4mL/kg bw on gestation days 7-27. The acid equivalent doses are 0, 104, 260, and 520 mg ae/kg/day. The day when copulation was observed was designated as day 0 of gestation. In-life maternal parameters examined included clinical observations, body weight, body weight gain, and feed consumption. On gestation day 28, all survivors were euthanized and examined for gross pathologic alterations and changes in liver, kidney, and gravid uterine weights. The numbers of corpora lutea, uterine implantations, resorptions and live/dead fetuses were determined. All fetuses were weighed, sexed and examined for external, visceral, and skeletal abnormalities. Also, the internal structures of the head were examined by serial sectioning for approximately one-half of the fetuses in each litter. At 520 mg ae/kg/day maternal toxicity was evidenced by decreased feed consumption and body weight gains.

One high-dose rabbit aborted (one control also aborted), and three others were euthanized early due to severe inanition and subsequent body weight loss. At 260 mg ae/kg/day, one rabbit was euthanized due to severe inanition (exhaustion due to lack of food) and body weight loss. Treatment-related clinical observations included decreased fecal output in the 260 and 520 mg ae/kg/day groups, and signs of mild incoordination in 0, 1, 2, and 19 rabbits from the 0, 104, 260, and 520 mg ae/kg/day dose groups, respectively. The incoordination was transient, occurred sporadically, and in the 104 and 260 mg/kg/day groups, was seen only once in each affected rabbit. Developmental effects were limited to decreased fetal body weights at 520 mg ae/kg/day. There was no evidence of teratogenicity.

The maternal LOAEL is 260 mg ae/kg/day and the maternal NOAEL is 104 mg ae/kg/day (200mg/kg/day of XDE-750 TIPA). The developmental LOAEL is 520 mg ae/kg/day (1000 mg/kg/day of XDE-750 TIPA) and the developmental NOAEL is 260 mg ae/kg/day (500 mg/kg/day of XDE-750 TIPA).

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

4.2.4 Reproductive Toxicity Study

Reproduction and Fertility Effects-Rat; OPPTS 870.3800; OECD 416

EXECUTIVE SUMMARY: In a 2-generation rat reproduction study, XDE-750, purity 94.5%, was administered to 30 Sprague Dawley rats per sex per group in the diet at concentrations of 0, 50, 250 or 1000 mg/kg bw/day (equal to 0, 52.0, 259 or 1030 mg/kg

bw/day for males, and 0, 49.3, 245 or 973 mg/kg bw/day for females). Each female in each generation was mated to produce one litter.

For parent animals, there were no treatment-related effects on mortality, clinical signs, body weight and body weight gain, food intake, reproductive function, reproductive parameters or histopathology. Full and/or empty cecal weights were increased in the P_1 generation, in the 250 and 1000 mg/kg bw/day groups, both sexes. In the P_2 generation, full and empty cecal weights were increased in the 1000 mg/kg bw/day group, both sexes, and in the 50 and 250 mg/kg bw/day groups, males only. At gross necropsy, cecal size was increased in the P_1 and P_2 generations, in the 250 and 1000 mg/kg bw/day groups, both sexes. In the absence of any histopathological changes to the ceca, and in the absence of any other treatment-related parental findings, the cecal findings were considered to be adaptive changes and were not considered to be adverse.

For pups, there were no treatment-related effects on clinical signs, viability/litter parameters, pup body weight and body weight gain, organ weights or gross pathology

For parental toxicity, the LOAEL could not be determined since there were no adverse, treatment-related effects. The NOAEL is 1000 mg/kg/day (1030/973 mg/kg/day).

For reproductive toxicity, the LOAEL could not be determined since there were no treatment-related effects. The NOAEL is 1000 mg/kg/day (1030/973 mg/kg/day).

For offspring toxicity, the LOAEL could not be determined since there were no treatment-related effects. The NOAEL is 1000 mg/kg/day (1030/973 mg/kg/day).

The multi-generation study in the rat is classified acceptable and satisfies the guideline requirement for a reproduction and fertility study (OPPTS 870.3800; OECD 416) in the rat.

4.2.5 Additional Information from Literature Sources

A literature search did not reveal studies with aminopyralid that would impact this risk assessment.

4.2.6 Pre-and/or Postnatal Toxicity

4.2.6.1 Determination of Susceptibility

There is no evidence of increased qualitative or quantitative susceptibility of the fetuses in the rat or rabbit developmental toxicity studies (XDE-750 and GF-871) or in a 2-generation reproduction study (rat) after exposure to aminopyralid.

4.2.6.2 Degree of Concern Analysis and Residual Uncertainties for Pre- and/or Post-natal

Susceptibility

There is no evidence of increased qualitative or quantitative susceptibility of the fetuses in the rat or rabbit developmental toxicity studies (XDE-750 and GF-871) or in a 2-generation reproduction study (rat) after exposure to aminopyralid. The toxicology database is complete with respect to pre and postnatal toxicity. Therefore, HED has no residual uncertainty regarding this finding.

4.3 Recommendation for a Developmental Neurotoxicity Study

4.3.1 Evidence that supports requiring a Developmental Neurotoxicity study

A Developmental Neurotoxicity study is not recommended at this time

4.3.2 Evidence that supports not requiring for a Developmental Neurotoxicity study

In an acute neurotoxicity study in rats with XDE-750, there were no treatment-related effects on the Functional Observational Battery (FOB), motor activity, or neuropathological observations. Clinical observations of rats in the 2000 mg/kg/day group revealed a higher incidence of fecal soiling in males and urine soiling in females compared to the controls. However, these effects were transient (most resolving within 3-4 days of treatment) and without gross or neuropathologic changes. In addition, a chronic neurotoxicity study in rats did not demonstrate effects that would suggest neurotoxicity. In developmental toxicity studies in rabbits with aminopyralid (XDE-750 and GF-871) incoordinated gait was observed in males and females in the mid- and high-dose groups. However this finding was transient, with complete reversal within two hours post-dosing. Incoordinated gait was not observed in any of the other toxicity studies reviewed.

4.4 Hazard Identification and Toxicity Endpoint Selection

A summary of toxicology endpoints is in Table 4.4.

4.4.1 Acute Reference Dose (aRfD) - Females age 13-49

An acute reference dose for females, ages 13-49, has not been established. Two developmental toxicity studies in rats (XDE-750 and GF-871), a developmental toxicity study in rabbits (XDE-750), and a 2-generation reproduction study in rats, did not demonstrate evidence of toxicity attributable to a single dose. The only developmental effect seen was a decrease in fetal body weights at 520 mg ae/kg/day. This finding was observed in a developmental toxicity study in rabbits (GF-871) and is not the result of a single dose. Therefore, there is no appropriate endpoint for establishing an acute RfD for women of child-bearing age.

4.4.2 Acute Reference Dose (aRfD) - General Population

An acute reference dose for the general population has not been established. In an acute

neurotoxicity study in rats, a NOAEL was set at 1000mg/kg/day based on toxic effects seen at 2000 mg/kg/day. These effects were urine soiling in females and fecal soiling in males. Since these effects occurred at such a high dose, there is no concern for an acute dietary risk. Therefore, an acute RfD for the general population is not required.

4.4.3 Chronic Reference Dose (cRfD)

Study:	Chronic toxicity/Carcinogenicity study-Rat (MRID 46235615)
NOAEL:	50 mg/kg/day
LOAEL:	500 mg/kg/day
Uncertainty Factor:	100x (10X interspecies extrapolation, 10X for intraspecies variations)

Comments: The rat combined chronic toxicity/carcinogenicity study was used to select the dose and endpoint for establishing the cRfD of 0.5 mg/kg/day. The NOAEL of 50 mg/kg/day and the LOAEL of 500 mg/kg/day was based on cecal enlargement, slight mucosal hyperplasia of the cecum in males and slightly decreased body weights. The duration of exposure is appropriate for this endpoint.

EXECUTIVE SUMMARY: In a combined chronic toxicity, oncogenicity, and neurotoxicity study (2004, MRID No.: 46235615), XDE-750 (94.5 % purity) was administered in the diet to groups of Fischer 344 rats, 65/sex/group, at 0, 5, 50, 500, or 1000 mg/kg/day. Ten/rats/sex/group were used for neurotoxicity assessment; 5 of these rats/sex/group were sacrificed at 12 month for gross and histopathologic examinations of the nervous tissues. Also at 12 months, 10 rats/sex/ group were necropsied for chronic toxicity examination. The remaining animals were maintained on their respective diets for up to 24 months. All rats were observed daily for mortality and clinical signs of toxicity. They were palpated monthly from months 12 to 24 for tissue masses. Body weight and food consumption were recorded. Hematology, clinical chemistry, and urinalysis were carried out at 3, 6, 12, 18, and 24 months. Ophthalmic examination was conducted prior to dosing and at the end of the study period. At terminal sacrifice, weights of selected organs were recorded, and the animals were subjected to gross and histopathological examination. For rats in the neurotoxicity groups, the following additional parameters were measured: motor activity and functional observatory battery (FOB) at pre-exposure, end of first month, the subsequently at months 3, 6, 9, and 12.

No treatment-related or toxicologically significant effects were observed on clinical signs, mortality, ophthalmoscopy, hematology, or clinical chemistry. The numbers of male and female rats (based on the main groups of 50/group) that survived to study termination were: ♂ = 31, 36, 33, 33, 33; ♀ = 41, 38, 39, 38, 39 at 0, 5, 50, 500, or 1000 mg/kg/day, respectively. Treatment induced toxicity included lower body weight and body-weight gain in both males and females at 1000 mg/kg/day. Body weight of males was also slightly depressed at 500 mg/kg/day. Food consumption was increased for high-dose male rats. Urinalysis changes were observed at ≥500 mg/kg/day. The changes included slightly increased urine volume as well as decreased specific gravity and pH. Urinalysis changes

were unaccompanied by renal histopathologic effects, and they were considered adaptative changes upon fluid homeostasis secondary to the cecal effects and renal excretion of XDE-750. The only target organ was the cecum, which was grossly enlarged. Cecal weights (with ingesta) were increased about four-fold in males and three-fold in females given 1000 mg/kg/day for 12 months, but the degree of increase was slightly less after 24 months. Very slight hyperplasia of the cecal mucosa was noted, but this was also less apparent after 24 months than at 12 months. No effects were attributed to XDE-750 at either 5 or 50 mg/kg/day. There were no tumours related to XDE-750 ingestion.

The LOAELs for systemic toxicity for the males and females are 500 and 1000 mg/kg/day, respectively. The NOAEL is 5 and 50 mg/kg/day for males and females, respectively. XDE-750 was not carcinogenic to Fischer 344 rats under the conditions of this study.

