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OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

August 27, 2008

SUBJECT: **Dimethenamid-P** Human Health Risk Assessment for Proposed Use of Dimethenamid-P on Turfgrass on Golf Courses

PC Code: 120051, 129051
Decision No.: 385104
Petition No.: NA
Risk Assessment Type: Single Chemical Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: D348401
Registration No.: 7969-239
Regulatory Action: Section 3
Case No.: NA
CAS No.: 87674-68-8, 163515-14-8
40 CFR: NA

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This document provides the Health Effects Division's (HED's) risk assessment of use of dimethenamid on turfgrass on golf courses. Supporting documents and previous dimethenamid risk assessments are provided below.

Dimethenamid-P. Human Health Risk Assessment for Use on Winter Squash, Pumpkin, Radish (Roots and Tops), Rutabaga (Roots and Tops), Turnip (Roots, Tops and Greens) and on Hops, Dried Cones. Petition No: 6E7152 DP36172, September 27, 2007
Dimethenamid-P Human Health Risk Assessment for Proposed Use on Grasses Grown for Seed Petition No: 0F6138, DP337887, May 29, 2007
Dimethenamid/Dimethenamid P Human Health Risk Assessment Petition No: 0E6196, DP304790
Drinking Water Exposure Assessment for the Section 3 New Use Registration of Dimethenamid-P on Golf Course DP348403 Date, May 28, 2008

David Miller 8/27/2008

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1.0 EXECUTIVE SUMMARY

This assessment provides information to support an amendment to a Section 3 registration for the use of dimethenamid-P in turfgrass on golf courses. This document addresses the exposures and risks associated with exposures resulting from currently registered uses of dimethenamid and dimethemamid-P and the proposed new use of dimethenamid-P on golf course turfgrass.

Use Profile

Dimethenamid ([RS]-dimethenamid) and dimethenamid-P ([S]-dimethenamid-P) are selective herbicides registered for the control of annual broadleaf and grass weeds in a variety of field and vegetable crops and grasses grown for seed. Dimethenamid is a racemic 50:50 S:R isomer. Dimethenamid-P is enriched in the biologically active S-isomer (90:10, S:R). BASF stopped producing, marketing and selling the 50:50 S:R isomer for use in the US in 2002-2003 and has replaced it with dimethenamid-P (90:10, S:R). The end use products containing the 50:50 S:R isomer (Frontier 6.0, EPA RegNo 7969-147 and Guardsman, EPA RegNo 7969-146) are no longer produced or marketed and existing stocks have been depleted. While the registration of the original 50:50 mixture is still active, BASF does not plan to renew the registration once it expires. Tolerances are established in 40 CFR §180.464(a) and (b) for both dimethenamid (50:50, S:R) and dimethenamid-P (90:10, S:R). Tolerances are established for residues of dimethenamid in/on numerous raw agricultural commodities at 0.01 ppm, which is the lowest limit of method validation (LLMV). Dimethenamid-P is applied using ground or aerial equipment to field and vegetable crops, perennial grasses grown for seed, containerized ornamentals, commercial evergreen plantations, maintained landscape ornamentals and general areas. There are currently no Dimethenamid-P products registered for homeowner use.

Proposed New Use

BASF is seeking to register the herbicide active ingredient dimethenamid-P as the liquid end-use product Tower herbicide (EPA Reg. No. 7969-239) for control or suppression of annual grasses, broadleaf weeds, and sedges in turfgrass grown on golf courses. The proposed maximum application rate is 1.5 lbs active ingredient (ai) per acre with a maximum seasonal use rate of 3.0 lbs ai per acre per season.

Hazard Identification

The existing toxicological database is primarily comprised of studies conducted with [RS]-dimethenamid (50:50, S:R). However, bridging studies indicate that the dimethenamid toxicology database is adequate for the risk assessment of dimethenamid-P. The acute toxicity data indicate that [S]-dimethenamid-P is Category II via the oral route of exposure, and Category III for exposure via the dermal and inhalation routes. It is moderately irritating to the eye (Category III) and slightly irritating to the skin (Category IV). Dimethenamid-P is a mild skin

sensitizer. The acute toxicity data for [RS]-dimethenamid are the same as those for [S]-dimethenamid-P for all exposures except acute oral (Category III).

Chronic studies in the rat, mouse and dog with [RS]-dimethenamid showed decreases in body weight and food efficiency at the lowest effect level. At higher dose levels, liver pathology, stomach hyperplasia, and some indication of kidney effects were seen. In some of the studies liver enzymes and cholesterol levels were increased at doses resulting in liver pathology. In 21-day dermal rabbit studies, decreases in male body weight were seen at the lowest effect level.

Developmental toxicity studies show increased post-implantation loss and minor skeletal variations in the rat, and late resorptions and minor skeletal variations in the rabbit at the highest doses tested. In the rabbit, the developmental effects occurred at the same dose as maternal toxicity, whereas in the rat, the developmental toxicity occurred at much higher doses than in the dams. The reproduction study showed decreases in body weight in both pups and parental animals at the same dose levels. The only other effects noted were increases in liver weights in parental animals (both sexes).

Metabolism studies with [RS]-dimethenamid showed extensive metabolism (> 30 metabolites). In the rat, dimethenamid-P parent was extensively metabolized, being essentially complete within 3 days with over 90% excreted in the urine, feces and bile within 7 days.

[RS]-dimethenamid has been classified as group "C"-possible human carcinogen, based on an increasing trend for liver tumors (males) seen in the chronic rat study. There were no dose-related tumors seen in the mouse carcinogenicity study.

Dose Response Assessment

Toxicological endpoints were selected for dietary/drinking water, occupational, and non-occupational exposure scenarios based on registered and proposed new uses of dimethenamid-P. Acute and chronic reference doses (RfDs) were selected for assessment of food and drinking water exposures. An acute RfD for females 13-49 was selected from a developmental toxicity study in rabbits. An acute RfD for the general population was not selected because no effect attributable to a single day oral exposure was observed in animal studies. A chronic RfD was selected from a chronic/carcinogenicity study in rats. Short and intermediate-term occupational and non-occupational exposures via the dermal route may occur based on the use pattern and label directions. Toxicological endpoints for dermal exposure were selected from 21 day dermal toxicity studies in rabbits. Only short-term inhalation worker exposures are expected based on prescribed use patterns. Toxicological endpoints from combined subchronic and chronic toxicity studies in dogs were selected for assessment of the inhalation exposure pathway for workers. [Note: endpoints for dermal and inhalation exposure have been revised from previous dimethenamid assessments based on HED's reevaluation of the toxicity data]. The uncertainty factor for dietary and non-dietary exposures is 100 (10x for interspecies extrapolation, 10x for intraspecies variation).

Exposure/Risk Assessment and Risk Characterization

Risk assessments were conducted for dietary (food and water), occupational and non-occupational exposure pathways based on registered uses and the request for a new use as an herbicide on golf course turf. The only non-occupational or residential exposure assessed for the proposed new turfgrass use is post-application exposures to golfers playing on treated turf. Worker exposures were assessed for handler and post-application activities.

Screening level acute and chronic dietary and drinking water exposure and risk assessments for dimethenamid conclude that for all commodities, the acute and chronic combined dietary and drinking water exposure estimates are well below HED's level of concern. Exposure and risk estimates for worker and residential exposure scenarios indicate that residential post-application and occupational handler and post-application exposures are not of concern at the maximum use rate for the proposed new use.

Use of Human Studies

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, listed in Appendix 1, have been determined to require a review of their ethical conduct. Some of these studies are also subject to review by the Human Studies Review Board. All of the studies used have received the appropriate review.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development, as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

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2.0 INGREDIENT PROFILE

2.1 Registered Products

There are 15 active dimethenamid-P registrations, six Section 3s and 8 SLNs (24(c)s). There are 7 active registrations for dimethenamid, six Section 3s and 1 SLN. As previously noted, BASF stopped producing, marketing and selling dimethenamid (50:50 S:R) for use in the US in 2002-2003. This product has been replaced by dimethenamid-P (90:10, S:R). The end use products containing the 50:50 S:R isomer are no longer produced or marketed and existing stocks have been depleted. While the registration of the original 50:50 mixture is still active BASF does not plan to renew the registration once it expires.

Table 1. Summary Report of Supported Registered Dimethenamid-P Products [S-dimethenamid]

Reg #	Name	Company Name	%AI
7969-155	S-Dimethenamid	BASF Corporation	97.2
7969-156	Outlook Herbicide	BASF Corporation	63.9
7969-192	Guardsman Max Herbicide	BASF Corporation	18.2
7969-200	G-Max Lite	BASF Corporation	24.1
7969-239	Tower Herbicide	BASF Corporation	63.9
7969-273	Freehand 1.75g Herbicide	BASF Corporation	0.75
7969-ETO	Bas 781 02h Herbicide	BASF Corporation	55.04
ID050006	Outlook Herbicide	BASF Corporation	63.9
OR060014	Outlook Herbicide	BASF Corporation	63.9
SC080001	G-Max Lite	BASF Corporation	24.1
SD030001	G-Max Lite	BASF Corporation	24.1
SD060001	Establish Life Herbicide	BASF Corporation	24.1
SD060005	Outlook Herbicide	BASF Corporation	63.9
SD080001	G-Max Lite Herbicide	BASF Corporation	24.1
WA060006	Outlook Herbicide	BASF Corporation	63.9

Table 2. Summary Report of Supported Registered Dimethenamid Products [RS-dimethenamid]

Reg #	Name	Company Name	%AI
241-361	Detail Herbicide	BASF Corporation	38.9
241-362	Pursuit Dimethenamid Herbicide	BASF Corporation	62.52
352-600	Dpx-Mx670 Mt	E. I. Du Pont Co., Inc.	24.8
7969-144	Frontier Herbicide	BASF Corporation	79.4
7969-145	Dimethenamid Technical	BASF Corporation	96.9
7969-147	Frontier 6.0 Herbicide	BASF Corporation	63.14
SD060004	Frontier 6.0 Herbicide	BASF Corporation	63.14

2.2 Registered Uses and Application Rates

Dimethenamid is registered for the control of annual broadleaf and grass weeds. Dimethenamid-P to field and vegetable crops, perennial grasses grown for seed, containerized ornamentals, commercial evergreen plantations, maintained landscape ornamentals and general areas. There are currently no Dimethenamid-P products registered for homeowner use. Maximum application rates for existing and proposed uses are provided in Table 3. Maximum rates are based on a review of active labels.

Table 3. Maximum Application Rates for [S] Dimethenamid-P Existing and Proposed Uses

Application Site	Max % AI	Maximum AR	Reg No.
Food Crops and grasses grown for seed	63.9	0.98 lb/ai A	7969-156
Landscape, grounds maintenance, ornamental production and (proposed new use) golf course turf	63.9	1.5 lb/ai A	7969-239

2.3 Structure, Nomenclature, and Physical/Chemical Properties

The nomenclature and physicochemical properties of dimethenamid are provided in Tables 4-7.

