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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 14-AUG-2002

SUBJECT: PP# 7E04825. **Tolylfluanid in/on Imported Apples, Grapes, Hops and Tomatoes. Health Effects Division (HED) Risk Assessment.**
PC Code: 309200. DP Barcode: D275570. Case#: 288573. Submission#: S595497.

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The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The RD of OPP has requested that HED evaluate hazard and exposure data and conduct dietary and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the proposed permanent tolerances for residues of tolylfluanid (1,1-dichloro-N-[(dimethylamino)-sulfonyl]-1-fluoro-N-(4-methylphenyl)methanesulfenamide) in/on imported apples, grapes, hops and tomatoes.

A summary of the findings and an assessment of human risk resulting from the proposed permanent tolerances for tolylfluanid is provided in this document. The risk assessment, the residue chemistry data review, and the dietary exposure risk assessment were provided by Jennifer Tyler (RAB1), and the hazard characterization by Guruva Reddy (RAB1).

Recommendation for Tolerances

Provided a revised Section F is submitted and a successful Agency petition method validation (PMV) of the analytical method is reported as outlined in Section 8.0 of this risk assessment, the residue chemistry and toxicology databases support the establishment of the permanent tolerances for residues of tolylfluanid *per se* in/on the following imported raw agricultural commodities (RACs):

Grape	11 ppm
Hop, dried cones	30 ppm
Tomato	2.0 ppm
Apple	5.0 ppm

Note to RD: Language should be added to 40 CFR 180.xxx specifying that "There are no U.S. registrations for grape; hop, dried cones; tomato; and apple as of *[date of Federal Register publication]*."

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1.0 EXECUTIVE SUMMARY

Tolylfluanid is a multi-acting fungicide with protective action against *Botrytis cinerea*, powdery and downy mildew, scab, early and late blight, and storage diseases such as *gleosporium*, *nectria*, and *monilia*. The petitioners, Bayer Corporation and Bayer AG, have submitted a petition for the establishment of permanent tolerances for residues of tolylfluanid in/on **imported** apples, grapes, hops and tomatoes. No tolerances have been established for residues of tolylfluanid in/on any food, feed, or processed commodities in the United States (U.S.). In addition, there are currently no registered or proposed domestic residential uses of tolylfluanid.

Hazard Assessment

Tolylfluanid has low acute toxicity via the oral and dermal routes of exposure (Category IV). It is a severe inhalation toxicant and eye irritant (Category II). Tolylfluanid is not a skin irritant (Category IV) or sensitizer. In neurotoxicity studies, tolylfluanid did not affect brain weights, gross pathology, histopathology or neuropathology. However, in an acute neurotoxicity study functional observational battery (FOB) effects, decreased motor and locomotor activities were observed in females at 150 mg/kg/day on day 0. However, these effects were resolved by day 7. The skeletal system (bones and teeth) was the primary target organ of tolylfluanid toxicity in the chronic rat and mouse studies. The liver was also identified as a target organ in the developmental and reproduction studies. The thyroid was identified as the target organ in the subchronic and chronic rat studies. The rat and dog appear to be equally sensitive to the effects of tolylfluanid. The mouse is less sensitive than the rat and dog. The no-observed-adverse-effect-levels (NOAELs) (12.5 - 23.1 mg/kg) and lowest-observed-adverse-effect-levels (LOAELs) (62 - 108 mg/kg) were similar between the subchronic and chronic rat and dog studies, with the exception of in the subchronic neurotoxicity rat study which had a LOAEL of 134 mg/kg based on decreased female body weights. No developmental toxicity was seen in rats at the limit dose (1000 mg/kg/day). Developmental toxicity was seen in the rabbit in the form of decreased fetal survival, increased malformations and variations at maternally toxic doses (75 mg/kg/day; highest dose tested (HDT)). In the 2-generation reproduction toxicity study, the NOAEL for the parental toxicity of 7.5 mg/kg was based on decreased body weights, body weight gains and liver weights seen at 57.5 mg/kg in the P females. Reproductive toxicity (reduced mean litter size) was also observed at this dose. The HED Cancer Assessment Review Committee (CARC) classified tolylfluanid as **"likely to be carcinogenic to humans"** by the oral route, based on follicular cell thyroid tumors in high-dose male and female rats (Memo, J. Kidwell 6/10/02; TXR# 0050810). The Committee further recommended a linear low-dose extrapolation approach for the quantification of human cancer risk based on the follicular cell thyroid tumors in rats. The unit risk, Q_1*, for tolylfluanid based upon male rat thyroid adenomas and/or carcinomas combined tumor rates is 1.59×10^{-3} in human equivalents (Memo, L. Brunsman 6/12/02; TXR# 0050791).