This study is acceptable and satisfies the data requirement for a chronic toxicity/oncogenicity study (OPPTS; OECD 408) in the rat.

$$\text{Chronic Rfd} = \frac{\text{50 mg/kg/day (NOAEL)}}{\text{100 (UF)}} = 0.5 \text{ mg/kg/day}$$

4.4.4 Incidental Oral Exposure (Short- and Intermediate-Term)

Short-Term Incidental Exposure (1-30 days)

Study:	Developmental toxicity study -Rabbit (MRID 46235632)
NOAEL:	104 mg/kg/day
LOAEL:	260 mg/kg/day
Uncertainty Factor:	100x (10X interspecies extrapolation, 10X for intraspecies variations)

Comments: A developmental rabbit study (GF-871) was used to select a dose and endpoint for evaluating short-term incidental oral exposure. The maternal NOAEL of 104 mg ae/kg/day and the maternal LOAEL of 260 mg ae/kg/day were based on severe inanition and body weight loss, decreased fecal output, and mild incoordinated gait. The duration of exposure is appropriate for this endpoint.

EXECUTIVE SUMMARY: see section 4.2.3

Intermediate-Term Incidental Exposure (1-6 months)

Study:	Developmental toxicity study -Rabbit (MRID 46235632)
NOAEL:	104 mg/kg/day

LOAEL: 260 mg/kg/day
Uncertainty Factor: 100x (10X interspecies extrapolation, 10X for intraspecies variations)

Comments: A developmental rabbit study (GF-871) was used to select a dose and endpoint for evaluating intermediate-term incidental oral exposure. The maternal NOAEL of 104 mg ae/kg/day and the maternal LOAEL of 260 mg ae/kg/day were based on severe inanition and body weight loss, decreased fecal output, and mild incoordinated gait. The duration of exposure is appropriate for this endpoint. A 13 week dog study was also considered for the intermediate-term incidental oral endpoint. However, this study was not selected since the NOAEL of 232 mg/kg/day was higher than the one used for the short-term incidental oral endpoint. The NOAEL of 104 mg ae/kg/day selected for the intermediate-term incidental oral endpoint is protective of effects seen in the 13 week dog study.

EXECUTIVE SUMMARY: see section 4.2.3

4.4.5 Dermal Absorption

No dermal absorption study is available for aminopyralid. However, a 28 dermal toxicity study in rats was submitted. In this study, no systemic toxicity occurred at the limit dose (1000 mg/kg/day) and the primary toxic effects of concern were adequately assessed in the study. Therefore, it is concluded that aminopyralid is not absorbed or is poorly absorbed through the skin.

4.4.6 Dermal Exposure (Short, Intermediate and Long Term)

A 28 day dermal study in rats was submitted for aminopyralid. There was no systemic toxicity at the highest dose tested of 1000 mg/kg/day. At 500 mg/kg/day, there was inflammation and slight epidermal hyperplasia in males only. Dermal endpoints for short-, intermediate-, and long-term dermal toxicity scenarios are not required because of low toxicity. Dermal toxicity (inflammation and slight hyperplasia) should be reflected on the chemical label as a potential concern.

4.4.7 Inhalation Exposure (Short, Intermediate and Long Term)

Short-Term Inhalation Exposure (1-30 days)

Study: Developmental rabbit toxicity study (MRID 46235632)
NOAEL: 104 mg ae/kg/day
LOAEL: 260 mg ae/kg/day
Uncertainty Factor: 100x (10X interspecies extrapolation, 10X for intraspecies variations)

Comments: A developmental rabbit study (GF-871) was used to select a dose and

endpoint for evaluating short-term inhalation exposure. The maternal NOAEL of 104 mg ae/kg/day and the maternal LOAEL of 260 mg ae/kg/day were based on severe inanition and body weight loss, decreased fecal output, and mild incoordinated gait. The duration of exposure is appropriate for this endpoint.

EXECUTIVE SUMMARY: see section 4.2.3

Intermediate-Term Inhalation Exposure (1-6 months)

Study:	Developmental rabbit toxicity study (MRID 46235632)
NOAEL:	104 mg ae/kg/day
LOAEL:	260 mg ae/kg/day
Uncertainty Factor:	100x (10X interspecies extrapolation, 10X for intraspecies variations)

Comments: A developmental rabbit study (GF-871) was used to select a dose and endpoint for evaluating intermediate-term inhalation exposure. The maternal NOAEL of 104 mg ae/kg/day and the maternal LOAEL of 260 mg ae/kg/day were based on severe inanition and body weight loss, decreased fecal output, and mild incoordinated gait. The duration of exposure is appropriate for this endpoint. A 13 week dog study was also considered for the intermediate-term inhalation endpoint. However, this study was not selected since the NOAEL of 232 mg/kg/day was higher than the one used for the short-term inhalation endpoint. The NOAEL of 104 mg ae/kg/day selected for the intermediate-term inhalation endpoint is protective of effects seen in the 13 week dog study.

EXECUTIVE SUMMARY: see section 4.2.3

Long-term inhalation exposure (>6 months)

Based on the proposed use patterns, there is no concern for long-term inhalation exposure at this time.

4.4.8 Levels of Concern for Occupational and Residential Exposure Assessments

Table 4.4. Summary of the Levels of Concern (LOC) for Occupational and Residential Exposure Risk Assessments for Aminopyralid.

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

Oral	100	100	N/A
Dermal	N/A	N/A	N/A
Inhalation	100	100	N/A

N/A = Not applicable

For occupational and residential exposure, short- and intermediate-term oral and inhalation risk assessments, a LOC of 100 is supported by the available data. The LOC is based on the conventional uncertainty factor of 100X (10X for intraspecies variation and 10X for interspecies extrapolation). Generally, HED does not have a concern for occupational or residential exposures when our calculated Margins of Exposure (MOEs) are greater than the LOC (i.e., greater MOEs indicate lesser risk).

4.4.9 Recommendation for Aggregate Exposure Risk Assessments

In accordance with the requirements of the FQPA (1996), HED has considered the potential for concurrent exposure to aminopyralid via oral, dermal, and inhalation routes. HED estimates aggregate exposure when exposure via different routes produces the same toxicological effects. Based on the available toxicological information, dermal exposures do not result in any adverse systemic effect; therefore, dermal exposures do not need to be included in the estimation of aggregate risk for any exposure duration. Short- and intermediate-term oral and inhalation exposures are being regulated based on effects seen in the developmental rabbit toxicity study. The use of a single study to evaluate multiple routes of exposure implicitly assumes that different routes of exposures will result in the same toxicological effects and should, therefore, be aggregated.

4.4.10 Classification of Carcinogenic Potential

There were no treatment-related increases in tumors in rat and mouse carcinogenicity studies.

Combined Chronic toxicity/ Carcinogenicity-Rat; OPPTS 870.4300; OECD 453

EXECUTIVE SUMMARY: see section 4.4.3

Carcinogenicity Feeding-Mouse; OPPTS 870.4200b; OECD 451

EXECUTIVE SUMMARY: in a carcinogenicity study (2003, MRID No.: 46235628), XDE-750, purity 94.5%, was administered to 50 CD-1 mice/sex/dose in the diet at dose levels of 0, 50, 250 or 1000 mg/kg/day (equal to 0, 50.2, 251 or 1000 mg/kg/day for males, and 0, 50.9, 252 or 1010 mg/kg/day for females) for 18 months.

There were no treatment-related effects on mortality, clinical signs, ophthalmology, body weight/body weight gain, food intake, food efficiency, hematology, organ weights, gross pathology or histopathological examination. The only oncogenic finding was an increased

incidence of pulmonary bronchiolo-alveolar carcinomas in the 1000 mg/kg/day group, males only. Historical control data for this tumour type indicated that the incidence observed in this study was within the normal range. Thus the slight increased in bronchiolo-alveolar tumours in the high-dose males was not considered to be treatment related.

The systemic LOAEL could not be determined since there were no adverse treatment-related findings. The NOAEL is 1000 mg/kg/day (equal to 1000 mg/kg/day for males and 1010 mg/kg/day for females).

This carcinogenicity study in the mouse is acceptable and satisfies the guideline requirement for a carcinogenicity study (OPPTS 870.4200;OECD 451) in the mouse.

Table 4.4. Summary of Toxicological Doses and Endpoints for Chemical for Use in Human Risk Assessments

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (general population)			No acute endpoint identified for this group.
Chronic Dietary (all populations)	NOAEL= 50 mg/kg/day UF=100 chronic RfD=0.5 mg/kg/day	cPAD= cRfd/FQPA SF cPAD=0.5 mg/kg/day	Chronic toxicity/carcinogenicity study LOAEL=500mg/kg/day based on cecal enlargement, slight mucosal hyperplasia in males and slightly decreased body weights.
Incidental Oral Short-Term (1 - 30 days)	NOAEL=104 mg ae/kg/day	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	Developmental rabbit study (GF-871) LOAEL=260 mg/kg/day based on severe inanition (exhaustion due to lack of food) and body weight loss, decreased fecal output, and mild incoordinated gait.
Incidental Oral Intermediate-Term (1 - 6 months)	NOAEL=104 mg ae/kg/day	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	Developmeotal rabbit study (GF-871) LOAEL=260 mg/kg/day based on severe inanition (exhaustion due to lack of food) and body weight loss, decreased fecal output, and mild incoordinated gait.

Table 4.4. Summary of Toxicological Doses and Endpoints for Chemical for Use in Human Risk Assessments			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short-Term (1 - 30 days)	N/A	N/A	No endpoint identified for this group. No absorption study available. No systemic toxicity seen at the limit dose (1000 mg/kg/day) in the 28-day dermal toxicity study in rats. **This risk assessment is not required.**
Dermal Intermediate-Term (1 - 6 months)	N/A	N/A	No endpoint identified for this group. No absorption study available. No systemic toxicity seen at the limit dose (1000 mg/kg/day) in the 28-day dermal toxicity study in rats. **This risk assessment is not required.**
Dermal Long-Term (> 6 months)	N/A	N/A	No endpoint identified for this group. No absorption study available. No systemic toxicity seen at the limit dose (1000 mg/kg/day) in the 28-day dermal toxicity study in rats. **This risk assessment is not required.**
Inhalation Short-Term (1 - 30 days)	NOAEL=104 mg ae/kg/day	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	Developmental rabbit study (GF-871) LOAEL=260 mg/kg/day based on severe inanition (loss of vitality due to lack of food) and body weight loss, decreased fecal output, and mild incoordinated gait.
Inhalation Intermediate-Term (1 - 6 months)	NOAEL=104 mg ae/kg/day	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	Developmental rabbit study (GF-871) LOAEL=260 mg/kg/day based on severe inanition (loss of vitality due to lack of food) and body weight loss, decreased fecal output, and mild incoordinated gait.
Inhalation Long-Term (> 6 months)	N/A	N/A	N/A
Cancer (oral, dermal, inhalation)	**Classification:** There was no treatment related increase in tumor incidence when compared to control. This chemical is not likely to be a carcinogen.		

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, N/A = Not Applicable

* Refer to Section 4.5

4.5 Special FQPA Safety Factor

Based on the hazard data, HED recommended the special FQPA SF be reduced to 1X because there were no/low concerns and no residual uncertainties with regard to pre- and/or postnatal toxicity. After evaluating the toxicological and exposure data, the aminopyralid risk assessment team recommends that the special FQPA SF be reduced to 1X. The recommendation is based on the following:

- The toxicity data showed no increase in susceptibility in fetuses and pups with *in utero* and post-natal exposure.
- The dietary food exposure assessment is based on HED-recommended tolerance-level residues and assumes 100% crop treated for all commodities, which results in very high-end estimates of dietary exposure.
- The dietary drinking water assessment is based on values generated by model and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations.
- Exposures due to recreational activities are based on default HED assumptions that result in high-end estimates of exposure.