Table 4. [RS] Dimethenamid Nomenclature

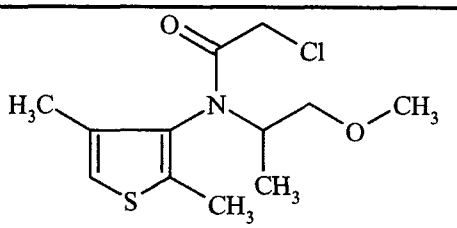
Chemical structure	
Common name	Dimethenamid (50:50, R and S -isomers)
Molecular Formula	$C_{12}H_{18}ClNO_2S$
Molecular Weight	275.8 g/mol
IUPAC name	(*RS*)-2-chloro-*N*-(2,4-dimethyl-3-thienyl)-*N*-(2-methoxy-1-methylethyl) acetamide
CAS name	2-chloro-*N*-(2,4-dimethyl-3-thienyl)-*N*-(2-methoxy-1-methylethyl)acetamide
CAS #	87674-68-8
PC Code	129051

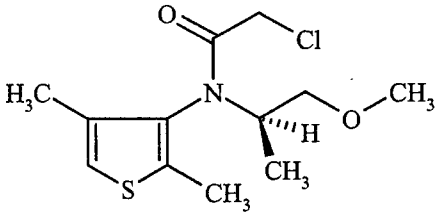
Table 5. [S] Dimethenamid-P Nomenclature (Dimethenamid-P)	
Chemical structure	
Common name	Dimethenamid-P (90:10, S:R isomer ratio)
Molecular Formula	$C_{12}H_{18}ClNO_2S$
Molecular Weight	275.8 g/mol
IUPAC name	(*S*)-2-chloro-*N*-(2,4-dimethyl-3-thienyl)-*N*-(2-methoxy-1-methylethyl) acetamide
CAS name	2-chloro-*N*-(2,4-dimethyl-3-thienyl)-*N*-[(1*S*)-2-methoxy-1-methylethyl] acetamide
CAS #	163515-14-8
PC Code	120051
Proposed End-use product (EP)	Tower ™ (1.5 lb ai/acre EC; EPA Reg. No. 7969-239)

Table 6. Physicochemical Properties of [RS] Dimethenamid		
Parameter	**Value**	**Reference**
Boiling point/range	123°C at 0.1 mm Hg	DP Num: 183774, 1/22/93, M. Flood
pH	8.4-6.9; continuously decreasing over a 45-minute period; 1% aqueous solution	DP Num: 183774, 1/22/93, M. Flood
Density	1.19 g/mL at 25°C; 1.19 specific gravity at 25°C	DP Num: 183774, 1/22/93, M. Flood
Water solubility	0.117 g/100 mL at 25°C (PAI)	DEB No. 7060, 1/18/91, M. Flood
Solvent solubility	Soluble in all proportions in acetone, n-octanol, methylene chloride, and carbon disulfide at 25°C	DP Num: 169997, 7/29/92, M. Flood
Vapor pressure	2.76×10^{-4} mm Hg at 25°C (PAI)	DEB No. 7060, 1/18/91, M. Flood
Dissociation constant, pK_a	No dissociation between pH 1-11 at 25°C (PAI)	DEB No. 7060, 1/18/91, M. Flood
Octanol/water partition coefficient, K_{OW}	141 (PAI)	DEB No. 7060, 1/18/91, M. Flood
UV/visible absorption	Not available	

Table 7 Physicochemical Properties of [S] Dimethenamid-P.		
Parameter	**Value**	**Reference**
Boiling point/range	123°C/0.07 torr	DP#: 238349, 12/1/97, H. Podall

Table 7 Physicochemical Properties of [S] Dimethenamid-P.		
Parameter	**Value**	**Reference**
pH	3.3 at 25°C (1% aqueous dispersion)	DP#: 238349, 12/1/97, H. Podall
Density	1.19 g/mL at 20°C	DP#: 238349, 12/1/97, H. Podall
Water solubility	1.45 g/L at 25°C	DP#: 238349, 12/1/97, H. Podall
Solvent solubility	20.8 g / 100mL in hexane. Soluble in tetrahydrofuran, isopropyl alcohol, ACN, DMSO, DCM, toluene, and n-octanol in all proportions.	DP#: 238349, 12/1/97, H. Podall
Vapor pressure	1.9 x 10-5 mm Hg at 25°C	DP#: 238349, 12/1/97, H. Podall
Dissociation constant, pK_a	No dissocitation between pH 1 and 11 at 25°C (PAI)	DP#: 217337, 7/26/95, M. Rodriguez
Octanol/water partition coefficient, $Log(K_{OW})$	Not applicable; soluble in n-octanol in all proportions	DP#: 238349, 12/1/97, H. Podall
UV/visible absorption spectrum	E = 7560; 33 nm	MRID No. 46710201

3.0 HAZARD CHARACTERIZATION/ASSESSMENT

3.1 Hazard Characterization

The toxicology database for dimethenamid is adequate for evaluating and characterizing dimethenamid toxicity and selecting endpoints for purposes of this risk assessment. The toxicity data base for the [RS] mixture is complete and the bridging studies to the [S]-dimethenamid-P toxicity data are complete. Bridging studies include the 6 acute studies, a subchronic study in rats, a developmental toxicity study in rats, and a battery of mutagenicity studies. While there are minor inconsistencies between the two sets of data, [RS]-dimethenamid and [S]-dimethenamid-P show similar toxicity.

The acute toxicity data indicate that [S]-dimethenamid-P is Category II via the oral route of exposure, and Category III via the dermal and inhalation routes of exposure. It is moderately irritating to the eye (Category III) and slightly irritating to the skin (Category IV); It is a mild skin sensitizer. The acute toxicity data for [RS]-dimethenamid is the same as [S]-Dimethenamid-P for all exposures except acute oral (Category III).

Chronic studies in the rat, mouse and dog with [RS]-dimethenamid showed decreases in body weight and food efficiency at the lowest effect level. At higher dose levels, liver pathology, stomach hyperplasia, and some indication of (unconfirmed) kidney effects were seen. In some of the studies liver enzymes and cholesterol levels were increased at doses resulting in liver pathology. In the 21-day dermal rabbit studies minor skin irritation was observed at all doses tested. Decreased body weight gain was seen in male rabbits at the lowest effect level.

The developmental toxicity studies show increased post-implantation loss and minor skeletal variations in the rat and late resorptions and minor skeletal variations in the rabbit at the highest doses tested. In the rabbit, the developmental effects occurred at the same dose as maternal toxicity, whereas in the rat, the developmental toxicity occurred at much higher doses than in the dams. In the developmental toxicity studies in the rat with [S]-dimethenamid-P, decreases in maternal body weight were shown at 1/8 the LOAEL for dams dosed with [RS]-dimethenamid. Since the toxicity in 90-day feeding studies in rats with [S]-dimethenamid-P and [RS]-dimethenamid were very similar, the finding of increased toxicity in pregnant dams may suggest that [S]-dimethenamid-P is more toxic to pregnant rats. The reproduction study showed decreases in body weight in both pups and parental animals at the same dose levels. The only other effects noted were increases in liver weights in parental animals (both sexes).

There is no concern for increased qualitative and/or quantitative susceptibility after exposure to dimethenamid in developmental toxicity studies in rats and rabbits, and a reproduction study in rats.

[RS]-dimethenamid has been classified as group "C"-possible human carcinogen, based on an increasing trend for liver tumors (males) seen in the chronic rat study. There were no dose-related tumors seen in the mouse carcinogenicity study. The cPOD chosen for human risk assessment is based on effects observed in the chronic rat study; it is considered protective of the cancer effects.

A battery of mutagenicity studies with [S]-dimethenamid-P are negative for genetic mutations, including unscheduled DNA synthesis. However, mutagenicity studies with [RS]-dimethenamid showed positive results for unscheduled DNA synthesis and there were equivocal results in two dominant lethal studies. (It is noted that late resorptions contributed mostly to the positive dominant lethal effects; claimed not to be characteristic of a dominant lethal effect). In some of the studies with [RS]-dimethenamid, the studies were considered positive, but should have been repeated because of equivocal results, such as precipitation and positive responses not related to dose.

The toxicity profiles for [RS]-dimethenamid and [S]-dimethenamid-P are provided in Appendix 1.2, Tables 1 and 2.

3.2 FQPA Hazard Considerations

The toxicity database is complete for a full hazard evaluation and is considered adequate to evaluate risks to infants and children. Analysis of the data indicates that there is no basis to require a developmental neurotoxicity study. Acute and subchronic neurotoxicity studies are required as part of the 40 CFR Part 158 data requirements for registration of a pesticide (food and non-food uses). An immunotoxicity study is also required. This is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses). There is no indication in the currently available data that the immune system is a

target for dimethenamid.

3.2.1 Developmental Toxicity

3.2.1.1 Rat Developmental Study 1

In a developmental toxicity study (MRID No. 44332243), [S]-dimethenamid-P (96.3% a.i.) was administered by gavage to Charles River Sprague-Dawley Crl:CD BR VAF/Plus rats (25 presumed pregnant females/group) at doses of 0, 25, 150 or 300 mg/kg/day during gestation days 6 through 15. No apparent effects were seen for the following parameters: maternal deaths, abortions, premature deliveries, gross pathology, liver weights, reproduction (corpora lutea, implantations, resorptions, and live fetuses), fetal weights or fetal examinations (gross, visceral or malfornrntions). At 300 mg/kg/day only, the following clinical signs were noted on at least one occasion: excess lacrimation, piloerection, excess salivation, decreased motor activity, orange substance on fur, swollen ocular membrane, ptosis, dark pink skin and coldness to touch. Body weights and weight gains were lower than controls in the 150 and 300 mg/kg/day groups during the dosing period. The only effect observed regarding fetuses was in the 150 and/or 300 mg/kg/day rats which exhibited an increase in the number of litters/fetuses with incomplete - ossification of the second sternal central and/or pelvic pubis.

The maternal LOAEL is 150 mg/kg/day based on a decrease in body weight/gain and feed consumption (clinical signs at 300 mg/kg/day). The maternal NOAEL is 25 mg/kg/day. The developmental LOAEL is 150 mg/kg/day based on an increased incidence of incomplete ossification of the second sternal central and/or pelvic pubis. The developmental NOEL is 25 mg/kg/day.

3.2.1.2 Rat Developmental Study 2

In a prenatal developmental toxicity study (MRID 41615904), [RS]-dimethenamid (98.3% a.i.) was administered to pregnant Crl:COBS CD(SD)BR rats (25/dose) daily via gavage in a dosing volume of 10 mL/kg at concentrations of 0, 50, 215, or 425 mg/kg/day on gestation days (GD) 6 through 15. All dams were sacrificed on GD 20 and their uterine contents examined. There were no effects of treatment on maternal survival or gross pathology. Two pregnant control dams were found dead on GD 16. One died from a gavage error. The other exhibited a dark red dried substance around the vaginal area and hindpaws, a pale liver, and dark red or brown viscous material in the stomach, vagina, and cervix. A number of dams exhibited dose-dependent increase in excess salivation 215 and 425 mg/kg/day. Increased incidence of thin appearance and urine-stained abdominal fur was observed at 425 mg/kg/day. Maternal body weight was decreased at 425 mg/kg on GD 12. Body weight gains were dose-dependently decreased by 16-35% during the dosing period (GD 6-16) at 215 and 425 mg/kg. Body weight gains decreased by 11% at 425 mg/kg for the entire gestation period. Absolute and relative liver weights were dose-dependently increased by 7-19% at 215 and 425 mg/kg. The only finding at 50 mg/kg was an increased relative liver weight of 6% over controls. There were no abortions and no treatment-related effects on the sex ratio, fetal weight, or fetal external, visceral or

skeletal examinations. At 425 mg/kg, one dam had complete litter resorption. The number of resorptions/dam was increased at this dose resulting in an increased post-implantation loss and a decrease in number of live fetuses/dam. The only finding at <425 mg/kg was an increased number of resorptions. However, at 215 mg/kg the number of live fetuses/dam at this dose was comparable to controls.

The maternal LOAEL is 215 mg/kg/day based on increased incidence and frequency of excess salivation, decreased body weight gains and food consumption, and increased absolute and relative liver weights. The maternal NOAEL is 50 mg/kg/day. The developmental LOAEL is 425 mg/kg/day based on increased resorptions, increased post-implantation loss, and decreased number of live fetuses. The developmental NOAEL is 215 mg/kg/day.

3.2.1.3 Rabbit Developmental Study

In a prenatal developmental toxicity study (MRID 41706809), [RS]-dimethenamid (92.0% a.i.) was administered to artificially inseminated New Zealand White rabbits (20/dose) daily via gavage in a dosing volume of 10 mL/kg at concentrations of 0, 37.5, 75, or 150 mg/kg/day on gestation days (GD) 6 through 18. All does were sacrificed on GD 29 and their uterine contents examined. Data were not included in the study report for uterine weights or adjusted maternal body weights. There were no unscheduled deaths during the study, and there were no effects of treatment on maternal clinical signs or gross pathology. At 150 mg/kg, two does aborted/prematurely delivered on GD 26 and 28. Body weight gain was decreased for GD 12-15 at 150 mg/kg/day. Food consumption was decreased by 24-40% at this dose for GD 12-15, 15-19, and 6-19. There were no effects of treatment on the number of litters, live fetuses/doe, dead fetuses, early resorptions, complete litter resorptions, fetal body weights, or sex ratio. At 150 mg/kg/day, the number of late resorptions was dose dependently increased, resulting in an increased number of resorptions/doe and increased post- implantation loss (11.90%) although the number of live fetuses/doe was comparable to controls. At 150 mg/kg, incidences of angulated hyoid alae, a variation, were increased and irregular ossification of the intraparietal(s) was increased. There were no treatment-related external or visceral findings.

The maternal LOAEL is 150 mg/kg/day based on abortions and decreased body weight gains and food consumption. The maternal NOAEL is 75 mg/kg/day. The developmental LOAEL is 150 mg/kg/day based on increased late resorptions, post- implantation loss, irregular parietal sutures and angulated hyoid alae. The developmental NOAEL is 75 mg/kg/day.

3.2.2 Reproductive Toxicity

In a two-generation reproduction toxicity study (MRID 41615905), [RS]-dimethenamid (92.6% a.i.) was administered continuously in the diet to Wistar/HAN rats (25/sex/dose) at nominal dose levels of 0, 100, 500, or 2000 ppm (equivalent to 0/0, 7/8, 36/40, and 150/160 mg/kg bw/day [M/F]). The P animals were given test article diet formulations for 70 days prior to mating to produce the F_1 litters. After weaning, F_1 animals (25/sex/dose) were selected to become the parents of the F_2 generation and were given the same concentration test formulation

as their parents. F_1 animals were given test formulations for 101 days prior to mating to produce the F_2 litters.