4.6 Endocrine disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

In the available toxicity studies on aminopyralid, there was no estrogen, androgen, and/or thyroid mediated toxicity.

5.0 Public Health Data

Aminopyralid is a new active ingredient, and as such, no public health data are currently available.

6.0 Exposure Characterization/Assessment

6.1 Dietary Exposure/Risk Pathway

6.1.1 Residue Profile

Aminopyralid. Petition for the Establishment of Permanent Tolerances for Use of Aminpyralid on Grasses and Wheat. Summary of Analytical Chemistry and Residue Data. PP#4F6827. M. Doherty, D305665. 7/12/05.

The petitioner is currently proposing food/feed uses on grasses grown in rangelands and permanent pastures and on wheat for the selective control of invasive and noxious broadleaf weeds. It is also proposed for weed control in sites such as parks, electric utility rights-of way, forestry, woodlands, and wildlife openings, with smaller amounts used in railroads, utility substations, pipelines, and pumping stations.

The proposed end-use product (EP) is a soluble concentrate liquid (SC/L) referred to by the trade name GF-871 (EPA Reg. No. 62719-LRI). The active ingredient in GF-871 is formulated as the triisopropanolammonium (TIPA) salt, with the product containing 40.6% of aminopyralid TIPA salt at an acid equivalent (ae) of 21.1% or 2 lb ae/gal. The 2 lb ae/gal SC/L formulation is proposed for broadcast foliar application at maximum rates of 0.11 lb ae/A (120 g ae/hectare) on rangeland and permanent pastures and 0.009 lb ae/A (10 g ae/ha) on wheat. The proposed PHIs are 0 days for wheat hay and 50 days for wheat grain and straw. No PHI is listed or proposed for grasses or wheat forage.

In support of the proposed uses, Dow AgroSciences has submitted a petition, PP#7F4851, for the establishment of permanent tolerances for residues of aminopyralid expressed as total parent, free and conjugated, in/on grass and wheat commodities; and for residues of aminopyralid, *per se* in/on livestock commodities.

The available data from metabolism studies with grass and wheat indicate that metabolism of aminopyralid is similar in these crops. In metabolism studies reflecting foliar applications to grass and wheat, aminopyralid was found to be metabolized to a multi-component mixture of water-soluble complexes which consist mostly of isomeric mixtures of acid- and base-labile N-glucosides and glucose ester conjugates of aminopyralid. The submitted poultry metabolism study indicates that the aminopyralid is rapidly excreted in laying hens with minimal transference of residues to eggs and tissues. Although the residues in the goat and hen studies were too low to allow adequate characterization/identification of residues, new studies are not being requested. The available metabolism data from the goat, hen, and rat (MRIDs 46235807 and 46235833) indicate that the majority of the administered aminopyralid is excreted as unchanged parent in all three species, and the small amount which is absorbed remains unchanged. Therefore, the residue of concern in livestock is aminopyralid, per se. This finding is supported by the residues of concern for the related compounds picloram and clopyralid which, in each case, show parent compound to be the major residue.

Adequate crop field trial data have been submitted for grasses reflecting the proposed use

pattern for the 2 lb ae/gal SC/L TIPA salt formulation. The final results for the ongoing storage stability study are needed to support the grass crop field trials. The submitted field trial residue data are adequate to satisfy data requirements for wheat even though geographic representation of the SC/L formulations are inadequate (only seven field trials were conducted with the SC/L formulation the petitioner wishes to register). The petitioner conducted side-by-side trials which indicated no significant differences between the EO and SC/L formulation types. Generally, HED prefers that side-by-side trials be conducted in diverse geographic regions. For aminopyralid, all side-by-side trials were conducted in Region 7. Since the data for aminopyralid show that there is no discernable effect of geographic location on residue levels, HED considers the data sufficient to support registration of the SC/L formulations in this case. The petitioner has included language on the proposed label recommending that a surfactant be used for wheat. The petitioner should modify the proposed label to remove the recommendation that a surfactant be used with application to wheat. If the petitioner wishes to include the option to use a surfactant for application to wheat, then all the required wheat crop field trials should reflect the use of surfactant in the test substance application. Adequate processing data have been submitted for wheat which indicate that a tolerance is needed for wheat bran. In addition, data for wheat aspirated grain fractions submitted in conjunction with the processing study indicate that a tolerance is needed for aspirated grain fractions. An adequate cattle feeding study has been submitted, and it has been determined that a poultry feeding study is not needed to support this petition. The proposed enforcement methods for plant and animal commodities are currently undergoing tolerance method validation by the Agency. The available confined rotational crop data indicate that field rotational crop studies are required to support the proposed rotational crop restrictions. There are currently no U.S. or international Codex tolerances established for aminopyralid.

HED has examined the residue chemistry database for the new active ingredient aminopyralid. Pending resolution of the deficiencies noted in Section 10, there are no residue chemistry issues that would preclude granting a conditional registration for this herbicide or establishment of permanent tolerances for aminopyralid as follows:

Tolerances for free and conjugated residues of aminopyralid, calculated as aminopyralid:

Grass, forage	25	ppm
Grass, hay	50	ppm
Wheat, forage	2.0	ppm
Wheat, hay	4.0	ppm
Wheat, grain	0.04	ppm
Wheat, straw	0.25	ppm
Wheat bran	0.1	ppm
Aspirated grain fractions	0.2	ppm

Tolerances for aminopyralid *per se*:

Milk	0.03	ppm
Cattle, meat	0.02	ppm
Goat, meat	0.02	ppm
Horse, meat	0.02	ppm

Sheep, meat	0.02	ppm
Cattle, fat	0.02	ppm
Goat, fat	0.02	ppm
Horse, fat	0.02	ppm
Sheep, fat	0.02	ppm
Cattle, meat byproducts, excluding kidney	0.02	ppm
Goat, meat byproducts, excluding kidney	0.02	ppm
Horse, meat byproducts, excluding kidney	0.02	ppm
Sheep, meat byproducts, excluding kidney	0.02	ppm
Cattle, kidney	0.3	ppm
Goat, kidney	0.3	ppm
Horse, kidney	0.3	ppm
Sheep, kidney	0.3	ppm

6.1.2 Water Exposure/Risk Pathway

Aminopyralid: Tier 1 Estimated Drinking Water Concentrations (EDWC) for Use in the Human Health Risk Assessment. R. Kashuba, D301682 2/3/05

Table 6.2. Summary of Estimated Surface and Ground Water Concentrations for Chemical.

Exposure Duration	Aminpyralid	
	Surface Water Conc., ppb[a]	Ground Water Conc., ppb[b]
Acute	10.024	0.630
Chronic (non-cancer)	1.937	0.630
Chronic (cancer)	1.937	0.630

[a] From the Tier II PRZM-EXAMS - Index Reservoir model. Input parameters are based on maximum application of aminopyralid to rangeland grasses.
[b] From the SCI-GROW model assuming a maximum seasonal use rate of 0.1 t lb ae/A, a K_{oc} of 1.05, and a half-life of 38.7 days.

6.1.3 Acute and Chronic Dietary Exposure and Risk

Aminopyralid Chronic Dietary Exposure Assessment for the Section 3 Registration Action. M. Doherty, D313003, 6/21/05.

A chronic dietary risk assessment was conducted using the Lifeline™ Model Version 2.0 which uses food consumption data from the United States Department of Agriculture's (USDA's) Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. This highly conservative assessment assumed tolerance-level residues and 100% crop treated. In addition to residues in/on food items, the assessment also addresses potential residues in drinking water. Based on the assumptions noted above, chronic exposure estimates range from 0.0002 to 0.0012 mg/kg/day (Table 6.1). Risk estimates for all population subgroups are less than 1% of the chronic population-adjusted dose (cPAD). Generally, HED is concerned about dietary exposure levels when risk estimates exceed 100% of the PAD. Dietary risk estimates for aminopyralid are

below HED's level of concern for all population subgroups, including those of infants and children.

Table 6.1. Chronic Dietary (food only) Exposure and Risk Estimates for Aminopyralid			
Population Subgroup	**PAD, mg/kg/day**	**Exposure, mg/kg/day**	**%PAD**
Acute Dietary Estimates			
None: No toxic effects attributable to a single dose were identified.			
Chronic Dietary Estimates			
U.S. Population	0.5	0.00030	<1
All infants (< 1 yr)	0.5	0.00052	<1
Children 1-2 yrs	0.5	0.00120	<1
Children 3-5 yrs	0.5	0.00088	<1
Children 6-12 yrs	0.5	0.00052	<1
Youth 13-19 yrs	0.5	0.00027	<1
Adults 20-49 yrs	0.5	0.00023	<1
Adults 50+ yrs	0.5	0.00023	<1
Females 13-49 yrs	0.5	0.00027	<1

6.2 Residential (Non-Occupational) Exposure/Risk Pathway

Occupational and Residential Exposure Risk Assessment for Proposed Uses of Aminopyralid. M. Collantes, D305672. 5/24/05.

6.2.1 Home Uses

At this time, there are no requested uses for aminopyralid that are considered home uses and neither handler nor postapplication residential exposures from uses around the home are expected to occur.

6.2.2 Recreational Uses

The petitioner is requesting registration of aminopyralid for the control of vegetation in campgrounds and other natural recreation areas. This use has the potential to result in postapplication incidental oral exposures for infants and children via hand-to-mouth transfer of residues and ingestion of aminopyralid-contaminated grass and soil. Postapplication exposure via inhalation is not expected to occur. For purposes of this assessment, a grass covered camp ground will serve as the worst case scenario in assessing postapplication exposure. The assumptions and MOEs for these three sources of non-dietary exposure to aminopyralid are summarized below. For a complete description of the MOE calculation, please refer to the Occupational and Residential Exposure Risk Assessment cited above. For all of these exposure scenarios, exposure estimates were compared to the NOAEL of 104 mg/kg/day from the rabbit developmental study, which is the appropriate NOAEL for assessing short-term exposures.

Hand-to-Mouth Transfer. The hand-to-mouth transfer scenarios were assessed using the HED Draft Standard Operating Procedures (SOP's) for Residential Exposure Assessments (12/18/97), and the Revisions to the Standard Operating Procedures (SOP's) for Residential Exposure Assessment (Science Advisory Council for Exposure Policy 12, Revised February 22, 2001). The following assumptions were used to estimate hand-to-mouth transfer exposure:

- Pesticide residues are transferred to the skin of children playing on treated areas and are subsequently ingested as a result of hand-to-mouth transfer.
- On the day of application, 5% of the application rate is available on turfgrass.
- Postapplication activities must be assessed on the same day that the pesticide is applied.
- The median surface area of both hands is 20 cm^2 for children. This value is based on the February 1999 recommendation from the Scientific Advisory Panel (SAP). The SAP characterized the hand-to-mouth event as involving 1 to 3 fingers per event (5.7 cm^2 to 17.1 cm^2). For screening purposes, a value of 20 cm^2 was selected to account for 3 fingers.
- There is a one-to-one relationship between the dislodgeable residues on the turf and on the surface area of the skin after contact.
- The mean rate of hand-to-mouth activity is 20 times/hour for short-term exposure scenarios.
- Duration of exposure for children is 2 hours per day for turf.
- The saliva extraction factor is 50%.
- Children weigh 15 kg.

A Tier 1 hand-to-mouth transfer short-term postapplication exposure assessment for **lawn broadcast** uses results in a MOE of 61,000 (Table 6.2) and therefore is not of concern.

Ingestion of Turfgrass. This scenario was assessed using the HED Draft Standard Operating Procedures (SOP's) for Residential Exposure Assessments (12/18/97), and the Revisions to the Standard Operating Procedures (SOP's) for Residential Exposure Assessment (Science Advisory Council for Exposure Policy 12, Revised February 22, 2001). The SOP 2.3.3, Postapplication Potential Dose Among Toddlers from the Ingestion of Pesticide-Treated Turfgrass, estimates doses among toddlers from incidental ingestion of residential turfgrass that has been previously treated with pesticides. This scenario assumes that turf is ingested by toddlers who play on treated areas. The following assumptions were used to estimate exposure:

- On the day of application, 20% of the application rate is available to be ingested.

- Postapplication exposure must be assessed on the same day pesticide is applied.
- The rate that children (3 years old) ingest grass is 25 cm^2/day.
- Children weigh 15 kg.

The short-term oral MOE for children ingesting aminopyralid-treated grass is 250,000 (Table 6.3) and therefore does not exceed HED's level of concern.

Ingestion of Soil. This scenario was assessed using the HED Draft Standard Operating Procedures (SOP's) for Residential Exposure Assessments (12/18/97), and the Revisions to the Standard Operating Procedures (SOP's) for Residential Exposure Assessment (Science Advisory Council for Exposure Policy 12, Revised February 22, 2001). The SOP 2.3.4, Postapplication Potential Dose Among Toddlers from Incidental Ingestion of Soil from Pesticide-Treated Residential Areas, estimates doses among toddlers from incidental ingestion of soil containing pesticide residues. This scenario assumes pesticide residues in soil are ingested by toddlers who play on treated areas as a result of normal mouthing activities. The following assumptions were used to estimate incidental ingestion of soil exposure:

- On the day of application, 100% of the application rate is located within the soil's uppermost 1 cm.
- Postapplication must be assessed on the same day the pesticide is applied.
- The rate that children ingest soil is 100 mg/day.
- Children weigh 15 kg.

The short-term oral MOE for children ingesting aminopryalid-contaminated soil is 19,000,000 (Table 6.4) and therefore does not exceed HED's level of concern.

Aggregate Non-dietary Exposure. In accordance with the requirements of the FQPA (1996), when the potential for residential exposure to the pesticide product exists, aggregate risk assessment(s) must be performed to consider potential exposure from the major sources: oral, dermal, and inhalation. As indicated previously, in the 28-day dermal toxicity study in rats, no systemic toxicity occurred at the limit dose. Therefore, it is concluded that aminopyralid is not absorbed or is poorly absorbed through the skin so a dermal endpoint was not selected. Although the same developmental study and respective common toxicity was used to assess both inhalation and oral routes of exposure, the residential use does not include indoor uses. Therefore, both handler and postapplication inhalation exposures are expected to be negligible and an inhalation exposure assessment was not required nor performed. Since the only source of residential exposure would result from oral exposure, an aggregate residential exposure assessment was not performed. Totaling the incidental oral exposure estimates gives a combined estimate of 0.0021 mg/kg/day. The MOE associated with this exposure estimate is 50,000.

6.2.3 Other (Spray Drift, etc.)

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for aminopyralid. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. On a chemical by chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift.

Table 6.2. Postapplication Exposure and Risk for Hand-to-Mouth Transfer of Pesticide Residues Using Residential SOP for Broadcast Use												
Scenario	AR [a]	F [b]	CF2 (ug/lb)	CF3 (A/cm^2)	DFR [c] (ug/cm^2)	SA (cm^2/event)	FQ (events/hr)	ET (hr/day)	CF1 (mg/ug)	SE	PDD [d] (mg/kg/day)	MOE [e]
GF-871 (21.1 % ae)	0.11 lb ae/A	0.05	4.54E8	2.47E-8	6.2E-2	20	20	2	0.001	0.5	0.0017	61,000

Notes:

a. AR = Application Rate (lb ae/A) = in accordance with product label
b. F = transferable residue for turfs;.
c. DFR = Dislodgeable foliar residue = AR x F x $(1\text{-}D)^0$ x CF2 x CF3
d. Short-term PDD = DFR_0 x SA x FQ x ET x SE x CF1/BW
e. Short-term MOE = NOAEL (104 ae mg/kg/day)/Short-term PDR

Table 6.3. Postapplication Exposure and Risk From Ingestion of Pesticide-Treated Turfgrass									
Scenario	AR (lb ae/A)	F	CF2 (ug/lb)	CF3 (A/cm^2)	GR_0 [a] (ug/cm^2)	tgR (cm^2/day)	CF1 (mg/ug)	PDD [b] (mg/kg/day)	MOE [c]
GF-871 (21.1 % ae)	0.11	0.2	4.54E8	2.47E-8	0.25	25	0.001	0.00041	250,000

a. GR_0 = grass residue on day 0 = AR x F x $(1\text{-}D)^0$ x CF2 x CF3
b. PDD = potential dose on day 0 = GR_0 x IgR x CF1 ÷BW
c. Short-term MOE = NOAEL (104 ae mg/kg/day)/PDD

Table 6.4. Postapplication Exposure and Risk From Ingestion of Pesticide-Treated Soil										
Scenario	AR (lb ae/A)	F (cm^{-1})	CF2 (ug/lb)	CF3 (A/cm^2)	CF4 (cm^2/g)	SR_0 [a] (ug/g)	IgR (mg/day)	CF1 (g/ug)	PDD [b] (mg/kg/day)	MOE [c]
GF-871 (21.1 % ae)	0.11	1	4.54E8	2.47E-8	0.67	0.83	100	0.000001	5.5E-6	19,000,000

a. SR_0 = AR x F x $(1\text{-}D)^0$ x CF2 x CF3 x CF4
b. PDD = SR_0 x IgR x CF1÷ BW
c. Short-term MOE = NOAEL (104 ae mg/kg/day)/ PPD

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7.0 Aggregate Risk Assessments and Risk Characterization

In evaluating the proposed uses of aminopyralid, HED has combined dietary (food and drinking water) and non-dietary (campground) sources of exposure to obtain an estimate of potential aggregate exposure. The non-dietary scenarios included in the aggregate assessment include incidental oral exposures from hand-to-mouth transfer of residues as well as exposures from ingestion of soil. These scenarios are short-term in duration and applicable to children only. At this time, there are no non-dietary scenarios for aminopyralid that are appropriate for assessing adults; therefore, the aggregate exposure estimates for adults are equivalent to the chronic dietary (food + water) estimates presented in Section 6.1.2.

HED acknowledges that the aggregate exposure and risk estimates for children are likely to overestimate actual exposures since our estimates assume simultaneous, constant exposures from dietary and non-dietary sources. An assessment that takes into account the timing of source-specific exposures and the likelihood of their co-occurring would be expected to produce more realistic, and lower, exposure and risk estimates.

7.1 Acute Aggregate Risk

No toxic effects attributable to a single dose were identified for aminopyralid. Therefore, an acute risk assessment is not warranted for this chemical.

7.2 Short-Term Aggregate Risk

In estimating short-term aggregate risk, HED has combined the chronic dietary (food + drinking water) exposure estimate and the total non-dietary exposure estimate for children. The chronic dietary exposure estimate reflects average dietary exposure and serves as an estimator of dietary exposure that co-occurs with potential short-term non-dietary exposure for children. The short-term aggregate exposure and risk estimates for aminopyralid are summarized in Table 7.1.

Table 7.1. Short-Term Aggregate Exposure and Risk Estimates for Aminopyralid

Population Subgroup	NOAEL, mg/kg/day	Exposure, mg/kg/day			Aggregate MOE
		Dietary	Total Non-Dietary	Total Aggregate	
All infants (< 1 yr)	104	0.00052	0.0021	0.00262	40,000
Children 1-2 yrs	104	0.00120	0.0021	0.00330	32,000
Children 3-5 yrs	104	0.00088	0.0021	0.00298	35,000
Children 6-12 yrs	104	0.00052	0.0021	0.00262	40,000

7.3 Intermediate-Term Aggregate Risk

Based on the currently requested uses, there are no scenarios that are likely to result in

intermediate-term exposure (30-180 days, continuous). Therefore, HED has not conducted an intermediate-term risk assessment for aminopyralid.

7.4 Long-Term Aggregate Risk

As noted above, dietary exposure (food + water) is the only source of exposure to aminopyralid that is expected to be long-term (180-365 days). Therefore, the long-term aggregate exposure and risk estimates are equivalent to the chronic dietary exposure and risk estimates discussed in Section 6.1.2. The data are shown again in Table 7.2 for convenience.

Table 7.2. Long-Term Aggregate Exposure and Risk Estimates for Aminopyralid

Population Subgroup	NOAEL, mg/kg/day	Exposure, mg/kg/day	%PAD
U.S. Population	0.5	0.00030	<1
All infants (< 1 yr)	0.5	0.00052	<1
Children 1-2 yrs	0.5	0.00120	<1
Children 3-5 yrs	0.5	0.00088	<1
Children 6-12 yrs	0.5	0.00052	<1
Youth 13-19 yrs	0.5	0.00027	<1
Adults 20-49 yrs	0.5	0.00023	<1
Adults 50+ yrs	0.5	0.00023	<1
Females 13-49 yrs	0.5	0.00027	<1

7.5 Cancer Risk

Aminopyralid is classified as not likely to be a human carcinogen. Therefore, HED has not conducted a cancer risk assessment.

8.0 Cumulative Risk Characterization/Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding for aminopyralid and any other substances. Furthermore, aminopyralid does not appear to have a toxic metabolite that is produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that aminopyralid has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Pathway

Occupational and Residential Exposure Risk Assessment for Proposed Uses of Aminopyralid. M. Collantes,

D305672. 5/24/05.

GF-871 is a herbicide for control of annual and perennial broadleaf weeds in wheat, on rangeland, premanent grass pastures, non-cropland areas (rights-of-ways, roadsides, and banks) and natural recreation areas (such as campgrounds and trail heads and trails). It is formulated as a liquid and contains 40.6% of the active ingredient aminopyralid in the form of its triisopropanolammonium salt or 21.1% aminopyralid acid equivalent (a.e.). Based on the proposed uses specified in the label, occupational exposure is expected to be short- and intermediate-term in duration. No long-term (chronic) exposure is expected.