There were no effects of treatment on maternal clinical signs or gross pathology. At 2000 ppm, body weights were decreased in the: (i) P males on premating days 8-22 and 36-70 and on postmating days 1 and 8; (ii) F1 males both during the premating interval after day 29 and throughout the postmating period; and (iii) P females on premating days 50 and 57. Body weight gains for the P males at this dose were decreased by 12% for the premating period. Food consumption was decreased in the: (i) P males on premating days 36-57 and 64- 70 and postmating days 8-23; (ii) P females on premating days 22-29 and 50-57; (iii) F1 males on premating days 1-8, 15-50, and 57-92 and postmating days 15-22. Absolute and relative (to body) liver weights were increased by 10-24% in both sexes in both generations. No adverse effects of treatment were noted at 100 or 500 ppm. The LOAEL for parental toxicity is 2000 ppm based on decreased body weights, body weight gains, and food consumption and on increased absolute and relative to body liver weights. The NOAEL is 500 ppm. At 2000 ppm, pup body weights were decreased in the F1 generation on post-natal days (PND) 14 and 21 and in the F2 generation on PND 7-21. No adverse effects of treatment were noted at 100 or 500 ppm. The LOAEL for offspring toxicity is 2000 ppm based on decreased pup body weights. The NOAEL is 500 ppm. There were no effects of treatment on pregnancy rate, fertility indices, gestation duration, post- implantation loss, number of pups born, litter size at birth, number of viable pups, viability indices, or sex ratio. The LOAEL for reproductive performance was not observed. The NOAEL for reproductive performance is 2000 ppm.

3.2.3 Pre-and/or Postnatal Toxicity

There is no concern for increased qualitative and/or quantitative susceptibility following *in utero* (rats and rabbits) and pre-and post-natal exposure (rats) to the [RS] or the [S] dimethenamid technical products.

There are no residual uncertainties with regard to pre- and/or postnatal toxicity. The dietary food exposure assessment utilizes proposed tolerance level residues and 100% crop treated information for all commodities, which results in very high-end estimates of dietary exposure. The dietary drinking water assessment (Tier 2 estimates) utilizes values generated by model and associated modeling parameters which are designed to provide health protective, high-end estimates of water concentrations.

3.2.4 Developmental Neurotoxicity – Requirement for a DNT Study

There is no evidence that dimethenamid is a neurotoxic chemical and there is no need for a developmental neurotoxicity study or additional uncertainty factors to account for neurotoxicity. There were clinical signs (decreased motor activity, ptosis, etc.) observed in dams at the highest dose tested (HDT) (300 mg/kg/day) in the developmental toxicity study in rats with dimethenamid-P [S]. The observations were low in frequency and considered to be a result of excessive toxicity. Decreased motor activity was noted 8 times in 6 rats and ptosis (droopy eye

lids) was noted 4 times in 4 rats (observations were made 375 times on the 25 rats in the highest dose group during the study with [S]-dimethenamid-P). Furthermore, these effects were not seen in other developmental studies in rats or rabbits, or reproduction and subchronic/chronic studies in rats.

3.2.5 Immunotoxicity

There are no indications in the available studies that organs associated with immune function, such as the thymus and spleen, are affected by dimethenamid. An immunotoxicity study is required. This is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses).

3.3 Toxicity Endpoint Selection

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

Selected Study: Developmental toxicity in rabbits (MRID 41706809). See Section 3.2.1

Dose and Endpoint for Establishing an aPAD: NOAEL is 75 mg/kg/day. LOAEL is 150 mg/kg/day based on developmental effects of increased resorptions, implantation loss and angulated hyoid alae.

Uncertainty Factor (UF): 100 This includes 10x for interspecies extrapolation and 10x for intraspecies variation.

Comments about Study/Endpoint: The resorptions and post implantation loss are presumed to be a single dose effect. The developmental endpoint is appropriate for females 13-49 and is of the appropriate duration. The endpoint is supported by a range-finding study in rats with [S]-dimethenamid-P, which showed increased resorptions at 400 mg/kg/day.

Acute RfD (females 13-49) = $\frac{\text{(NOAEL) 75 mg/kg}}{\text{(UF) 100}}$ = 0.75 mg/kg

3.3.2 Acute Reference Dose (aRfD) - General Population

An acute RfD for the general population or other subgroups was not selected because no effect attributable to a single (or few) day(s) oral exposure was observed in animal studies.

3.3.3 Chronic Reference Dose (RfD) – All Populations

Selected Study: chronic toxicity/carcinogenicity study in rats (MRIDs 41706808 and 42030102)

In a chronic toxicity and carcinogenicity study 50 Crl: CD (SD) BR rats/sex/dose were exposed to [RS] dimethenamid (91.3% a.i.; Batch #: AD 8605) in the diet for up to 24 months at doses of 0, 100, 700, or 1500 ppm (equivalent to 5.1/6.8, 36/49, and 80/109 mg/kg/day in males/females). An additional group of 20 rats/sex/dose were similarly treated and sacrificed at 12 months. Mortality, water consumption, clinical signs, ophthalmology, hematology, and urinalysis for both sexes at all doses were unaffected by treatment. No treatment-related adverse differences in any parameter were observed in the 100 ppm group. At ≥700 ppm, the final body weights were decreased by 6-23% in both sexes. Body weight gain was decreased by 6-19% in both sexes at Weeks 0-10 and by 15- 26% in the females at Weeks 10-80. Overall body weight gain (Weeks 0-104) was decreased by 16-31% in the 1500 ppm group. Food consumption (Weeks 1-10) was decreased by 4-9% in both sexes at 700 and 1500 ppm. Food conversion ratio (Weeks 1-25) was increased by 11-20% in both sexes, except 700 ppm males. The following increased incidence of lesions in the liver were observed in the 700 and 1500 ppm groups: (i) pale areas in the liver in the males (28-34% treated vs 12% controls) and in 1500 ppm females (38% treated vs 20% controls); (ii) altered eosinophilic hepatocytes in males (12-20% treated vs 4% controls); and (iii) bile duct hyperplasia in females (22-40% treated vs 6% controls).

The LOAEL is 700 ppm (equivalent to 36/49 mg/kg/day in males/females), based on decreased body weight and body weight gain in both sexes, increased food conversion ratios in females, and increased microscopic hepatic lesions in both sexes. The NOAEL is 100 ppm (equivalent to 5.1/6.8 mg/kg/day in males/females).

Dose and Endpoint for Establishing an cPAD: The NOAEL is 5.1/6.8 mg/kg/day for male/female. The LOAEL is 36/49 mg/kg/day for male/female based on decreased body weight and body weight gain from week 1-10 and week 10-104 in both sexes, and increased microscopic hepatic lesions in both sexes.

Uncertainty Factor (UF): 100 This includes 10X for interspecies extrapolation and 10x for intraspecies variation.

$$\textbf{Chronic RfD} = \frac{\textbf{(NOAEL) 5.1 mg/kg/day}}{\textbf{(UF) 100}} = \textbf{0.05 mg/kg/day}$$

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

There are no residential uses for dimethenamid. Therefore incidental oral exposure endpoints are not required and not selected for this assessment.

3.3.5 Dermal Absorption

There are no dermal absorption studies available with dimethenamid.

3.3.6 Dermal Exposure (Short and Intermediate-Term)

Selected Studies: Co-critical 21-day dermal toxicity studies in rabbits (MRID 41662414, MRID 41951301)

[RS] dimethenamid was tested in two 21-day dermal toxicity studies in New Zealand White Rabbits. In the first study (MRID 41662414) [RS] dimethenamid (91.4%) was applied to shaved skin of 5 albino rabbits/sex/dose at dose levels of 0, 50, 150 and 500 mg/kg/day for 6 hours/day, 5 days/week for 3 weeks. Minimal to mild skin irritation was observed in male and female rabbits at 50, 150 and 500 mg/kg/day after 21 day repeated dermal application. Signs of toxicity were limited to decreased body weight gain in male rabbits at the 500 mg/kg/day dose level. The LOAEL is 500 mg/kg/day based on decreased body weight gain.

In a second study (MRID 41951301) [RS] dimethenamid (78.8%) was administered to twenty males and 20 females at dose levels of 0, 30, 300 and 1000 mg/kg/day for 6 hours/day, 5 days/week for 3 weeks. The dermal application of 1000 mg/kg/day for 21 days exceeded the maximum tolerated dose producing severe local and systemic toxicity. This resulted in the death of 5/5 males and 4/5 females. Dose levels of 30 mg/kg/day were associated with minor local toxicity (erythema/edema) but no adverse systemic effects were observed at these doses. The LOAEL is 1000 mg/kg/day based on severe systemic toxicity and mortality. The NOAEL is 300 mg/kg/day.

[Note: this endpoint has been revised from previous dimethenamid assessment based on reevaluation of the toxicity data. The dermal endpoint selected for use in prior dimethenamid risk assessments was based on an oral subchronic toxicity study in dogs with application of an estimated dermal absorption factor based on a ratio of LOAELs for body weight effects from a 21 day dermal toxicity study and a rabbit developmental study.]

Dose and Endpoint Selected: The NOAEL is 300 mg/kg/day. The LOAEL is 500 mg/kg/day based on decreased body weight gain.

Uncertainty Factor (UF): An MOE 100 is required for the short- and intermediate-term scenarios for dermal exposure is based on the conventional uncertainty factor of 100. This includes 10x for interspecies extrapolation and 10x for intraspecies variation.

Comments about Study/Endpoint: The selected endpoint is considered protective of developmental effects. The acute dietary endpoint is based on a developmental rabbit study which indicates that maternal and offspring effects occurred at the same dose levels. Maternal effects include body weight and developmental effects at the LOAEL of 150 mg/kg/day. Developmental effects are not measured in the dermal toxicity study. However, body weight effects are measured in the dermal toxicity study. Body weight and developmental effects occur at the same level in the maternal animals based on the developmental study. Since developmental effects are not seen at doses lower than the maternal LOAEL of 150 at which

body weight effects occur and the dermal toxicity study measures body weight effects, the dermal toxicity study may be considered protective of developmental effects and can be used for endpoint selection. The two 21-day dermal toxicity studies together provide data that can be used determine the LOAELs and NOAELs for dermal toxicity.

3.3.7 Inhalation Exposure (Short-Term)

Selected Studies: Co-critical subchronic oral toxicity study in dogs (MRID 41615902) and chronic oral study in dogs (MRID 41615903)

In a subchronic oral toxicity study [RS] dimethenamid (91.4% a.i., Batch # 8605) was administered in the diet to 4 beagle dogs/sex/dose for up to 13 weeks at nominal doses of 0, 100, 750, or 2000 ppm (equivalent to 0/0, 4.72/4.98, 33.6/39.7, and 89.6/87.4 mg/kg/day in males/females). No treatment-related adverse effect was observed on mortality, clinical signs, ophthalmology, hematology, and urinalysis for both sexes at all doses. No treatment-related effects were observed at 100 ppm. At 750 body weight gain was decreased in females, relative liver weights were increased in both sexes, periportal hepatocellular vacuolation was observed in both sexes and liver sinusoidal dilation was observed in 1 female. At 2000 ppm, final body weight was decreased in the females, body weight gain overall food consumption was decreased in both sexes. Absolute liver weights were increased in both sexes by 25-32% and relative liver weights were increased in both sexes and periportal hepatocellular vacuolation was observed in all animals at 2000 ppm. Liver sinusoidal dilation was observed in 3/4 males and 3/4 females. The LOAEL is 750 ppm based on decreased body weight and body weight gain in females, increased relative to body liver weight in both sexes, increased periportal cytoplasmic vacuolation in liver in both sexes, and dilation of liver sinusoids in females. The NOAEL for this study is 100 ppm.

In a chronic oral study [RS] dimethenamid (91.3% a.i., Lot/batch #8605) was administered to 4 beagle dogs/sex/dose in the diet at doses of 0, 25, 250, or 1250 ppm (equivalent to 0/0, 1.95/2.1, 10.1/9.1, and 48.7/49.3 mg/kg/day [M/F]) for up to one year. There were no unscheduled deaths during the study and no effects of treatment on clinical signs, ophthalmoscopy, hematology, urinalysis, or gross pathology. No treatment-related effects were observed at 25 or 250 ppm. At 1250 ppm alkaline phosphatase was increased in the females by 109-218% throughout the study. In both sexes relative liver weights were increased by 29-31%. Microscopically, minimal to moderate periportal vacuolation was observed in the liver in males and females. The vacuoles did not contain lipid when stained with Oil Red O. The livers of one male and one female with vacuolation were stained with PAS; this stain revealed that the vacuolation was not due to glycogen. The findings indicate a hydropic degenerative change. The LOAEL is 1250 ppm based on decreased body weights, body weight gains, food consumption and food efficiency, increased cholesterol, alkaline phosphatase, liver weights, and increased incidences of periportal vacuolation and midzonal hepatocyte enlargement in both sexes. The NOAEL is 250 ppm.