9.1 Short- and Intermediate-Term Handler Risk

GF-871 may be applied as a broadcast treatment by ground and aerial equipment to wheat at rates ranging from 0.0089 to 0.0092 lb ae/acre. It may also be applied by ground, aerial and hand spray as a broadcast and spot treatment to rangeland, grass pastures, non-crop land areas, and natural areas (such as wildlife management areas, natural recreation areas, campgrounds, trailheads and trails) at an application rate of 0.11 lb a.e. per acre. The MOEs associated with occupational exposure are summarized in Table 9. All of these MOEs are significantly greater than 100 and therefore reflect risks which are well below HED's level of concern. For a complete description of the MOE calculations, please refer to the Occupational and Residential Exposure Risk Assessment cited above.

Table 9. Short- and Intermediate-Term Occupational Exposure and Risk Estimates for Aminopyralid*.

Scenario	Use Site	Unit Exposure [1] (mg/lb ai)	Application Rate [2]	Amount Treated [3] A or ft^2	Daily Dose [4] (mg/kg/day)	Inhalation MOE [5]
Mixer/loader						
GF-871 Liquid (21.1 % ae) Groundboom	wheat	0.0012	broadcast - 0.0089 lb ac/A	200	0.000036	3,000,000
			spot treatment- 0.0092 lb ae/A or 0.00000021 lb ae/ft^2	1000 ft^2	4.2×10^{-9}	2.5×10^{10}
GF-871 Liquid (21.16 % ae) Aerial			broadcast - 0.0089 lb ae/A	1200	0.00021	500,000
GF-871 (21.1 % ae) Groundboom	rangeland, permanent grass pastures, non-crop land areas, natural recreation areas (campgrounds)	0.0012	0.11 lb a.e/A	200	0.00044	240,000
GF-871 (21.1 % ae) Aerial				1200	0.00264	40,000
GF-871 (21.1 % ae) Handgun				< 1	< 0.0000022	> 47,000,000

Scenario	Use Site	Unit Exposure [1] (mg/lb ai)	Application Rate [1]	Amount Treated [3] A or ft^2	Daily Dose [4] (mg/kg/day)	Inhalation MOE [5]
Applicator						
GF-871 Liquid (21.1 % ai) Groundboom	wheat	0.00074	broadcast - 0.0089 lb ae/A	200	0.000022	5,000,000
			spot treatment- 0.0092 lb ae/A or 0.00000021 lb ae/ft^2	1000 ft^2	2.6×10^{-9}	4×10^{10}
GF-871 Liquid (21.1 % ai) Aerial		0.000068	broadcast - 0.0089 lb ae/A	1200	0.000012	8,700,000
GF-871 (21.1 % ae) Groundboom	rangeland, permanent grass pastures, non-crop land areas, natural recreation areas (campgrounds)	0.00074	0.11 lb a.e/A	200	0.00027	400,000
GF-871 (21.1 % ae) Aerial		0.000068		1200	0.00015	700,000
GF-871 (21.1 % ae) Handgun		0.079		< t	< 0.00015	>700,000
Flagger						
GF-871 21.1% a.e.	Wheat, rangeland, permanent grass pastures, non-crop land areas, natural recreation areas (campgrounds)	0.011	0.0089 lb ae/A	1200	0.00196	54,000
			0.11 lb ae/A		0.0242	4,300

1. Unit exposures where derived from PHED
2. Application Rate based on proposed labels
3. HED(Science Advisory Council Exposure Policy 9.1, September 25, 2001
4. Daily Dose = $\frac{\text{Unit Exposure x application rate x Amount treated}}{\text{Body Weight (60 kg)}}$
5. Short- and Intermediate-term Inhalation MOE = $\frac{\text{NOAEL (104 ae mg/kg/day)}}{\text{Daily Dose}}$

10.0 Data Needs and Label Requirements

10.1 Toxicology

There are no toxicological data gaps.

10.2 Residue Chemistry

860.1200 Directions for Use

- The petitioner should modify the proposed label to amend the recommendation regarding use of a surfactant; the label should be modified by removing the recommendations to use a surfactant in conjunction with application of aminopyralid to wheat. If the petitioner wishes to include the option to use a surfactant for application to wheat, then all the required wheat crop field trials should reflect the use of surfactant in the test substance application.

- The petitioner should modify the proposed label to specify a rotational crop plant-back interval of 4 months for barley, canola (rapeseed), flax, grasses, field corn, grain sorghum, oats, mustard, popcorn, and sweet corn.

860.1340 Residue Analytical Methods

- HED is concerned that the proposed enforcement method may not be able to differentiate between aminopyralid, picloram, and clopyralid. HED is requesting that the petitioner complete an interference study using these three compounds as a condition of registration.

- The analytical methods for aminopyralid have not completed validation by the Agency. They are currently being evaluated.

860.1380 Storage Stability

- The available storage stability data for grass are not adequate to support the storage intervals and conditions for samples from the submitted grass crop field trials. To fully support the sample storage intervals and conditions, storage stability data for aminopyralid are needed for grass forage and hay reflecting up to approximately 15 months of frozen storage. The petitioner has stated that a final storage stability study, reflecting storage intervals of up to 18 months, will be submitted upon completion. HED recommends that the final study be made a condition of registration.

860.1650 Submittal of Analytical Reference Standards

- As of 09/07/2004, no reference standard for aminopyralid was available at the EPA National Pesticide Standards Repository. The petitioner should submit a reference standard for aminopyralid to the repository. In addition, because the proposed enforcement methods require the use of an internal standard for quantification, the petitioner should submit a quantity of the internal standard, $^{13}C_2{}^{15}N$-aminopyralid, to the repository.

10.3 Occupational and Residential Exposure

None.

Table 10. Tolerance Summary for Aminopyralid.			
Commodity	Proposed Toleraoce (ppm)	Recommended Tolerance (ppm)	Comments/ *Correct commodity definition*
Aminopyralid expressed as total parent, free and conjugated			
Grass, forage	25	25	
Grass, hay	60	50	
Wheat, forage	2.0	2.0	
Wheat, hay	4.0	4.0	
Wheat, grain	0.05	0.04	
Wheat, straw	0.5	0.25	
Wheat bran	0.1	0.10	*Wheat, bran*
Wheat middlings	0.02	Remove	No tolerance needed.
Wheat shorts	0.05	Remove	No tolerance needed.
Wheat flour	0.01	Remove	No tolerance needed.
Wheat germ	0.02	Remove	No tolerance needed.
Wheat, aspirated grain fractions	0.5	0.20	*Aspirated grain fractians*
Aminopyralid *per se*			
Milk	0.02	0.03	
Milk, cream	0.02	Remove	No tolerance needed.
Meat of cattle, goats, hogs, horses, and sheep	0.05	0.02	*Cattle, meat*
		0.02	*Goat, meat*
		--	No tolerance needed for hog meat.
		0.02	*Horse, meat*
		0.02	*Sheep, meat*
Fat of cattle, goats, hogs, horses, and sheep	0.05	0.02	*Cattle, fat*
		0.02	*Goot, fat*
		--	No tolerance needed for hog fat.
		0.02	*Harse, fat*
		0.02	*Sheep, fat*
Liver of cattle, goats, hogs, horses, and sheep	0.05	0.02	*Cattle, meat byproducts, except kidney*
		0.02	*Goot, meat byproducts, except kidney*
		--	No tolerance needed for hog meat byproducts.
		0.02	*Horse, meat byproducts, except kidney*
		0.02	*Sheep, meat byproducts, except kidney*

Table 10. Tolerance Summary for Aminopyralid.			
Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments/ *Correct commodity definition*
Kidney of cattle, goats, hogs, horses, and sheep	1.0	0.30	*Cattle, kidney*
		0.30	*Goat, kidney*
		--	No tolerance needed for hog kidney.
		0.30	*Horse, kidney*
		0.30	*Sheep, kidney*

References:

Occupational and Residential Exposure Risk Assessment for Proposed Uses of Aminopyralid. M. Collantes, D305672. 5/24/05.

Aminopyralid. Petition for the Establishment of Permanent Tolerances for Use of Aminpyralid on Grasses and Wheat. Summary of Analytical Chemistry and Residue Data. PP#4F6827. M. Doherty, D305665. 7/12/05.

Aminopyralid Chronic Dietary Exposure Assessment for the Section 3 Registration Action. M. Doherty, D313003, 6/21/05.

Aminopyralid: Tier I Estimated Drinking Water Concentrations (EDWC) for Use in the Human Health Risk Assessment. R. Kashuba, D301682. 2/3/05

Toxicological Appendices

1.0 TOXICOLOGY DATA REQUIREMENTS

The requirements (40 CFR 158.340) for food use for aminopyralid are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21/28-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	---
870.3465	90-Day Inhalation	no	---
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5395	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	---
870.6100b	90-Day Neurotoxicity (hen)	no	---
870.6200a	Acute Neurotox. Screening Battery (rat)	no	---
870.6200b	90 Day Neurotox. Screening Battery (rat)	no	---
870.6300	Develop. Neuro	no	---
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	---
Special Studies for Ocular Effects		no	---

2.0 NON-CRITICAL TOXICOLOGY STUDIES

Oral Subchronic Toxicity Study (XDE-750)-Rat; OPPTS 870.3100; OECD 408

EXECUTIVE SUMMARY: In a subchronic toxicity study (2001, MRID No.: 46235621), technical XDE-750, purity 94.5%, was administered to 10 Fischer 344 rats/sex/dose in the diet at dose levels of 0, 10, 100, 500 and 1000 mg/kg/day (equal to 0, 10.9, 109, 543 and 1090 mg/kg/day for males, and 0, 10.7, 108, 540 and 1060 mg/kg/day for females). An additional 10 rats per sex were assigned to the 0 and 1000 mg/kg/day groups (equal to 1120/1030 mg/kg/day) for a 4-week recovery period following treatment.

There were no adverse, treatment-related effects on mortality, body weights, food consumption, ophthalmologic and clinical observations, hematology, clinical chemistry or urinalysis. Full cecal weights were increased in the 500 and 1000 mg/kg/day groups (both sexes) and empty cecal weights were increased in the 1000 mg/kg/day group (both sexes) and in the 500 mg/kg/day group (males only). At gross pathological examination, there was an increase in the size of the cecum for all animals in the 1000 mg/kg/day group. Histopathological examination revealed hyperplasia of the mucosal epithelium of the ileum and cecum in the 1000 mg/kg/day group, males only. Following the 4-week recovery period, there was complete recovery of the hyperplasia of the mucosal epithelium of the ileum and cecum, and partial recovery of the increased cecal weights in the 1000 mg/kg/day group.

For males, the LOAEL is 1000 mg/kg/day (1090 mg/kg/day), based on hyperplasia of the mucosal epithelium of the ileum and cecum. The NOAEL is 500 mg/kg/day (543 mg/kg/day). For females, the LOAEL could not be determined since there were no adverse treatment-related findings observed at any dose level tested. The increased size of the cecum and increased full cecal weights observed in the 1000 mg/kg/day group were not considered adverse effects since there were no corresponding histopathological findings. The NOAEL is 1000 mg/kg/day (1060 mg/kg/day).

This study is acceptable and satisfies the guideline requirement for a subchronic oral toxicity study (OPPTS 870.3100; OECD 408) in the rat.

Oral Subchronic Toxicity Study (GF-871)-Rat; OPPTS 870.3100; OECD 408

EXECUTIVE SUMMARY:

In a subchronic toxicity study (2004, MRID No.: 46235622), GF-871 (containing 41.3 % XDE-750) was administered in the diet to groups of Fischer 344 rats, 10/sex/group, at targeted doses of 0, 465, 1211, or 2421 mg/kg/day or 0, 192, 500, or 1000 mg/kg/day in terms of XDE-750 TIPA. The acid equivalent doses are 0, 100, 260, and 520 mg ae/kg/day. All rats were observed daily for mortality and clinical signs of toxicity. Ophthalmologic examination was conducted prior to dosing and before study termination. Body weight of individual animals was recorded pre-dosing, and then at weekly intervals. Food consumption was recorded weekly. At termination sacrifice, hematology (including prothrombin time), clinical chemistry, urinalysis, selected organ weights, gross and histopathologic examinations were carried out.

There were no treatment-related effects on body weight, feed consumption, ophthalmologic and

clinical observations, hematologic and clinical chemistry parameters. Rats, both sexes, given 260 or 520 mg ae/kg/day had treatment-related statistically identified increases in absolute and relative full cecal weights. When the ceca were emptied of their contents, the absolute and relative weights of the empty ceca were statistically identified as increased for males given 520 mg ae/kg/day. The increases in cecal weights were unaccompanied by histopathological changes and were considered to be a non-adverse osmotic effect. The only other treatment-related alterations, which were considered secondary to increased resorption of colonic water with compensatory renal excretion, were minimal increases in urine volume for high-dose males and females, and a minimal decrease in urine specific gravity for high-dose females.

The LOAEL could not be determined. The NOAEL is 520 mg ae/kg/day for both sexes, the highest dose tested.

This study is acceptable and satisfies the guideline requirement for a subchronic oral toxicity study (OPPTS 870.3100; OECD 408) in the rat.

Repeat-Dose Oral Toxicity Study (XDE-750)-Rat

EXECUTIVE SUMMARY: In a repeat-dose feeding toxicity study (2001, MRID No.: 46235625), technical XDE-750, purity 95.4%, was administered to 5 Fischer 344 rats per sex per group in the diet at dose levels of 0, 10, 100, 500 or 1000 mg/kg/day (equal to 0, 11.4, 113.7, 561.1 or 1125.6 mg/kg/day for males, and 0, 12.2, 110.2, 550.5 or 1093.7 mg/kg/day for females).

There were no adverse, treatment-related effects on mortality, body weights, food consumption, ophthalmologic and clinical observations, organ weights, hematology, clinical chemistry, urinalysis or histopathology. The size of the cecum was increased in the 500 and 1000 mg/kg/day groups, both sexes. Since there were no associated histopathological changes, this was not considered to be an adverse effect, but rather reflective of physiological changes to the digestive tract following ingestion of XDE-750.

The LOAEL could not be determined. The NOAEL is 1000 mg/kg/day.

This study in the rat is acceptable and satisfies the guideline requirement for a repeat-dose oral study in the rat (OPPTS 870.3100; OECD 407).

Oral Subchronic Toxicity Study (XDE-750)-Mouse; OPPTS 870.3100; OECD 408

EXECUTIVE SUMMARY: In a subchronic toxicity study (2001, MRID No.: 46235618), technical XDE-750, purity 94.5%, was administered to 10 CD-1 mice per sex per group in the diet at dose levels of 0, 10, 100, 500 or 1000 mg/kg/day (equal to 0, 10.2, 101, 512 or 1020 mg/kg/day for males, and 0, 102, 103, 515 or 1020 mg/kg/day for females).

There were no treatment-related effects on mortality, body weights, food consumption, ophthalmologic and clinical observations, organ weights, hematology, clinical chemistry, gross pathology or histopathology.

The LOAEL could not be determined. The NOAEL is 1000 mg/kg/day (1020.0/1020.0 mg/kg/day).

This study is acceptable and satisfies the guideline requirement for a subchronic oral toxicity study (OPPTS 870.3100; OECD 408) in the mouse.

Repeat-Dose Oral Toxicity Study (XDE-750)-Mouse

EXECUTIVE SUMMARY: In a repeat-dose feeding toxicity study (2000, MRID No.: 46235624), technical XDE-750, purity 95.4%, was administered to 5 CD-1 mice per sex per group in the diet at dose levels of 0, 10, 100, 500 or 1000 mg/kg/day (equal to 0, 11.0, 102.0, 524.7 or 1038.0 mg/kg/day for males, and 0, 10.8, 105.0, 530.4 or 1058.0 mg/kg/day for females).

There were no adverse, treatment-related effects on mortality, body weights, food consumption, ophthalmologic and clinical observations, organ weights, hematology, clinical chemistry, urinalysis or histopathology. WBC count was lower in the 1000 mg/kg/day group, both sexes, without corresponding histopathological changes. This finding could possibly represent an increase in the destruction of circulating WBCs, and so is considered to be an adverse effect. Histopathological findings considered to be treatment-related were limited to 2 males in the high-dose group, manifested as a generalized decrease in hepatocyte glycogen, and hepatocyte hypertrophy with altered tinctorial properties. These effects were not considered adverse in the absence of any corresponding clinical chemistry of histopathological findings or liver weight changes.

The LOAEL was 1000 mg/kg/day based on a decrease in WBC count. The NOAEL is 500 mg/kg/day (524.7/530.3 mg/kg/day).

This study in the mouse is acceptable and satisfies the guideline requirement for a repeat-dose oral study (OPPTS 870.3100; OECD 407) in the mouse.

Oral Subchronic Toxicity Study (XDE-750)-Dog; OPPTS 870.3150; OECD 409

EXECUTIVE SUMMARY: In a subchronic toxicity study (2002, MRID No.: 46235623), technical XDE-750, purity 94.5%, was administered to 4 Beagles per sex per group in the diet at concentrations of 0, 0.15%, 0.75% or 3.0% or 0, 1500, 7500, and 30000 ppm (equal to 0, 54.5, 282 or 1070 mg/kg/day for males, and 0, 52.7, 232 or 929 mg/kg/day for females) for a period of 13 weeks.

There were no treatment-related effects on body weights, food consumption, ophthalmologic and clinical observations or clinical pathology parameters. Liver weights were increased in the 3.0% group, both sexes. However, in the absence of any corresponding clinical chemistry findings or gross/microscopic changes to the liver, this effect was considered adaptive rather than adverse. Treatment-related histopathological changes to the stomach were observed for all animals in the 3.0 % group, manifested as slight diffuse hyperplasia and hypertrophy of the mucosal epithelium.

The LOAEL is 3.0% or 30,000 ppm (equal to 1070 mg/kg/day for males and 929 mg/kg/day for females), based on stomach histopathology. The NOAEL is 0.75% or 1500 ppm (equal to 282 mg/kg/day for males and 232 mg/kg/day for females).

This study in the dog is acceptable and satisfies the guideline requirement for a subchronic oral toxicity study (OPPTS 870.3150; OECD 409) in the dog.

Chronic Toxicity Study-Dog; OPPTS 870.4100; OECD 452

EXECUTIVE SUMMARY: In a chronic toxicity study (2003, MRID No.: 46235627), technical XDE-750, purity 94.5%, was administered to 4 Beagles per sex per group in the diet at concentrations of 0, 0.03%, 0.30% or 3.0% or 0, 300, 3000, and 30000 ppm (equal to 0, 9.9, 99.2 or 967 mg/kg/day for males, and 0, 9.2, 93.2 or 1038 mg/kg/day for females) for a period of one year.

There were no treatment-related effects on body weights, food consumption, ophthalmologic and clinical observations or clinical pathology parameters. Liver weights were higher in the 3.0% group, both sexes, with very slight hepatocyte hypertrophy noted at histopathological examination. These liver effects were considered to be adaptive rather than adverse. In the stomach, gross examination revealed diffuse thickening of the stomach mucosa for females in the 3.0% group. Histopathological changes in the stomach were observed for all animals in the 3.0% group, manifest as slight diffuse hyperplasia and hypertrophy of the mucosal epithelium of the stomach, slight lymphoid hyperplasia of the gastric mucosa and very slight/slight chronic mucosal inflammation.

The LOAEL is 3.0% or 30,000 ppm (equal to 967 mg/kg/day for males and 1038 mg/kg/day for females), based on stomach histopathology. The NOAEL is 0.30% or 3000 ppm (equal to 99.2 mg/kg/day for males and 93.2 mg/kg/day for females).

This study is acceptable and satisfies the guideline requirement for a 1-year oral toxicity study (OPPTS 870.4100; OECD 452) in the dog.

Repeat-Dose Oral Toxicity Study (XDE-750)-Dog

EXECUTIVE SUMMARY: In a repeat-dose feeding toxicity study (2000, MRID No.: 46235620), XDE-750 Technical, purity 95.4%, was administered to 2 Beagles per sex per group in the diet at concentrations of 0, 0.15%, 0.45% or 1.5% or 0, 1500, 4500, and 15000 ppm (equal to 0, 62, 93 or 543 mg/kg/day for males, and 0, 62, 177 or 556 mg/kg/day for females) for a period of 4 weeks. There were no treatment-related effects on body weights, ophthalmologic and clinical observations, clinical pathology parameters, organ weights, gross and histopathological examinations. Food intake was lower in the 3.0% group, both sexes, but was not considered adverse in the absence of any treatment-related effect on body weight gain. The only other findings were decreased RBC count, Hgb and HCT, noted for females at all dose levels. However, these effects were marginal and fell close to historical control values. In addition, there

were no corresponding histopathological findings, and so these were not considered to be adverse effects.

The LOAEL could not be determined. The NOAEL is 1.5% or 15,000 ppm (equal to 543 mg/kg/day for males and 556 mg/kg/day for females).

This 4-week feeding toxicity study in the dog is classified as supplementary. It does not satisfy the guideline requirement for a repeat-dose oral study (OPPTS 870.3150, [§82-1]; OECD 407) in dogs. However, it was a preliminary study conducted to aid in the determination of the dose levels to be used for the subchronic and chronic oral toxicity studies. The study is considered acceptable for this purpose.

Acute Oral Neurotoxicity Study (XDE-750)-Rat; OPPTS 870.6200; OECD 424

EXECUTIVE SUMMARY: In an acute neurotoxicity study (2002, MRID No.: 46235616), groups of randomly assigned Fischer 344 rats (10/sex) were given a single oral dose of technical XDE-750 (94.5% purity) in 0.5% aqueous Methocel® at 0, 500, 1000 or 2000 mg/kg/day. The rats were fasted overnight prior to dosing. They were observed daily for signs of toxicity, mortality, and moribundity for 2 weeks after dosing. Body weight was recorded pre-exposure and on days 1, 8, and 15. Clinical examinations were conducted on all animals on test days 2-4. This examination included careful hand-held evaluations of the skin, fur, mucous membranes, respiratory and nervous system function (including tremors and convulsions), swelling, masses and animal behaviour. Daily cage-side examinations were made on each day of the study and to the extent possible the above parameters were evaluated. Functional Observational Battery (FOB) and motor activity testing were performed prior to dosing, and on days 1, 8 and 15. Two weeks after dosing, the rats were sacrificed and central and peripheral nervous tissues of 5 rats/sex/group were perfusion-fixed *in situ* and subjected to neuropathological examinations.