[Note: this endpoint has been revised from previous dimethenamid assessment based on

reevaluation of the toxicity data. The inhalation endpoint selected for use in prior dimethenamid risk assessments was based solely on the oral subchronic toxicity study in dogs.]

Dose and Endpoint Selected – The NOAEL is 10.1 mg/kg/day from the chronic dog study. The LOAEL is 33.6 mg/kg/day from the subchronic dog study based on decreased body weight and body weight gain in females, increased relative to body liver weight in both sexes, increased periportal cytoplasmic vacuolation in liver in both sexes, and dilation of liver sinusoids in females.

Uncertainty Factor (UF): An MOE of 100 is required for the short- and intermediate-term scenarios for inhalation exposure is based on the conventional uncertainty factor of 100. This includes 10x for interspecies extrapolation and 10x for intraspecies variation.

Comments about Study/Endpoint: Based on the doses tested, the subchronic and chronic dog studies together provide data that can be used determine the LOAEL and NOAEL for establishing endpoints for inhalation exposure.

3.3.8 Classification of Carcinogenic Potential

The Carcinogenicity Peer Review of dimethenamid on 23/MAR/1995 (TXR# 012143) and 15/JUN/1992 (TXR# 012831) stated that the weight of evidence classification was Group C - possible human carcinogen. The chronic point of departure (cPOD) is protective for potential carcinogenic effects. This decision was based on a statistically significant increasing trend for liver cell tumors (benign and malignant combined) in male rats. Dimethenamid has shown positive results in some genotoxicity tests and is structurally related to other chloroacetanilide carcinogens (i.e., acetochlor, metolachlor). An acceptable study in mice showed no dose related tumors.

[Note: The cancer classification has not been updated based on the EPA's 2005 Guidelines for Carcinogen Risk Assessment. However, any reclassification would not affect the conclusion that the cPOD is protective for carcinogenic effects and would therefore not affect the risk assessment.]

3.4 Margins of Exposure

A summary of target Levels of Concern for risk assessment is provided in Table 8.

Table 8. Target Levels of Concern/Margin of Exposure for Dimethenamid

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

Table 8. Target Levels of Concern/Margin of Exposure for Dimethenamid			
Route/Duration	**Short-Term (1-30 Days)**	**Intermediate-Term (1 - 6 Months)**	**Long-Term (> 6 Months)**
Dermal	100	N/A	N/A
Inhalation	N/A	N/A	N/A

3.5 Recommendation for Aggregate Exposure Risk Assessments

When there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. Since there are no residential incidental oral exposures to dimethenamid, aggregate exposure from risk from food and non-food oral exposures is not required. Dermal and inhalation exposures to workers should not be aggregated for dimethenamid because the toxicity endpoints for these exposure routes are not based on common toxicity effects (i.e., body weight changes are considered to be non-specific, and there are no common specific target organ effects observed in the oral and inhalation toxicity studies.)

3.6 Summary of Endpoints Selected for Risk Assessment

Toxicological doses/endpoints selected for the dimethenamid risk assessment are provided in Tables 9 and 10.

Table 9. Summary of Toxicological Doses and Endpoints for Dimethenamid for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, LOC for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (General Population, including Infants and Children)	An acute RfD for the general population or any population subgroups was not selected because no effect attributable to a single (or few) day(s) oral exposure was observed in animal studies.			
Acute Dietary (Females 13-49 years of age)	NOAEL = 75mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Acute RfD = 0.75mg/kg/day aPAD = 0.75 mg/kg/day	Developmental toxicity study in rabbits Maternal; LOAEL = 150 mg/kg/day based on abortions and decreased body weight gain and food consumption. Developmental; LOAEL = 150 mg/kg/day based on post-implantation loss
Chronic Dietary (All Populations)	NOAEL= 5 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Chronic RfD = 0.05 mg/kg/day cPAD = 0.05 mg/kg/day	Chronic/carcinogenicity study in rats LOAEL = M/F; 36/49 mg/kg/day based on decreased body weight and body weight gain in both sexes, increased food conversion ratios in females, and increased microscopic hepatic lesions in both sexes.
Incidental Oral	There are no residential uses for dimethenamid. Therefore incidental oral exposure endpoints are not required and not selected for this assessment.			
Dermal Short- Term (1-30 days)	NOAEL= 300 mg/kg/day	UF_A= 10x UF_H=10x	Occupational LOC for MOE = 100	21 Day dermal toxicity study in rabbits LOAEL = 500 mg/kg/day based on decreased body weight gain

Table 9. Summary of Toxicological Doses and Endpoints for Dimethenamid for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, LOC for Risk Assessment**	**Study and Toxicological Effects**
Inhalation	There are no residential uses for dimethenamid. Therefore inhalation exposure endpoints are not required and not selected for this assessment.			
Cancer (oral, dermal, inhalation)	"C" Possible human carcinogen. (No Q_1*). The cRfD is considered protective of the cancer effects.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key date (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 10. Summary of Toxicological Doses and Endpoints for [Chemical] for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short- Term (1-30 days) and Intermediate-Term (1-6 months)	NOAEL= 300 mg/kg/day	UF_A= 10x UF_H=10x	Occupational LOC for MOE = 100	21 Day dermal toxicity study in rabbits LOAEL = 500 mg/kg/day based on decreased body weight gain
Inhalation Short- Term (1-30 days)	NOAEL= 10.1 mg/kg/day	UF_A= 10 x UF_H= 10 x	Occupational LOC for MOE = 100	Subchronic and chronic oral toxicity studies in dogs. NOAEL is from the chronic dog study. LOAEL = 33.6 mg/kg/day from the subchronic dog study based on decreased body weight and body weight gain in females, increased relative to body liver weight in both sexes, increased periportal cytoplasmic vacuolation in liver in both sexes, and dilation of liver sinusoids in females.
Cancer (oral, dermal, inhalation)	"C" Possible human carcinogen. (No Q_1*). The cRfD is considered protective of the cancer effects.			

3.7 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).

4.0 PUBLIC HEALTH DATA

Available sources of incident data in humans were reviewed for dimethenamid-P. These sources included the Incident Data System consisting of reports submitted to EPA by registrants and the public since 1992, California Pesticide Illness Surveillance Program which has reports (primarily occupational) since 1982, seven states funded by NIOSH provided data on occupational cases for 1998-2002, reports to the nation's Poison Control Centers for 1993-2001, and reports in the scientific literature reported on Medline. Among the above databases only one had a single report of a spray drift victim who developed a rash, eye irritation, and other symptoms. The dermal and eye effects were considered consistent with the toxicity profile of dimethenamid-P, but the systemic effects were not. No conclusions can be drawn from this one incident, and no recommendations are warranted.

5.0 DIETARY AND DRINKING WATER EXPOSURE ASSESSMENT

5.1 Dietary Profile

5.1.1 Metabolism in Primary Crops

The nature of the residue in plants is adequately understood. Soybean and corn metabolism studies are available and have been reviewed by the HED Metabolism Committee (M. Flood, 11/10/1992; and M. Bradley, 12/8/1993). The metabolism of dimethenamid-P in plants involves conjugation with glutathione, with subsequent transformation of the glutathione moiety to yield a variety of metabolites. The residue of concern for purposes of the tolerance expression (and risk assessment) was determined to be dimethenamid *per se.*

A more recent sugar beet metabolism study indicated that the metabolite profile was similar for roots and tops, and dimethenamid-P was not detected in/on either commodity. For both roots and tops, the majority of ^{14}C-residues were characterized as minor unknowns each present at ≤8% of the TRR. One unknown polar fraction accounted for >10% of the TRR in roots, but was present at <0.01 ppm. The metabolic pathway for [^{14}C] dimethenamid in sugar beets proceeds *via* a pathway similar to that observed in corn and soybeans. However, two metabolites not identified in corn or in soybean were found in sugar beets. These are the sulfoxide of the cysteine conjugate and the N-malonyl conjugate of the cysteine conjugate, and together accounted for <6 % of the TRR in sugar beets. (D. Dotson, DP#: 288341, 4/14/2004)

5.1.2 Metabolism in Rotational Crops

The requirements for confined accumulation in rotational crops are satisfied. An adequate confined rotational crop study was reviewed by the Agency. The study includes data on winter wheat planted 141 days after treatment (DAT), lettuce planted 322 DAT, and carrots planted 332 DAT. The maximum concentration of any metabolite/degradate in harvested wheat was 0.01 ppm for the sulfoxide of thiolactic acid conjugate. Based on these data, HED concluded that a 4-month rotational interval is adequate for fall-seeded cereal grains and other crops may be planted the following spring. These recommendations are consistent with the rotational crop restrictions on the current label for the 6 lb/gal EC formulation of dimethenamid-P.

5.1.3 Metabolism in Livestock

The Agency does not expect finite dimethenamid-P residue to occur in livestock commodities even though dimethenamid-P may be used on animal feedstuff such as field corn and sugar beets. Finite residues of dimethenamid-P are not expected in livestock commodities due to the very low (less than detection) levels of dimethenamid-P seen in residue field trial studies on these feed items. After considering the extensive metabolism of dimethenamid in animals, the exaggerated dosing levels used in the animal metabolism studies, and the expected low level of dietary exposure of livestock to dimethenamid, the HED Metabolism Assessment Review Committee (MARC) concluded that tolerances (enforcement and risk assessment) are not required for livestock commodities (M. Flood, 11/10/1992). Also, due to low residue values and limited use in livestock feed, the use of dimethenamid-P on grasses grown for seed does not require the establishment of tolerances on livestock commodities.

5.1.4 Analytical Methodology

An adequate enforcement method is available for determining dimethenamid-P residues in plants and soil. The gas chromatography with a nitrogen phosphorus detector (GC/NPD) Method AM-0884-0193-1 has been validated by the Agency and submitted for publication in FDA's Pesticide Analytical Manual, Volume II. The method does not separate the R and S isomers of dimethenamid and the limit of quantitation (LOQ) is 0.01. As tolerances are not required for animal commodities, no analytical methods for livestock commodities are required.

5.1.5 Multiresidue Methods

The FDA PESTDATA database dated 11/2001 (PAM Volume I, Appendix I) indicates that dimethenamid is not recovered using Multiresidue Methods Section 303 (Mills, Onley, and Gaither Method; Protocol E, nonfatty food) or Section 304 (Mills Method; Protocol F, fatty food).

5.1.6 Toxicity Profile of Major Metabolites and Degradates

Little information is available on the toxicity of the major dimethenamid-P metabolites. The hydroxy dimethenamid-P metabolite formed in livestock appears to be formed in the rat also, and is, therefore, part of the total toxic exposure for these animals. It is unlikely to be more toxic than the parent. The desphenyl metabolite is also unlikely to be more toxic than the parent. It is difficult to know, however, what effect the removal of the entire benzene ring will have on the toxicology. This metabolite is not formed in rats and, therefore, is not a part of the toxic profile to which the rat is exposed when dosed with the parent. After correction for molecular weight differences, the LD_{50} of the parent and of the desphenyl metabolite are similar.

5.1.7 Magnitude of the Residue in Crops

The residue data on the level of dimethenamid residue in treated food are adequate for dry beans, corn (filed, pop, and sweet), onions (dry bulb), peanuts, potatoes, grain sorghum, soybean, sugar beet, dry bulb onions, garlic, dry bulb shallots, tuberous/corm vegetables, sugar and garden beets, horseradish, turnip, radish, winter squash, and hops. The number and geographic distribution of the field trials are adequate, the appropriate samples were collected at the proposed PHIs, and the trials were conducted at the maximum labeled use rates. Samples were analyzed for the residues of concern using adequate methods, and the sample storage conditions and intervals are supported by the available storage stability data.

Dimethenamid residues in field trials for primary crops were <0.01 ppm (less than the LOD) in all but a few instances. Dimethenamid residues <0.01-0.07 ppm in/on bean forage (note that current labels prohibit the feeding of treated bean forage to livestock). In turnip field trials, residues of dimethenamid were non-detectable in/on all 16 root samples and <0.01-0.093 ppm in/on 16 samples of tops harvested at 14-16 DAT. Average residues were 0.018 ppm in tops and <0.01 ppm in roots. The field trial data on turnips will support the equivalent use on rutabagas. Because the radish, top and turnip, top data are over 10x difference (0.01 ppm and 0.1 ppm, respectively) not the 5x defined in OPP policy, the data do not support a crop group tolerance. OPP determined that the field trial data on winter squash will support the equivalent use on pumpkins. Residues of dimethenamid were <0.05 ppm in/on all samples of dried hop cones.

In studies on grasses grown in warm-season (Western U.S.) and cold-season (Northwest U.S.) regions dimethenamid-P residues in forage and hay ranged from below LOQ (0.01 ppm) to a maximum of 0.05 and 0.26 ppm, respectively (60 day PHI). Dimethenamid-P residues were below the LOQ of 0.01 ppm in all seed screening and straw samples collected at normal seed harvest , with the exception of one treated seed screening sample that had a residue value of 0.01 ppm, and one treated straw sample that had a residue value of 0.02 ppm.

5.1.8 Residue in Processed Commodities

The requirements for "magnitude of the residue" in processed food/feed are satisfied for

corn, peanut, potato, soybean, and sugar beet. The available data indicate that residues of dimethenamid do not concentrate in processed commodities of corn grain, peanuts, potatoes, soybean seeds, or sugar beets.

5.1.9 Residue in Rotational Crops

The requirements for confined accumulation in rotational crops is satisfied. An adequate confined rotational crop provides data on winter wheat, lettuce and carrots. The maximum concentration of any metabolite/degradate in harvested wheat was 0.01 ppm for the sulfoxide of thiolactic acid conjugate. Based on these data, HED concluded that a 4-month rotational interval is adequate for fall-seeded cereal grains and other crops may be planted the following Spring. The current use directions specify that treated areas may be replanted at any time with crops which have dimethenamid tolerances

5.2 Drinking Water Profile

5.2.1 Environmental Fate and Transport

Based on environmental fate properties measured in laboratory studies, dimethenamid is moderately persistent ($t_{1/2}$=30 to 38 days) in soil. It has limited partitioning to soil mineral or organic fractions, leading to high mobility. If the compound were to reach surface water, it may persist because it is stable to hydrolysis at pHs 5, 7, and 9 and has limited aquatic photolysis. The major route of dissipation is through soil metabolism with an aerobic soil half-life of 31 days and an anaerobic soil half-life of 54 days. Terrestrial field studies found that dimethenamid dissipated with half-lives of 2 to 43 days with no leaching detected below 30 cm depth. Based on its physical properties, volatilization from soil or water is not expected to be a major dissipation route for dimethenamid and it is expected to have a low potential to bioaccumulate.

In laboratory studies, one major degradate, oxalamide (M23), was formed through aerobic soil metabolism at up to 14.8% of the applied parent compound. The major degradates M3 (dechlorinated parent), M10 (methyl sulfone derivative of M3), and M13 (methyl sulfoxide derivative of M3) were formed through anaerobic aquatic metabolism at levels up to 20.6%, 9.8%, and 12.4% of the applied, respectively.

5.2.2 Estimated Drinking Water Concentrations

Estimated drinking water concentrations (EDWCs) for assessing dietary risk are based on the use with the highest potential exposure. In past assessments, S-dimethenamid EDWCs generated using Tier II models PRZM/EXAMS predicted that maximum acute exposure will result from use on green onions and chronic exposure from use on ornamentals, as presented in Table 11. EDWCs for the proposed new use on golf course turf do not exceed those previously recommended values.

EDWCs for golf course turf are based on modeling done for the assessment for

ornamentals and for landscape maintenance. Results of Tier II aquatic exposure modeling depend on environmental conditions, as represented by crop-specific scenarios, as well as on application rates and methods and chemical-specific fate properties. For modeling EDWCs for golf course turf, the most conservative crop-specific scenario would be that developed for Florida turf, which was also used previously in modeling exposure from the ornamental use. The application rate proposed for golf course turf is the same as that for ornamentals, and there are no new data available which would lead to a change in modeled fate inputs. Therefore, EDWCs for golf course turf would be the same as for ornamentals using the Florida turf scenario with a ground spray application, and the proposed new use will not lead to a change in recommended EDWCs. Degradates have not been included in EDWCs. HED has not yet established whether these degradates are expected to be toxic, but the calculated human health risks from dimethenamid are low enough that their inclusion would not be expected to change the risk conclusions. If drinking water exposure becomes a driver in dietary risk assessment, degradate exposure will need to be reconsidered.

Table 11. Maximum EDWCs (µg/L) from current and proposed uses of s-dimethenamid

Use	Surface Water [a]			Groundwater [b]
	Modeled Scenario	Acute 1-in-10 year peak	Chronic 1-in-10 year average	Acute and Chronic
Green onions	GA onions	**66.7***	8.4	0.34
Ornamental	FL turf (aerial)	50.2	14.0	1.0
	OR xmas tree	42.1	**20.2***	1.0
Golf Course Turf [c]	FL turf (ground)	43.2	11.7	1.0

[a] Generated using Tier II linked simulation models PRZM (3.12.2) /EXAMS (2.98.04.06).
[b] Generated using Tier I model SCIGROW (2.3).
[c] Reported EDWCs were modeled for the ornamental use applied through ground spray (DP Barcode D326961, D326977, 327936). All modeled scenarios and inputs for use on golf course turf are the same as for that use, so EDWCs are also the same.
* EDWCs recommended for dietary assessment are in bold

5.3 Dietary and Drinking Water Exposure and Risk

Screening level acute and chronic dietary and drinking water exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model with the Food Commodity Intake Database (DEEM-FCID™). Dietary risk assessment incorporates both exposure and toxicity of a given pesticide. For acute and chronic dietary assessments, the risk is expressed as a percentage of a maximum acceptable dose (i.e., the dose which HED has concluded will result in no unreasonable adverse health effects). This dose is referred to as the population adjusted dose (PAD). The PAD is equivalent to the reference dose (RfD) divided by the additional Safety Factor, if applied. For acute and non-cancer chronic exposures, HED is concerned when estimated dietary risk exceeds 100% of the PAD.

5.3.1 Acute Dietary and Drinking Water Analysis

HED conducted screening level acute dietary and drinking water exposure assessment for food use of dimethenamid. The assessment was conducted for all commodities and incorporated the Environmental Fate and Effects Division's (EFED's) highest acute estimated drinking water

concentration (EDWC) is from the green onion use (66.7 ppb). The assessment assumed tolerance level residues in plant commodities and 100% crop treated. Results of the acute dietary assessment (Table 12) indicate that exposure and risk estimates for the population subgroup of concern, females 13-49 years, are below HED's level of concern. The DEEM acute dietary exposure estimate for females 13-49 years of age is <1% of the acute PAD (aPAD).

Table 12. Results of Acute Dietary Exposure Analysis at the 95th Percentile of Exposure.			
Population Subgroup	aPAD (mg/kg/day)	Exposure (mg/kg/day)	% aPAD
Females 13-49	0.75	0.003285	<1

5.3.2 Chronic Dietary and Drinking Water Analysis

HED conducted screening chronic dietary and drinking water exposure assessment for the food uses of dimethenamid. The assessment assumed tolerance level residues in plant commodities and 100% crop treated. The chronic or average estimated surface water concentration of 20.2 ppb from the Tier 1 PRZM-EXAMS model was used to assess contributions from drinking water. Results of the Tier 1 chronic dietary assessment (Table 13) indicate that the general U.S. population and all other population subgroups have exposure and risk estimates below HED's level of concern. The DEEM chronic dietary exposure estimate for children < 1 year old, the most highly exposed population subgroup, is 3% of the chronic PAD (cPAD).

Table 13. Summary of Chronic Dietary and Drinking Water Exposure and Risk for Dimethenamid			
Population Subgroup	**cPAD (mg/kg/day)**	**Dietary Exposure (mg/kg/day)**	**%cPAD**
General U.S. Population	0.05	0.000471	<1
All Infants (< 1 year old)		0.001460	3
Children 1-2 years old		0.000728	2
Children 3-5 years old		0.000692	1
Children 6-12 years old		0.000480	1
Youth 13-19 years old		0.000359	<1
Adults 20-49 years old		0.000434	<1
Adults 50+ years old		0.000447	<1
Females 13-49 years old		0.000431	<1

6.0 RESIDENTIAL EXPOSURE AND RISK

6.1 Exposure Scenarios

The proposed new use label for dimethenamid is limited to application of the product to turfgrass on golf courses. There are no registered homeowner uses of dimethenamid. Therefore, residential handler exposure was not evaluated. However, post-application exposure is possible for recreational golfers and the golfer scenario was therefore assessed.

6.2 Exposure Data and Assumptions

Maximum application rates for all of the exposure scenarios assessed are based on information provided in the proposed dimethenamid-P label. Based on the label, the maximum application rate is 1.5 lbs ai per acre with a maximum seasonal application of 3.0 lbs ai per acre. The post-application risk assessment is based on generic assumptions from the Recommended Revisions to the Residential SOPs, and recommended approaches by HED' Science Advisory Council for Exposure (ExpoSAC).

Exposure Assumptions

The following standard exposure assumptions were used in estimating post-application risks to golfers from exposure to dimethemamid from use on golf-course turf.

- Average body weight is 70 kg.
- Turf Transferrable residue is 5% of the application rate for the fraction initially available.

- Transfer coefficient is 500 cm^2/hour for golfers
- Exposure duration is 4 hours day
- Exposure is assumed to occur on the day of application (day 0)

6.3 Residential Exposure and Risk Estimates

A target LOC or MOE of 100 is considered adequate residential exposure and risk. All residential exposures are assessed as short-term based on label prescribed uses. Exposure and risk estimates indicate MOEs are not of concern (MOEs > 100) at the maximum use rate for the residential post-application exposure scenario assessed. A summary of residential post-application exposure and risk calculations, assumptions, and results is provided in Table 14.

Table 14. Estimated Dimethenamid Exposure & MOEs for Golfer Post-application Exposure to Treated Golf Course Turf LOC/MOE = 100

Exposure Scenario	AR (lb ai/A)	TTR/DFR (mg/cm^2)	TC (cm^2/hr)	Exposure Duration (hrs/day)	Dermal dose (mg/kg/day)	Dermal MOE
Adult Golfers	1.5	0.0008	500	4	0.0240	12500

[1] Application rates are based on maximum values based on proposed label.

[2] TTR or DFR (mg/cm^2) = Application Rate (lb ai/A) x CF (4.54E+5 mg/lb) x CF (2.47E-8 A/ cm^2) x 5% (initial fraction of ai retained on turf) Application rates are based
[3] TC cm^2/hr = Transfer coefficients and associated activities (ExpoSAC Policy Memo #003.1)
[4] Dermal Dose (mg/kg/day) = TTR (mg/cm^2) x TC (cm^2/hr) x 4 (hrs/day)/70 kg (body weight)
[8] Dermal MOE = short-term endpoint for dermal (NOAEL 300 mkd)/Daily Dermal Dose

7.0 AGGREGATE EXPOSURE AND RISK ASSESSMENT

The aggregate risk assessment integrates the assessments conducted for dietary/drinking water and residential exposure. Since there is potential for concurrent exposure via the food, water and residential pathways, all routes of exposure have been considered. The short term aggregate risk is the estimated risk associated with combined risks from average food exposures, average drinking water exposures, incidental oral exposures and inhalation exposures. Dietary/drinking water and residential oral exposures are not aggregated for dimethenamid because incidental oral exposures are not expected based on the registered uses. Inhalation and dermal exposures are not aggregated because toxicity endpoints for those routes are not based on common specific target organ toxicity effects.

8.0 OCCUPATIONAL EXPOSURE AND RISK

Based on data a review of active and proposed new use labels, four occupational exposure scenarios have been assessed for this RED. Short and intermediate-term dermal exposures and short-term inhalation are assessed for occupational exposure scenarios based on toxicity data and expected exposure patterns.

8.1 Exposure Scenarios

Occupational handler and post-application exposure scenarios were assessed for the risk assessment of the proposed new turf use. The term "handler" applies to individuals who mix, load, and apply the pesticide product.

8.1.1 Handler Exposure Scenarios

1) Mixing/Loading Liquid for Groundboom Application
2) Applying Sprays with Open Cab Groundboom Sprayer
3) Mixing/Loading Liquid and Applying Sprays with Handgun Sprayer
4) Mixing/Loading Liquid and Applying Sprays with Low Pressure Handwand and/or
   Backpack Sprayer

8.1.2 Post-Application Exposure Scenarios

Occupational post-application inhalation exposure is expected to be negligible. Dermal exposure is possible for workers mowing/maintaining the turfgrass. Therefore post-application dermal exposures to golf course workers was assessed

8.2 Occupational Exposure Data and Assumptions

8.2.1 Exposure Data

8.2.1.1 Application Parameters

Maximum application rates for all of the exposure scenarios assessed are based on information provided in the proposed dimethenamid-P label. Based on the label, the maximum application rate is 1.5 lbs ai per acre with a maximum seasonal application of 3.0 lbs ai per acre.