There were no treatment-related effects on ophthalmoscopy, body weight, the FOB, motor activity, gross pathology, or on neuropathologic evaluation. Clinical observations of rats treated with 2000 mg/kg/day revealed a higher incidence of fecal soiling in males and urine soiling in females compared to controls. However, these effects were transient (most resolving within 3-4 days following treatment) and occurred in the absence of any gross or neuropathologic changes.

The LOAEL is 2000 mg/kg/day based on fecal soiling in males and urine soiling in females. The NOAEL is 1000 mg/kg/day.

This study is classified acceptable and satisfies the guideline requirement for an acute oral neurotoxicity study (OPPTS 870.6200; OECD 424).in the rat.

Chronic Oral Neurotoxicity Study (XDE-750)-Rat; OPPTS 870.6200; OECD 424

EXECUTIVE SUMMARY: A one-year neurotoxicity study (2003, MRID No.: 46235617) was conducted as part of a two-year chronic toxicity/oncogenicity study to assess the effects of dietary exposure to technical XDE-750 at levels of 0, 5, 50, 500, and 1000 mg/kg/day in male and female

Fischer 344 rats. The neurotoxicity subgroup contained 10 rats/sex/dose, and was evaluated pre-exposure, and at 1, 3, 6, 9, and 12 months of exposure using a functional observational battery (FOB), determinations of grip performance, rectal temperature, landing foot splay, and an automated test of motor activity. Following 12 months of exposure, five rats/sex from the control and high-dose groups were perfused, and tissues from the central and peripheral nervous system were submitted for neuropathologic examination.

No treatment-related effects were seen on any of the FOB parameter assessed, or on motor activity at any time during the study. Within the neurotoxicity subgroup, no significant treatment-related effects were seen on body weight, though significant body weight effects were seen in males treated with 1000 or 500 mg/kg/day (5.3 and 3.2% less than control; respectively) when all study animals (n = 65/sex/group; chronic neurotoxicity/chronic toxicity/oncogenicity) were considered. An increase in the level of defecation during the open-field activity of the FOB was seen in males of the high-dose group, and less consistently in the mid-dose groups. This effect was not considered a neurotoxic effect, but rather reflected a non-specific effect. There were no treatment-related gross or histopathologic findings in the central or peripheral nervous system following one year of dietary exposure to XDE-750. In summary, there were no effects of XDE-750 on any parameter that would suggest a neurotoxic effect.

The LOAEL was not determined. The NOAEL for XDE-750 neurotoxicity in Fischer 344 rats is 1000 mg/kg/day, the highest dose level tested.

This study is classified acceptable and satisfies the guideline requirement for a one-year oral neurotoxicity study (OPPTS 870.6200; OECD 424) in the rat.

28 Day Dermal (XDE-750)-Rat;OPPTS 870.3200; OECD 410

EXECUTIVE SUMMARY: In a dermal toxicity study (2002, MRID No.: 46235626), technical XDE-750, purity 94.5%, was applied to the shaved skin of 10 New Zealand White rabbits/sex/dose at dose levels of 0, 100, 500 or 1000 mg/kg/day, 6 hours/day, 7 days/week for 28 days.

There were no adverse, treatment-related effects on mortality, clinical signs, ophthalmology, body weight, food consumption, clinical chemistry, hematology, organ weights or gross pathology. The only finding was slight epidermal hyperplasia observed in the 500 and 1000 mg/kg/day study groups, males only.

The LOAEL for systemic toxicity could not be determined. The NOAEL is 1000 mg/kg/day, the highest dose tested.

The LOAEL for dermal toxicity in males is 500 mg/kg/day based on slight epidermal hyperplasia. The NOAEL is 100 mg/kg/day. For females, LOAEL could not be determined and the NOAEL is 1000 mg/kg/day, the highest dose tested.

This study is acceptable and satisfies the guideline requirement for a dermal toxicity study

(OPPTS 870.3250; OECD 410) in the rat.

Metabolism Study (XDE-750)-Rat; OPPTS 870.7485; OECD 417

EXECUTIVE SUMMARY: In a metabolism study (2004, MRID No.: 46235807), [^{14}C]XDE-750 (radiochemical purity 98.6%), was administered to 4 male Fischer 344 rats/dose as a single gavage dose of 50 or 1000 mg/kg/day, or 14 daily doses (50 mg/kg/day) of unlabelled XDE-750 (purity 99.5%) followed by a single gavage dose of 50 mg/kg/day [^{14}C]XDE-750 on day 15. Excreta were collected at 0, 6 (urine only), 12 (urine only), 24, 48, 72, 96, 120, 144 and 168 hours post-dosing.

Study results indicated that radiolabelled XDE-750 is rapidly absorbed, distributed and excreted following oral administration in rats. Total 24-hour recoveries of the radioactivity were high for all groups (~41-59% and 33-43% of the administered dose in urine and feces, respectively). The absorption and excretion patterns of the ^{14}C moiety were similar among all groups. Study results indicated that XDE-750 was not metabolized to volatile compounds, including CO_2. The average α-phase elimination half-lives (T1/2 α) of ^{14}C-XDE-750 equivalents were 2.85, 3.27 and 3.78 hours for the single low, repeated low and single high dose groups, respectively. The average β-phase urinary elimination half-lives (T1/2 β) of ^{14}C-XDE-750 equivalents were 10.23, 12.25 and 10.88 hours for the single low, repeated low and single high dose groups, respectively. Tissue distribution and bioaccumulation of XDE-750 were minimal; <0.73% of the administered dose was recovered in tissues 7 days after oral administration for all dosing groups. Highest levels of radioactivity were found in the skin and carcass. XDE-750 was excreted unchanged indicating an absence of metabolism. XDE-750 represented ≥96% of the AD in the urine, and 100% of the AD in feces. Three unknown components (≤4%) found in urine were also detected in similar quantities in the analysis of the dose formulation, suggesting that they were trace impurities in the radiolabelled material.

This study in the rat is classified acceptable and satisfies the guideline requirement for a metabolism study (OPPTS 870.7485; OECD 417) in the rat.

Dissociation and Metabolism-Rat

EXECUTIVE SUMMARY: In a metabolism study, (2004, MRID No.: 46235833) [^{14}C]XDE-750 (radiochemical purity 98.25%), or [^{14}C]XDE-750-TIPA (radiochemical purity 98.25%) was administered to 4 male Fischer 344 rats/dose as a single gavage dose of 50 or 96 mg/kg/day, respectively. Excreta were collected at 0, 6 (urine only), 12 (urine only), 24, 48, 72, 96 and 120 hours post-dosing. Plasma was prepared from blood collected at 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48 and 120 hours post-dosing.

A single oral administration of ^{14}C-XDE-750 or ^{14}C-XDE-750-TIPA was rapidly absorbed by the rat. The excretion of 38.3% (for ^{14}C-XDE-750) and 34.6% (for ^{14}C-XDE-750-TIPA) of the administered radioactivity in the urine within six hours confirms that the amino-dichloro-

picolinate (or anion) portion of the molecule was rapidly absorbed regardless of whether it was administered as the acid or as the TIPA salt formulation. Plasma AUCs were 23.0 and 19.0 µg eq-hour/g plasma; half-lives from the α phase of plasma elimination were 0.338 and 0.509 hours; and half-lives from the β phase of plasma elimination were 8.8 and 13.0 hours for the XDE-750 and XDE-750-TIPA dosed groups, respectively. These data indicate that pharmacokinetic behavior was similar between the two compounds. Based on the amount of radioactivity recovered in the urine through 120 hours, a minimum of 46.3% and 42.5% of the orally administered ^{14}C- XDE-750 and the ^{14}C-XDE-750-TIPA was absorbed. Radioactivity was also rapidly eliminated with 93.5% (44.7% in urine; 48.8% in feces) and 93.3% (41.5% in urine; 51.8% in feces) of the administered doses of ^{14}C-XDE 750 and ^{14}C-XDE-750-TIPA recovered in excreta within 24 hours post-dosing. Urinary rates of elimination calculated for the two compounds were also similar. Half-lives estimated for the rapid initial (α) phase of the urinary elimination curve were 2.8 hours for the ^{14}C-XDE-750 dosed group and 2.5 hours for the ^{14}C-XDE-750-TIPA dosed group. Half-lives estimated for the slower terminal (β) phase were 7.8 hours for the ^{14}C-XDE-750 dosed group and 10.7 hours for the ^{14}C-XDE-750-TIPA dosed group. The amino-dichloro-picolinate portion of the molecule(s) was excreted primarily unchanged following a single oral administration of either formulation. Parent XDE-750 represented >99% of the radioactivity detected in the urine and feces of both dose groups. The only unidentified metabolite was detected in urine from the ^{14}C-XDE-750-TIPA dosed group, and represented 0.34% of the administered dose. The results from this study indicate that ^{14}C-XDE-750 and ^{14}C-XDE-750-TIPA, when administered orally to rats, are bioequivalent in terms of absorption, distribution, metabolism, and excretion of the amino-dichloro-picolinate portion of the molecule(s).

This study is classified as supplementary since it was not conducted according to GLP nor according to any specific guideline. It is a special study designed specifically to compare the tissue distribution, excretion and metabolic profiles (via urine and feces) of ^{14}C-XDE-750 and the TIPA salt of ^{14}C-XDE-750. The study is considered acceptable for this purpose.

Bacterial Reverse Mutation Assay (XDE-750); OPPTS 870.5100; OECD 471

EXECUTIVE SUMMARY: In a reverse gene mutation assay (2004, MRID No.: 46235636) in bacteria, strains TA98, TA100, TA1535 and TA1537 of *Salmonella typhimurium* and strain WP2*uvr*A of *Escherichia coli* were exposed to XDE-750, purity 94.5%, dissolved in dimethylsulfoxide at concentrations of 0, 100, 333, 1000, 3300 or 5000 µg/plate in the presence and absence of an Aroclor 1254-stimulated rat liver metabolic activation system using the preincubation test. The results of the initial mutagenicity assay were confirmed in a second, independently conducted assay.

Cytotoxicity was not observed, nor was a precipitate formed at any dose level tested. The positive controls induced the appropriate responses in the corresponding strains. **There was no evidence of treatment-induced mutant colonies above background levels.**

This study is classified as acceptable and satisfies the guideline requirement for an *in vitro* mutagenicity (bacterial reverse gene mutation) study (OPPTS 870.5100; OECD 471).