8.2.1.2 Occupational Exposure Data

Data from the Pesticide Handlers Exposure Database (PHED) and/or Outdoor Residential Exposure Task Force (ORETF) was used to assess handler and post-application exposures in the absence of chemical-specific data. The handler exposure data for the turf handgun sprayer scenario are from the ORETF data. All other exposure assumptions are based on PHED data. The transfer coefficients used in the post-application exposure assessment are from an interim transfer coefficient guidance document developed by HED's Science Advisory Council for Exposure using proprietary data from the Agricultural Re-entry Task Force (ARTF) data base (SOP #3.1)

8.2.2 Exposure Assumptions

The following standard exposure assumptions were used in estimating risks to workers from exposure to dimethemamid from use on golf-course turf.

8.2.2.1 Handler Exposures

- Average body weight of an adult handler is 70 kg.
- Exposure duration is short-term and intermediate-term for all workers assessed.
- Maximum application rates as determined by label review were used for all types and methods of application.
- SOP daily volumes handled and/or area treated used for the scenarios assessed are:
  - 40 acres treated per day for groundboom mixing, loading and application
  - 5 acres treated per day for mixing, loading and applying with a handgun sprayer
  - 40 gallons of spray solution used per day for mixing, loading and applying with a low pressure handwand or backpack sprayer applications

8.2.2.2 Post Application Exposures

- Average body weight is 70 kg.

- Turf Transferrable residue is 5% of the application rate for the fraction initially available.
- Transfer coefficient is 3400 cm^2/hour for mowing and other maintenance activities
- Exposure duration is 8 hours day
- Exposure is assumed to occur on the day of application (day 0)

8.3 Occupational Exposure and Risk Estimates

8.3.1 Handler Exposure and Risk Estimates

A target LOC or MOE of 100 is considered adequate for dermal and inhalation occupational exposure and risk. All worker exposures are assessed as short-and intermediate-term based on label prescribed uses and expected exposure durations. Exposure and risk estimates indicate MOEs are not of concern (MOEs $\geq$ 100) at the maximum use rate for all of the occupational handler exposure scenarios assessed. A summary of occupational exposure and risk calculations, assumptions, and results is provided in Table 15.

Table 15. Estimated Dimethenamid Exposure & MOEs for Handlers for Use on Golf Course Turf LOC/MOE = 100

Exp Scenario [1]	Inhalation Unit Exposure (ug/lb ai) [2]	Dermal Unit Exposure (mg/lb ai) [2]	Appl Rate [3]	Area Treated [4]	Inhalation Dose (m/k/d) [5]	Inhalation MOE [6]	Dermal Dose (m/k/d) [7]	Dermal MOE [8]
Mixing/Loading Liquid for Groundboom Application	1.2	2.9	1.5 lb ai/A	40 acre/day	0.0010	9700	2.486	120
Applying Sprays with Open Cab Groundboom Sprayer	0.74	0.014	1.5 lb ai/A	40 acre/day	0.0006	16000	0.012	25000
Mixing/Loading Liquid and Applying Sprays with Handgun Sprayer*	1.9	0.5	1.5 lb ai/A	5 acre/day	0.0002	49000	0.3107	1000
Mixing/Loading Liquid and Applying Sprays with Low Pressure Handwand and/or Backpack Sprayer	30	100	0.25 lb ai/gal	40 gal/day	0.0043	2300	0.4143	700

[1] Use patterns are from the proposed labels Baseline PPE unit exposures. Values are reported in the PHED Surrogate Exposure Guide dated August 1998 or are from data submitted by the Outdoor Residential Exposure Task Force dated May 2000.

[2] Baseline PPE unit exposures. Values are reported in the PHED Surrogate Exposure Guide dated August 1998 or are from data submitted by the Outdoor Residential Exposure Task Force dated May 2000. *Note: Dermal Unit Exposure for Handgun Sprayer are based on PPE values representing use of chemical-resistant gloves. No baseline PPE unit exposure are available for this scenario

[3] Application rates are based on maximum values based on proposed label. Most application rates upon which the analysis is based are presented as lb ai/A. In some cases, the application rate is based on applying a solution at concentrations specified by the label (i.e., presented as lb ai/gallon).

[4] Amount treated is based on the area or gallons that can be reasonably applied in a single day for each exposure scenario of concern based on the application method and formulation/packaging type. (Standard EPA/OPP/HED values). 5 gal per day application rate for backpack spray mosquito application based on label specified application rate of 2 mph.

[5] Inhalation dose (mg/kg/day) = [unit exposure (ug/lb ai) * 0.001 mg/ g unit conversion * Inhalation absorption (100%) * Application rate (lb ai/acre or lb ai/gallon) * Daily area treated/amount handled (acres or gallons)] / Body weight (70 kg).

[6] Inhalation MOE = short-term endpoint for inhalation (NOAEL 10 mkd)/ Daily Inhalation Dose.

[7] Dermal Dose (mg/kg/day) = [unit exposure (mg/lb ai) * Application rate (lb ai/acre or lb ai/gallon) * Daily area treated/amount handled (acres or gallons)] / Body weight (70 kg).

[8] Dermal MOE = short-term and intermediate-term endpoint for dermal (NOAEL 300 mkd)/Daily Dermal Dose.

8.3.2 Post-Application Exposure and Risk Estimates

A target LOC or MOE of 100 is considered adequate for dermal and inhalation occupational exposure and risk. All worker exposures are assessed as short-and intermediate-term based on label prescribed uses and expected exposure durations. Exposure and risk estimates indicate MOEs are not of concern (MOEs > 100) at the maximum use rate for occupational post-application exposure. A summary of occupational exposure and risk calculations, assumptions, and results is provided in Table 16.

Table 16. Estimated Dimethenamid Exposure & MOEs for Occupational Post-application Exposure to Treated Golf Course Turf LOC/MOE = 100

Exposure Scenario	AR (lb ai/A)	TTR/DFR (mg/cm^2)	TC (cm^2/hr)	Exposure Duration (hrs/day)	Dermal dose (mg/kg/day)	Dermal MOE
Mowing/Maintenance	1.5	0.0008	3400	8	0.3268	900

[1] Application rates are based on maximum values based on proposed label.

[2] TTR or DFR (mg/cm^2) = Application Rate (lb ai/A) x CF (4.54E+5 mg/lb) x CF (2.47E-8 A/ cm^2) x 5% (initial fraction of ai retained on turf) Application rates are based

[3] TC cm^2/hr = Transfer coefficients and associated activities (ExpoSAC Policy Memo #003.1)

[4] Dermal Dose (mg/kg/day) = TTR (mg/cm^2) x TC (cm^2/hr) x 4 (hrs/day) / Body weight (70 kg).

[8] Dermal MOE = short-term endpoint for dermal (NOAEL 300 mkd)/Daily Dermal Dose

9.0 CUMULATIVE RISK

Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

EPA does not have, at this time, available data to determine whether dimethenamid has a common mechanism of toxicity with other substances. 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 as to dimethenamid and any other substances and, dimethenamid does not appear to produce a toxic metabolite produced by other substances which have tolerances in the U. S. For the purposes of this tolerance reassessment action, therefore, EPA has not assumed that dimethenamid 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 OPP 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/fedrgstr/EPA_PEST/2002/January/Day_16/.

10.0 DATA NEEDS

10.1 Toxicology Data Requirements

- Acute Neurotoxicity (GLN 870.6200a)
- Subchronic Neurotoxicity study (GLN 870.6200b)
- Immunotoxicity (GLN 870.7800)

APPENDICES

1.0 TOXICOLOGY DATA SUMMARY

1.1 Guideline Data Requirements

Table 1. Guideline Data Requirements			
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	no
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	-
870.3465	90-Day Inhalation	yes	yes
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
870.5900	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)	yes	no
870.6200b	90-Day Neuro. Screening Battery (rat)	yes	no
870.6300	Develop. Neuro	no	-
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	-	-
870.7800	Dermal Penetration	Yes	no

1.2 Toxicity Profiles

Table 2 Acute Toxicity Profile -[RS]-dimethenamid [PC 129051]				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute oral/rats [Sprague Dawley] TXR# 008285	41662409 (1989) 44097602 (1992)	LD_{50} = 2140 mg/kg (males) LD_{50} = 1297 mg/kg (females) LD_{50} = 1570 mg/kg mean both sexes LD_{50} = 500	III II-III
870.1200	Acute dermal/rabbits [NZW]	41662410 (1988)	LD_{50} = >2000 mg/kg	III
870.1300	Acute inhalation/rats [Wistar] TXR# 008285	41662411 (1986)	LC_{50} = 4.99 mg/L	III
870.2400	Acute eye irritation/rabbits	41662412 (1988)	Minimally irritating	III
870.2500	Acute dermal irritation/ rabbits	41662413 (1988)	Minimally irritating	IV
870.2600	Skin sensitization [Guinea Pigs]	41662407 (1987)	Mild skin sensitizer	Sensitizer

Table 3 Acute Toxicity Profile -[S] dimethenamid-P [PC 120051]				
Guideline No.	**Study Type**	**MRID(s)**	**Results *values for [S]**	**Toxicity Category***
870.1100	Acute oral/rats [Sprague Dawley]	44097603 (1996)	LD_{50} = 429 mg/kg males LD50 = 531 mg/kg females LD50 =480 mg/kg both sexes.	II
870.1200	Acute dermal/rabbits [NZW]	44332234 (1996)	LD_{50} = >2000 mg/kg	III
870.1300	Acute inhalation [Sprague Dawley]	44332235 (1996)	LC_{50} = 2.2 mg/L	III
870.2400	Acute eye irritation [NZW]	44332238 (1996)	Minimally irritating	III
870.2500	Acute dermal irritation [NZW]	44332239 (1996)	Minimally irritating	IV
870.2600	Skin sensitization [Guinea Pigs]	44097604	Mild skin sensitizer	Sensitizer

Table 4 Subchronic, Chronic and Other Toxicity Profile for [RS]-dimethenamid		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100 90-Day Feeding/Sprague Dawley rat	41615901 (1986) Doses: 0, 50, 150, 500, 1500, 3000 ppm [M/F: 0/0/, 3.5/3.9, 10.0/11.8, 33.5/40.1, 98/119, 204/238 mg/kg/day] Acceptable in TXR# 008285	NOAEL=33.5/40.1 mg/kg/day [500 ppm] LOAEL=98/119 mg/kg/day [1500 ppm] based on decreased body weight and body weight gain, increased total protein in males; in females, increased cholesterol, increased adj liver weight and centrilobular hepatocytic enlargement.
870.3150 90-Day oral toxicity (dog)	41615902 (1986 [Doses: 0, 100, 750, 2000 ppm][M/F: 0/0, 4.72/4.98, 33.6/39.7, 89.6/87.4 mg/kg/day] [From std tables(dry): 0, 2.5, 18.75, 50 mg/kg/day] [From std tables(wet): 0, 7.5, 56.25, 150 mg/kg/day] Acceptable TXR# 008285	NOAEL = 4.72/4.98 mg/kg/day [100 ppm] LOAEL =33.6/39.7 mg/kg/day [750 ppm] based on decreased body weight and body weight gain in females, increased rel. liver wt in both sexes, increased periportal vacuolation in both sexes and dilation of liver sinusoids in females.
870.3200 21/28-Day dermal toxicity (NZW rabbit)	41662414 (1989) Doses: 0, 50, 150, 500 mg/kg/day Acceptable in TXR# 010012	LOAEL = 500 mg/kg/day based on decreased body weight gain.
870.3200 21/28-Day dermal toxicity (NZW rabbit)	41513010 (1991) Doses: 0, 30, 300, 1000 mg/kg/day	LOAEL = 1000 mg/kg/day based on severe systemic toxicity and mortality. The NOAEL is 300 mg/kg/day.
870.3700a Prenatal developmental in (Sprague Dawley rats)	41615904 (1987) [Doses: 0, 50, 215, 425 mg/kg/day] Vehicle is 0.5% CMC, 10 ml/kg Acceptable in TXR# 008285	Maternal NOAEL = 50 mg/kg/day LOAEL =215 mg/kg/day based on body weight decrement on GD 12 (but not a single dose effect) and body weight and food consumption decrease, both GD 6-9 & 6-16 Developmental NOAEL = 215 mg/kg/day LOAEL=425 mg/kg/day based on increased post implantation loss.
Prenatal Developmental (NZW/Rabbit)	41706809 (1988) Doses: 0, 37.5, 75, 150 mg/kg/day Acceptable TXR# 008469 N/L change from previous	Maternal NOAEL=75 mg/kg/day LOAEL=150 mg/kg/day based on slight body weight decrement (80g, GD 12-15), body weight loss (75g GD 15-19) and 2 abortions and in a 20 litter/group range-finding study, death (13/20) and abortions (7/20) at 250 mg/kg/day Developmental NOAEL=75 mg/kg/day LOAEL=150 mg/kg/day based on SS fetal incidence of irregular parietals and hyoid angulated. Litter incidence was nominally elevated by 50% and 100%, respectively, and nominally increased post implantation loss (double control).

Table 4 Subchronic, Chronic and Other Toxicity Profile for [RS]-dimethenamid		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3800 Reproduction and fertility effects (Wistar rats)	41615905 (1990) Doses: 0, 100, 500, 2000 ppm [M/F; 0/0, 7/8, 36/40, 150/160 mg/kg/day] Acceptable TXR# 008285	Parental/Systemic NOAEL = 36/40 mg/kg/day [500 ppm] LOAEL =150/160 mg/kg/day [2000 ppm] based on decrease body weight, body weight gain, food consumption and abs & relative liver weight increase. Reproductive NOAEL = 150/160 mg/kg/day [2000 ppm] LOAEL = None Offspring NOAEL = 40 mg/kg/day [500 ppm] LOAEL = 160mg/kg/day [2000 ppm] based on f1 pup weight decrement at LD 21 and f2 pup weight decrease at LD day 7and 21.
870.4100b Chronic toxicity (dog)	41615903 (1990) 0, 25, 250, 1250 ppm [M/F 0/0, 1.95/2.1, 10.1/9.1, 48.7/49.3 mg/kg/day] [From std tables(dry): 0, 0.625, 6.25, 31.25 mg/kg/day] [From std tables(wet): 0, 2.5, 18.75, 50 mg/kg/day] Acceptable TXR# 008285	NOAEL = 10.1/9.1 mg/kg/day [250ppm] LOAEL =48.7/49.3 mg/kg/day [1250ppm] based on decreased body wt & body wt gains [43% to 60%,0-26wk] both sexes 100% in males wk 26-52] alkaline phosphatase increased in females 109-2185 through out study and 80% in males. Portal vacuolation in males; vacuoles not lipid or glycogen
870.4200 b Carcinogenicity (mouse)	41662415 (1990) 0,30, 300, 1500, 3000 ppm [M/F: 0/0, 3.8/4.1, 40.8/40.1, 205/200, 431/411 mg/kg/day Acceptable TXR# 008315	NOAEL = 300 ppm (M/F: 40.8/40.1 mg/kg/day) LOAEL = 1500 ppm (M/F: 205/200 mg/kg/day) based on decreased body weight gain in both sexes. No treatment related tumors were seen at adequate doses.
870.4300 Chronic/ carcinogenicity (Sprague Dawley rat)	41706808 & 42030102 (1990) 0, 100, 700,1500 ppm [M/F: 0/0, 5.1/6.8, 36/49, 80/109 mg/kg/day] Acceptable TXR# 008315 & 008975	NOAEL = 100 ppm [M/F: 5.1/6.8 mg/kg/day] LOAEL = 7000 ppm [M/F: 36/49 mg/kg/day] based on decreased body weight and body weight gain in both sexes and microscopic hepatic lesions in both sexes. A dose related increased incidence of liver tumors in males (benign and malignant combined) were seen at 1500 ppm, both exceeding historical controls. Cancer Peer Rev (TXR# 012143 & 012831) characterized [RS]-dimethenamid as a Group C - possible human carcinogen, and recommended that for the purpose of risk assessment the Reference dose approach should be used for human risk assessment)
Gene Mutation 870.5100 Bacterial Reverse mutation	41596542 (1989) Reverse mutation in *S. typhimurium* strains TA 98, TA100, TA1535, TA1537, TA1538 Acceptable TXR# 008285	Strains tested at 1000-10000 µg/plate, -S9 and 1000-6500 µg/plate, +S9. Cytotoxicity and precipitation were noted at higher doses. Test was negative, +/-S9.

Table 4 Subchronic, Chronic and Other Toxicity Profile for [RS]-dimethenamid		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
Cytogenetics 870.5395 Mouse erythrocyte micronucleus test	43648401 (1993) *In vivo* Bone marrow erythrocyte micronucleus test Acceptable inn TXR# 011053	CD-1 mice dosed at 710 mg/kg in two daily doses. LD50 = 1417 mg/kg. Bone marrow erythrocytes harvested 24 and 48 hours later. Test negative.
Cytogenetics 870.5395 Mouse erythrocyte micronucleus test	41822703 (1986) *In vivo* Bone marrow erythrocyte micronucleus test. Unacceptable in TXR# 008469	Mice dosed 0-1000 mg/kg in single doses. Mice showed no toxicity; only one mouse died. Test negative.
Chromosomal aberration test 870.5375	41596543 (1985) *In vitro* chromosomal aberration test in chinese hamster ovaries (CHO) Unacceptable in TXR# 008285 & acceptable in TXR# 009070	Cells in 125-150 µg/mL, -S9 and 400 to 500 µg/mL, +S9; all doses were cytotoxic. Study needs repeating at no cytotoxic doses. Test considered equivocally positive.
UDS in rat hepatocytes 870.5550	41822702 (1986) *In vitro* unscheduled DNA synthesis in rat hepatocytes Unacceptable in TXR# 008469	Cell in 1.0-100 nl/mL. No cytotoxicity was seen. Test was negative.
UDS in rat hepatocytes 870.5550	43648402 (1993) In vivo unscheduled DNA Synthesis in rat hepatocytes Acceptable to EEC requirements TXR# 011053	Fisher 344 rat administered SAN 582H doses of 158 or 500 mg/kg. Sampled 2-4 and 12-14 hours after dosing. Only 0.2-3.6% cells in repair, but negative control was less than zero. Test was negative for UDS at 158 and 500 mg/kg.
UDS in rat hepatocytes 870.5550	41596544 (1989) *In vitro* unscheduled DNA synthesis in rat hepatocytes Acceptable in TXR# 008285	SAN 582H administered at 0.01 to 50 µg/mL. Unscheduled DNA synthesis was seen well below cytotoxic doses. Unequivocally positive for UDS. Test positive.
UDS in rat hepatocytes 870.5550	41662416 (1990) *In vitro* unscheduled DNA synthesis in rat hepatocytes. Acceptable in TXR# 008469	SAN 582H administered at 0.0128 to 1000 µg/mL to rat primary cultures of hepatocytes. Doses at 1000 µg/mL were cytotoxic. No UDS was noted. Test negative for UDS.
Dominant Lethal 870.5450	43209201 (1994) (Hazleton) Dominant lethal in CR rats	Male Charles River rats (40-55) administered SAN 582H in single oral doses of 275, 550 or 1100 mg/kg were mated starting at 10 weeks to 40-55 female undosed CR rats. Increased dead implants at week 1 and week 2 may suggest a

Table 4 Subchronic, Chronic and Other Toxicity Profile for [RS]-dimethenamid		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
	Acceptable in TXR# 011053	dominant lethal effect. These were mostly late implant deaths, which some consultants claim are not characteristic of a dominant lethal effect. .
Dominant Lethal 870.5450	43814401 (1995) (Microbiological Assoc.) Dominant lethal in Sprague Dawley rats	Male Sprague Dawley rats (40-60) administered SAN 582H in single oral doses of 275, 550 or 1100 mg/kg were mated starting the day after dosing in Trial 1 and 2 days after dosing in Trial 2 to 80-120 female undosed Sprague Dawley rats . Each male was mated to 2 females over a five day sequence. Results equivocal, but not considered to negate results from MRID# 43209201. Note: Both the high dose rabbit and rat developmental studies showed increased late and early resorptions.
BALB/3T3 cell transformation NG	41822701 (1986) per-1996 *in vitro* cell transformation Unacceptable in TXR# 008469	BALB/3T3 cells administered SAN 582H at 15.0 to 100 µg/mL. No transformed cells were noted, but several inadequacies were noted in the test report. Number of cells transformed. Cell transformation yields variable results and is not an acceptable methodology. Test negative
870.7485 Metabolism and pharmacokinetics (Wistar rats)	41596545 (1989) & 42289501 (1992) Single low and high doses of [^{14}C] SAN 582H and after repeat doses of SAN 582H were administered Unacceptable in TXR# 008285 Acceptable in TXR# 009867.	Extensively metabolized, being essentially complete within 3 days and over 90% being excreted in the urine, feces and bile within 7 days. Total excretion products with the highest concentrations (in % of administered dose) in the male and female, respectively, were parent 1.4% and 1.2%, *M1- 3.3 & 7.2%, *M2- 3.6% & 9.8%, M3- 0.6% & 0.4%, M14- 2.8% & 3.3%, *M16- 5.1% & 3.3%, M17- 0.6% & 3.3%, M19-1.1% & 1.4%. Parent was initially conjugated with glutathione and most metabolism taking place with the glutathione conjugate. No significant differences in metabolism were seen between males and females. Up to 45 putative metabolites were reported in the urine and up to 50 were reported in the feces. Of these metabolites, 31 were identified. Of the unidentified metabolites none exceeded 3.0% and most being less than 1% of the administered dose.
Chemical name of excretion products exceeding 5% in the multidose 10 mg/kg study in males or females.	M1 is N-(2,4-dimethyl-3-thienyl)-N-(2-hydroxy-1-methylethyl)-2-(methyl-thio)-acetamide M2 is N-(2,4-dimethyl-3-thienyl)-MN-(2-hydroxy-1-methylethyl)-2-(methyl-sulfinyl)-acetamide M16 is N-(2-hydroxymethyl-4-methyl-3-thienyl)-N-(2-methoxy-1-metylethyl)-2-(methylsulfinyl)-acetamide	

Table 5. Subchronic, Chronic and Other Toxicity Profile for [S]-dimethenamid-P (PC 120051)

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day Feeding/Sprague Dawley Rat	44332242 (1996) Doses: 0, 500, 1500, 3000 ppm [M/F: 0/0/, 37/40, 110/125, 222/256 mg/kg/day] Acceptable in TXR# 0050183	NOAEL=37/40 mg/kg/day [500 ppm] LOAEL=110/125 mg/kg/day [1500 ppm] based on decreased body weight and body weight gain in males and females, increased gamma-glutamyl transferase in both sexes, increased cholesterol in males, increased abs. and rel. liver weight and periportal hepatocytic hypertrophy and periportal eosinophilic inclusions in males, centrilobular hypertrophy in females and liver necrosis in females.
870.3700a Prenatal developmental in (Sprague Dawley rats)	44332243 (1996) [Doses: 0, 25, 150, 300 mg/kg/day] Vehicle is 0.5% CMC, 10 ml/kg Acceptable in TXR# 0050183	Maternal LOAEL = 150 mg/kg/day based on a decrease in body weight/gain and feed consumption (clinical signs at 300 mg/kg/day). Maternal NOAEL is 25 mg/kg/day. Developmental LOAEL is 150 mg/kg/day based on an increased incidence of incomplete ossification of the second sternal centra and/or pelvic pubis. The developmental NOEL is 25 mg/kg/day.
Gene Mutation 870.5100 Bacterial Reverse mutation	Reverse mutation 44332244 (1997) *S. typhimurium* TA1535; *E. coli* WP2uvrA Acceptable in TRX# 0052635	*S. typhimurium* exposed to 500-4000 µg/plate +/- S9. *E. coli* exposed to 20-5000 µg/plate +/-S9 using the Std plate incorp method or 4-2500 µg/plate +/-S9 using the preincubation modification to the std test. Highest doses were cytotoxic. All assays were negative.
Gene Mutation 870.5100 Bacterial Reverse mutation	Reverse mutation 44332245 (1997) *S. typhimurin* TA1535, TA1537, TA 98, TA100; *E. coli* WP2uvrA Acceptable in TRX# 0052635	Exposed to 20-5000 µg/plate in a plate incorporation assay. Marginal cytotoxicity at limit dose of 5000 µg/plate +/- S9. Assays were negative with both bacteria +/- S9.
Gene Mutation 870.5100 Bacterial Reverse mutation	Reverse mutation 44332246 (1997) *S. typhimurin* TA100. Acceptable in TRX# 0052635	Repeat of MRID# 44123502. *S. typhimurium* TA100 was exposed to 100-5000 µg/plate -S9. Assay was negative.
Gene Mutation 870.5100 Bacterial Reverse mutation	Reverse mutation 44123502 (1996) & resubmitted 44332250 (1996) *S. typhimurin* TA1535, TA1537, TA 98, TA100; *E. coli* WP2uvrA Acceptable in TRX# 0052636	Exposed to 100-5000 µg/plate, +/-S9, in a plate incorporation assay. Insolubility seen at 333 & 5000 µg/plate, but no toxicity at any dose. +/- S9. Assays were negative with both bacteria + S9, however, -S9 induced 1.5 fold increases at 333 µg/plate and 4.1 fold increases in reverents in TA100 strain at 5000 µg/plate. This mutagenic response was reproducible at 100 to 5000 µg/plate.
Mammalian cell	In vitro CHO/HGPRT	Chinese hamster ovary (CHO) cells were exposed to 100-

Table 5. Subchronic, Chronic and Other Toxicity Profile for [S]-dimethenamid-P (PC 120051)		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
mutation 870.5300	mutation assay 44123501 (1996) & resubmission as 44332248 Acceptable TXR# 12312	400 µg/mL, -S9, and 100-450 µg/mL, +S9. Slight cytotoxicity was seen at the highest dose and severe toxicity was seen at ≥500 µg/mL. Test was negative for mutagenic effects, +/- S9.
Cytogenetics in Chinese Hamster Ovary (CHO) cells 870.5375	Chromosomal aberrations *in vitro* 44332247 (1996) Acceptable TXR# 0052635	CHO cells were exposed to 2-120 µg/mL -S9; cytotoxic at ≥120 µg/mL. CHO cells were exposed to 15-120 µg/mL +S9; cytotoxic at ≥500 µg/mL. Assay was negative +/-S9.
Cytogenetics; mouse erythrocyte micronucleus test 870.5395	ICR mice *in vivo* test 44332249 (1996) Acceptable TRX# 0052635	Mice (5/sex) were exposed to i.p. injections of 103, 205, 410 mg/kg. Assay was negative, indicating no clastogenic or aneugenic response.
Other Effects 870.5550 UDS in mammalian cell culture	Rat hepatocyte cell *in vitro* test 44332251 (1996) Acceptable TRX# 0052635	Cells tested at 7.8-125 µg/mL. Cytotoxicity and insolubility were seen at ≥250 µg/mL. Test was negative for UDS.