Bacterial Reverse Mutation Assay (XDE-750 triisopropanolammonium salt); OPPTS 870.5100; OECD 471

EXECUTIVE SUMMARY: In two *in vitro* gene mutation assays (MRID 46235637) (initial and confirmatory), *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* strain WP2*uvr*A were exposed to GF-871 (contain 41.3% XDE-750 TIPA salt). The dose levels tested were 0, 33.3, 100, 333, 1000, 3330, and 5000 µg (based on XDE-750 TIPA)/plate, with or without S9 metabolic activation. The S9 fraction was derived from Aroclor 1254-induced male rat livers. Appropriate positive controls were included in the assays.

No cytotoxicity was seen up to 5000 µg XDE-750 TIPA per plate. No test article precipitate was observed on any of the plates in the presence or absence of S9 mix. In the main and confirmatory mutagenicity tests, exposure to the test material did not result in increases in the number of revertants in any of the bacterial strains, at any dose level in either the absence and in the presence of metabolic activation. All the positive control compounds produced the expected increase in the number of revertant colonies, demonstrating the sensitivity of the test system.

This study is acceptable and satisfies the guideline requirement for a microbial gene mutation study (OPPS 870.5100; OECD 471).

***In Vitro* Mammalian Cell Gene Mutation Test (XDE-750); 870.5300, OECD 476**

EXECUTIVE SUMMARY: In a mammalian cell gene mutation assay (MRID 46235801) at the hypoxanthine-guanine-phosphoribosyl transferase (HGPRT) locus, Chinese hamster ovary (CHO) cells cultured *in vitro* were exposed to XDE-750, purity 94.5%, in dimethylsulfoxide (DMSO), at concentrations of 0, 31.25, 62.5, 125, 250, 500, 1000, 1500 or 2070 µg/mL both in the absence and in the presence of metabolic activation. A second assay was conducted, using concentrations of 0, 250, 500, 1000, 1500 or 2070 µg/mL both in the absence and in the presence of metabolic activation.

The treated cultures both in the presence and absence of S-9 mix exhibited little to no cytotoxicity at any concentration tested. The positive controls did induce the appropriate response. **There was no evidence of induced mutant colonies over background.**

This study is classified as acceptable and satisfies the requirement for an *in vitro* mutagenicity (mammalian forward gene mutation) study (OPPTS 870.5300, OECD 476).

***In Vitro* Mammalian Cell Gene Mutation Test (GF-871); 870.5300, OECD 476**

EXECUTIVE SUMMARY: In a mammalian cell gene mutation assay (MRID 46235804), GF-871 (an aqueous formulation containing 41.3% XDE-750 TIPA) was evaluated in an *in vitro* Chinese hamster ovary cell/hypoxanthine-guanine-phosphoribosyl transferase (CHO/HGPRT)

forward gene mutation assay. The genotoxic potential of GF-871 was assessed in the absence and presence of S9 activation at 250, 500, 1000, 2000, or 4000 µg XDE-750 TIPA /mL (limit dose of approximately 10 mM). The adequacy of the experimental protocol for detection of induced mutation was confirmed by positive controls, ethyl methanesulfonate for assays without S9 and 20-methylcholanthrene for assays with S9. Vehicle control cultures were treated with the solvent used to dissolve the test material.

The results indicated acceptable cell survival (85.7-131.4 %) in cultures treated with GF-871. The mutation frequencies (MF) observed in cultures treated with GF-871 at any concentration in the absence and presence of S9 were similar to the concurrent vehicle control values. All MF were within a reasonable range of historical background values. The positive control chemicals in the absence and presence of S9 induced significant increases in MF verifying the adequacy of the test protocol. **Thus, it was concluded that GF-871 did not induce a gene mutation response in the assay system employed.**

This study is classified as acceptable and satisfies the requirement for an *in vitro* mutagenicity (mammalian cell gene mutation) study (OPPTS 870.5300, OECD 476).

***In Vitro* Mammalian Cell Chromosome Aberration Test (XDE-750); OPPTS 870.5375**

EXECUTIVE SUMMARY: In a mammalian cell cytogenetics assay (MRID 46235802), primary rat lymphocyte cultures were exposed to XDE-750 (purity 94.5%) in 1% dimethylsulfoxide, at concentrations of 0, 32.3, 64.7, 129.4, 258.8, 517.5, 1035 or 2070 µg/mL with and without metabolic (S9) activation (4 h treatment and 24 h cell harvest). A second assay was conducted at 0, 125, 250, 500, 750, 1000, 1400, 1700 or 2070 µg/mL in the absence of S9 activation and 0, 62.5, 125, 500, 1000 or 2070 µg/mL with S9 activation (24 h continuous treatment with cell harvest at end of treatment). A third assay to confirm the results noted in assay 2 in the absence of S9 activation was conducted at 400, 600, 800, 1000, 1200, 1400, 1600, 1700, 1800 or 2070 µg/mL (24 h continuous treatment with cell harvest at end of treatment). XDE-750 was tested up to cytotoxic concentrations. Mitotic indices (MI) were ~63-64 % of control for assay 1 at 2070 µg/mL with or without S9, <50 % of control at ≥1000 µg/mL without S9 and 84 % of control with S9 at 2070 µg/mL for assay 2, and <50 % at ≥1200 µg/mL without S9 for assay 3. There was a statistically significant increase in the percent of metaphases with aberrations (excluding gaps) in rat lymphocyte cultures treated with XDE-750 at 1000, 1400 and 1700 µg/mL, in the absence of S9 activation, for cells exposed to the test material for 24 h. The response was reproducible but was only observed at levels causing a ≥50 % reduction in MI. The predominant type of chromosome aberration was chromatid break. The findings suggested cytotoxicity. Additionally, the magnitude of the response was relatively weak with the frequencies of aberrant cells in XDE-750-treated cultures being only slightly greater than the upper end of the laboratory historical control data. Positive controls induced the appropriate response. **It is, therefore, concluded that XDE-750 is not a clastogenic agent in the presence of metabolic activation but induced a weak clastogenic effect only at cytotoxic levels with metabolic activation.**

This study is classified as acceptable and satisfies the requirement for an *In vitro* mammalian cytogenetics (chromosomal aberration) study (OPPTS 870.5375).

In Vitro Mammalian Cell Chromosome Aberration Test (GF-871); OPPTS 870.5375

EXECUTIVE SUMMARY: In an *in vitro* chromosomal aberration assay (2004, MRID No.: 46235803), GF-871 (an aqueous formulation containing 41.3% XDE-750 TIPA) was evaluated using rat lymphocytes. Approximately 48 h after the initiation of whole blood cultures, cells were treated in the absence of S-9 for 4 or 24 h and for 4 h in the presence of S-9 activation with concentrations ranging from 0 (negative control) to 4000 µg XDE-750 TIPA per mL (limit dose of ~10 mM) of culture medium. Based on the mitotic indices, cultures treated for 4 h with targeted concentrations of 0, 1000, 2000, and 4000 µg/mL in the absence and presence of S-9 activation and cultures treated for 24 h without S9 at 0, 500, 1000, and 2000 µg/mL were assessed for incidence of chromosomal aberrations. S9 mix, purchased from Molecular Toxicology Inc, Boone, NC, was prepared form Aroclor-1254 treated male Sprague Dawley rats.

There were no significant increases in the frequencies of cells with aberrations in the 4 h activation assay or the 24 h continuous treatment without activation. There was a statistically significant increase in the frequencies of cells with aberrations in the 4 h non-activation treatment at concentrations of 1000 and 4000 µg/mL treatment, but not at 2000 µg/mL (2.0%). The frequencies of aberrations at these two concentrations (2.5 and 3.0%, respectively) were not considered to be biologically significant since the aberration frequencies were within the laboratory historical negative control values and there was no dose response. The statistical finding was attributed to the chance occurrence of 0% aberrant cells in the negative controls. In a confirmatory assay, cultures were treated for 4 h in the absence of S-9 activation at targeted concentrations ranging from 0 to 4000 µg/mL. The incidence of chromosomal abnormalities was assessed from cultures treated at 0, 1000, 2000, and 4000 µg/mL. Statistical analyses of the data did not identify a significant difference between the negative control and any of the treated cultures. Cultures treated with the positive control chemicals (mitomycin C without S-9 and cyclophosphamide with S-9) had significantly higher incidences of abnormal cells. **Thus, GF-871 was considered to be non-genotoxic in this *in vitro* chromosomal aberration assay with rat lymphocytes.**

This study is classified as acceptable and satisfies the requirement for an *In vitro* mammalian cytogenetics (chromosomal aberration) study (OPPTS 870.5375).

Mammalian Erythrocyte Micronucleus Test (XDE-750); OPPTS 870.5395; OECD 474

EXECUTIVE SUMMARY: In a mouse bone marrow micronucleus assay (MRID 46235805), 6 male CD-1 (ICR)BR mice/dose were dosed once daily for 2 consecutive days by oral gavage with XDE-750, purity 94.5%, at dose levels of 0 (vehicle control), 500, 1000 or 2000 mg/kg bw. Bone marrow cells were harvested from mice at 24 hours post-treatment. The vehicle was 0.5% Methocel.

There was no treatment-related mortality, nor clinical signs of toxicity. The positive control induced the appropriate response. **There was no treatment-related increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow at any dose level tested, after any treatment time. It is, therefore, concluded that XDE-750 did not induce a clastogenic**

effect in either sex at any sacrifice time.

This study is acceptable and satisfies the guideline requirement for an *in vivo* mammalian erythrocyte- mouse micronucleus assay (OPPTS 870.5395)

Mammalian Erythrocyte Micronucleus test (GF-871); OPPTS 870.5395; OECD 474

EXECUTIVE SUMMARY: The *in vivo* genotoxic potential of GF-871 (a formulation containing 41.3% XDE-750 TIPA) was evaluated by examining the incidence of micronucleated polychromatic erythrocytes (MN-PCE) in the bone marrow (MRID 46235806). The test material was administered to male CD-1 mice, 6/group, by oral gavage at 0 (negative control), 500, 1000, or 2000 (limit dose) mg XDE-750 TIPA/kg bw/d for 2 days. The highest dose level of 2000 mg/kg bw was based upon the results of a range-finding test where at this dose, no treatment-related deaths, toxicity or changes in body temperature were observed in male or female mice. The mice were sacrificed 24 h after dosing. Bone marrow cells from both femurs were collected and evaluated. A total of 2000 polychromatic erythrocytes from each mouse was examined for micronucleus (MN) formation. The proportion of PCE among erythrocytes was determined based upon 200 erythrocytes per animal and the results expressed as a percentage. Mice treated orally with 120 mg/kg bw cyclophosphamide monohydrate and sacrificed 24 h later served as positive controls. All animals survived to the end of the observation period with no treatment-related signs of toxicity.

There were no statistically significant increases in the frequencies of MN-PCE in groups treated with GF-871 as compared to the negative controls. The positive control mice showed a significant increase in the frequency of MN-PCE as compared to the negative control animals. There were no statistically significant differences in the percent PCE in groups treated with the test material as compared to negative controls, while the positive control group showed a significant decrease in the relative proportion of PCE among erythrocytes. **Under the experimental conditions used, GF-871 was considered to be negative in the mouse bone marrow micronucleus test.**

This study is acceptable and satisfies the guideline requirement for an *in vivo* mammalian erythrocyte- mouse micronucleus assay (OPPTS 870.5395)