1.3 Studies Reviewed for Ethical Conduct

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The PHED Task Force, 1995. The Pesticide Handlers Exposure Database, Version 1.1. Task Force members Health Canada, U.S. Environmental Protection Agency, and the National Agricultural Chemicals Association, released February, 1995.

2.0 ADDITIONAL TOXICOLOGY STUDIES

Oral Toxicity

870.3100 90-Day Feeding/Sprague Dawley rat

In a subchronic oral toxicity study (MRID 41615901), SAN 582 H (91.5% a.i., Batch # 8605) was administered in the diet to 10 Sprague-Dawley rats/sex/dose levels of 0, 50, 150, 500, 1500, or 3000 ppm (equivalent to 0/0, 3.5/3.9, 10.0/11.8, 33.5/40.1, 98/119, and 204/238 mg/kg/day in males/females) for up to 13 weeks. Additionally, 10 rats/sex were similarly treated at 0 or 3000 ppm for 13 weeks and then observed during a recovery period of 4 weeks.

No treatment-related adverse effect was observed on mortality, clinical signs, food and water consumption, ophthalmology, hematology, urinalysis and gross pathology for both sexes at all doses. A treatment-related effect was not observed at 50, 150, and 500 ppm.

At >=1500 ppm, final body weight (Week 13) was decreased ($p<0.05$) by 9-11% in males. At 3000 ppm, body weights were decreased ($p<0.01$) by 8-10% in both sexes during Weeks 7 and/or 13. Body weight gain (Weeks 7-13) and overall (Weeks 0-13) body weight gain were decreased ($p<0.05$) by 17-31% in the >=1500 ppm males. At 3000 ppm, decreases ($p<0.05$) in body weight gain were observed in males at Weeks 0-7 (decr 22%) and in females throughout the study (decr 22-33%). Food conversion ratio (Weeks 1-13) was increased (statistical analysis not performed) by 9-24% in both sexes at >=1500 ppm. Findings which were indicative of hepatotoxicity were observed at the two highest doses as follows: (i) serum cholesterol was increased ($p<0.01$) by 31-38% in females; (ii) total serum protein was increased ($p<0.01$) by 17-33% in the males; (iii) liver weight (adjusted using the final body weight as a covariate) was increased ($p<0.05$) by 12-28% in 1500 and 3000 ppm females and 3000 ppm males; and (iv) minimal to moderate enlargement of centrilobular hepatocytes was observed in females (9-10 treated vs 0 controls, n=10). Additionally, at 3000 ppm, increases ($p<0.01$) were observed in cholesterol (incr 42%) in males and gamma-glutamyl transpeptidase (incr 100-200%) in both sexes

There was evidence of recovery in each parameter; although, the recovery was not always complete. For instance, in the 3000 ppm females, microscopic hepatic lesions were observed in 2/10 rats, and body weight remained decreased ($p<0.05$) by 6%.

The LOAEL is 1500 ppm (equivalent to 98/119 mg/kg/day in males/females) based on decreased body weight and body weight gain and increased total serum protein in males; increased food conversion ratios in both sexes; and increased serum cholesterol, increased adjusted liver weight, and centrilobular hepatocyte enlargement in females. The NOAEL for this study is 500 ppm (equivalent to 33.5/40.1 mg/kg/day in males/females).

This study is classified **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.3100; OECD 408) for a 90-Day oral toxicity study in rat

870.3100 90-Day Feeding/Sprague Dawley Rat

In a subchronic toxicity study (MRID No. 44332242), SAN 1289 H (S-dimethenamid) (96.3% purity active ingredient total dimethenamid and 91.1% S-dimethenamid) was administered by dietary admix to Charles River Sprague-Dawley CD [Crl;CD BR] rats (10/sex/group) at doses of 0, 500, 1,500 or 3,000 ppm (mg/kg body weight/day: males = 0, 37, 110 or 222; females = 0, 40, 125 or 256) for at least 90 days.

No apparent effects were seen for the following parameters: clinical signs, mortality, food consumption, ophthalmology, hematology, urinalysis or macroscopic pathology.

Body weight gains were below respective control values Ž 1,500 ppm for both sexes, primarily during the first week of the study (8-12% less). Probable effects on the liver were noted 1,500 ppm for both sexes as evidenced by the following: an increase in gamma-glutamyl transferase levels; an increase in absolute and/or relative liver weights; and microscopic pathology (centrilobular hypertrophy and/or periportal hypertrophy andlor periportal eosinophilic inclusions and/or necrosis).

The systemic toxicity NOEL = 500 ppm (mg/kg/day: males = 37; females = 40)
The systemic toxicity LOEL = 1,500 ppm (mg/kg/day: males = 110; females = 125) based on the following for both sexes: decrease in body weight gain primarily during the first week, increase in gamma-glutamyl transferase levels, increase in absolute/relative liver weights and microscopic pathology liver changes

This study is acceptable and satisfies the data requirement for OPPTS 870.3100 for a subchronic toxicity study in rats.

870.4200 b Carcinogenicity (mouse)

In a carcinogenicity study (MRID 41662415), 52 Crl: CD1 (ICR) BR mice/sex/dose were exposed to SAN 582 H (91.4% a.i.; Batch #: 8605) in the diet for up to 94 weeks at concentrations of 0, 30, 300, 1500, or 3000 ppm (equivalent to 0/0, 3.8/4.1, 40.8/40.1, 205/200, and 431/411 mg/kg/day in males/females). An additional group of 16 mice/sex were similarly treated at 0 or 3000 ppm and sacrificed at 65 weeks.

No treatment-related adverse effect was observed on mortality, clinical signs, food consumption, hematology, and gross pathology for both sexes at all doses. There was no indication of carcinogenic potential. A treatment-related adverse effect was not observed at 30 or 300 ppm.

Generally, only minor decreases in body weights were observed. Body weight gain (Weeks 0-52) decreased ($p<0.05$) by 13-29% in the 1500 and 3000 ppm groups. Body weight gain (Weeks 0-13) decreased ($p<0.05$) by 12% in the 3000 ppm males. Food conversion ratio (Weeks 1-13) was increased by 10-13% in the 3000 ppm group.

At the terminal sacrifice (n=51-52), cortical mineralization in the kidney in males was observed at 3000 ppm (16% treated vs 2% controls). This finding was considered to be equivocal without corroborating evidence of nephrotoxicity. Minimal centrilobular enlarged hepatocytes were observed at the interim sacrifice (n=12-16) in the 3000 ppm group (23-53% treated vs 0% controls). Minimal to moderate enlarged hepatocytes were observed at the terminal sacrifice (n=51-52) in the 1500 ppm group (18-29% treated vs 0-6% controls) and the 3000 ppm group (53-60% treated). The liver weight (with final body weight as a covariate) was increased ($p<0.05$) in the 3000 ppm group at Week 65 by 15-26% and in the 1500 and 3000 ppm females at Week 94 by 22-25%. The type of hepatocytomegaly was not specified. It is possible that the liver effects were due to hepatocellular hypertrophy resulting from an adaptive response; consequently, it is unclear if the compound is resulting in adverse liver effects.

The LOAEL is 1500 ppm (equivalent to 205/200 mg/kg/day in males/females) based on decreased body weight gain in both sexes. The NOAEL for this study is 300 ppm (equivalent to 40.8/40.1 mg/kg/day in males/females).

At the doses tested, there was not a treatment-related increase in tumor incidence when compared to controls. Dosing was considered adequate based on decreased body weight gain at >= 1500 ppm and increased food conversion ratio at 3000 ppm.

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

870.4300 Chronic/carcinogenicity (Sprague Dawley rat)

In a chronic toxicity and carcinogenicity study (MRIDs 41706808 and 42030102), 50 Crl: CD (SD) BR rats/sex/dose were exposed to SAN 582 H (91.3% a.i.; Batch #: AD 8605) in the diet for up to 24 months at doses of 0, 100, 700, or 1500 ppm (equivalent to 5.1/6.8, 36/49, and 80/109 mg/kg/day in males/females). An additional group of 20 rats/sex/dose were similarly treated and sacrificed at 12 months.

Mortality, water consumption, clinical signs, ophthalmology, hematology, and urinalysis for both sexes at all doses were unaffected by treatment. No treatment-related adverse differences in any parameter were observed in the 100 ppm group.

At >=700 ppm, the final body weights (Week 104) were decreased by 6-23% in both sexes. Body weight gain was decreased ($p<=0.05$) by 6-19% in both sexes at Weeks 0-10 and by 15-26% in the females at Weeks 10-80. Overall body weight gain (Weeks 0-104) was decreased ($p<=0.05$) by 16-31% in the 1500 ppm group. Food consumption (Weeks 1-10) was decreased ($p<=0.05$) by 4-9% in both sexes at 700 and 1500 ppm. Food conversion ratio (Weeks 1-25) was increased by 11-20% in both sexes, except 700 ppm males. The liver was a target organ, with the following increased incidence of lesions observed in the 700 and 1500 ppm groups: (i) pale areas in the liver in the males (28-34% treated vs 12% controls) and in 1500 ppm females (38% treated vs 20% controls); (ii) altered eosinophilic hepatocytes in males (12-20% treated vs 4%

controls); and (iii) bile duct hyperplasia in females (22-40% treated vs 6% controls).

Additionally at 1500 ppm, gamma-glutamyl transpeptidase was increased ($p<=0.05$) by 61-163% in the males throughout the study. In the liver, the organ weight (with final body weight as a covariate) was increased ($p<=0.05$) in the females at Weeks 53 and 105 by 11-16%. Grossly, there was an increased incidence of liver masses in the males (8% treated vs 2% controls), and cysts in both sexes (10-12% treated vs 0-2% controls). Microscopically, cystically dilated bile ducts were increased in the females (14% treated vs 2% controls). The incidence of other microscopic lesions were also increased as follows: hyperplasia in the stomach (40% treated vs 12% controls) and in the parathyroid (36% treated vs 10% controls) in males; and ovarian tubular hyperplasia (44% treated vs 24% controls).

The LOAEL is 700 ppm (equivalent to 36/49 mg/kg/day in males/females), based on decreased body weight and body weight gain in both sexes, increased food conversion ratios in females, and increased microscopic hepatic lesions in both sexes. The NOAEL is 100 ppm (equivalent to 5.1/6.8 mg/kg/day in males/females).

At the doses tested, there was a treatment-related increase in the incidence of benign liver and ovarian tubular tumors when compared to controls. At 1500 ppm, an increased incidence of benign liver cell tumors were observed in the males (6% treated vs 0% controls), which exceeded the historical controls (0-1.8%). Additionally, an increased incidence of ovarian tubular adenomas were observed (12% treated vs 4% controls), which exceeded the historical controls (0-9.1%). Dosing was considered adequate based on changes in body weight, body weight gain, food consumption, food conversion ratios, clinical chemistry, organ weights, and gross and microscopic lesions.

This study is classified as acceptable/guideline and satisfies the guideline requirements (OPPTS 870.4300; OECD 453) for a combined chronic toxicity/carcinogenicity study in rats. The Carcinogenicity Peer Review of dimethenamid of 3/23/95 (TXR# 012143) and 6/15/92 (TXR# 012831) stated that the weight of evidence classification was Group C - possible human carcinogen and recomended that for the purpose of risk characterization the Reference dose approach should be used for quantification of human risk. This decision was based on a statistically significant increasing trend for liver cell tumors in male rats and statistically significant increasing trend for ovarian tubular adenomas in female rats, neither of which show significance by pair wise comparision. Dimethenamid has shown positive results in some genotoxicity tests and is structurally related to other carcinogens. An acceptable study in mice showed no dose related tumors.

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