Dose Response Assessment and Food Quality Protection Act (FQPA) Decision

On 5/9/02, the HED Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for tolylfluanid with regard to the acute and chronic reference doses (RfDs) (Memo, G. Reddy 6/12/02; TXR NO. 0050802). The potential

for increased susceptibility of infants and children from exposure to tolylfluanid was also evaluated as required by FQPA of 1996 according to the 2002 OPP 10x Guidance Document. On 6/17/02, the HED FQPA Safety Factor Committee (SFC) met to evaluate the hazard and exposure data for tolylfluanid with regard to making a decision on the additional safety factor for the protection of infants and children (Memo, B. Tarplee 8/1/02; TXR NO. 0051023). The FQPA SFC recommended that a **database uncertainty factor (UF_{DB}) of 3x** be applied to the acute and chronic RfDs to account for the comparative thyroid assay (adult versus young animals) data requirement. The FQPA SFC also recommended that the **special FQPA safety factor be removed (1x)** in assessing the potential risk posed by this chemical.

Risk assessments were conducted for the specific exposure scenarios listed below. A 300-fold uncertainty factor (UF; 3x UF_{DB}, 10x for interspecies extrapolation and 10x for intraspecies variation) was incorporated into the acute and chronic RfD. The RfD is equal to the NOAEL divided by the 300x UF. The acute or chronic population adjusted dose (aPAD or cPAD) is equal to the acute or chronic RfD divided by the 1x special FQPA safety factor.

acute dietary (females 13-50 years old)	NOAEL = 25 mg/kg/day	acute RfD = aPAD = 0.083 mg/kg/day
acute dietary (general U.S. population, including infants and children)	NOAEL = 50 mg/kg/day	acute RfD = aPAD = 0.17 mg/kg/day
chronic dietary	NOAEL = 7.9 mg/kg/day	chronic RfD = cPAD = 0.026 mg/kg/day
cancer dietary	$Q_1^* = 1.59 \times 10^{-3}$	

Occupational and Residential Exposure Estimates

As this petition is for tolerances for imported commodities only, occupational and residential exposure assessments were not conducted.

Dietary Exposure Estimates

Acute and chronic dietary exposure analyses were conducted using the Dietary Exposure Evaluation Model (DEEM™, ver 7.76), which utilizes consumption data from the USDA 1989-92 Nationwide Continuing Surveys of Food Intake by Individuals (CSFII). For acute and chronic dietary risk estimates, HED's level of concern is for estimates that exceed 100% aPAD or cPAD, respectively. For cancer dietary risk estimates, HED is generally concerned with cancer risks that exceed 1×10^{-6}.

For the acute, chronic and cancer analyses, modified DEEM™ processing factors based on the results of processing studies were used for raisins and apple and grape juice/juice concentrates. Default DEEM™ processing factors were used for all other processed commodities.

The HIARC selected separate acute dietary endpoints for females 13-50 years old and the general U.S. population (including infants and children). Partially refined separate acute dietary exposure assessments were performed for females 13-50 years old and the general U.S. population (including infants and children), incorporating anticipated residues (ARs; parent and additional metabolites of concern not in tolerance expression) calculated from field trial data for

all proposed tolylfluanid food uses. In addition, it was assumed that all proposed food items contain tolylfluanid residues (i.e., 100% crop treated (CT)). The acute dietary exposure estimates are below HED's level of concern (<100% aPAD) at the 95th exposure percentile for females 13-50 years old (42% aPAD), the general U.S. population (31% of the aPAD) and all other population subgroups. The most highly exposed population subgroup is infants <1 year old, at 100% of the aPAD. The acute dietary exposure assessment was conservative, using several upper-end assumptions (including ARs at levels higher than recommended tolerances to include all residues of concern; see Section 4.2.2.1 of this risk assessment). Inclusion of additional data, such as % CT and import consumption data and/or monitoring data (including metabolites of concern), could be made in order to refine the acute dietary exposure assessment.

Chronic and cancer dietary exposure assessments were conducted for the general U.S. population and all population subgroups (including infants and children), incorporating ARs (parent and additional metabolites of concern not in tolerance expression) calculated from field trial for all commodities, and % import share information provided by the Biological Economic Analysis Division (BEAD) for apple, grapes, and tomatoes. The chronic dietary exposure estimates are below HED's level of concern (<100% cPAD) for the general U.S. population (3.2% of the cPAD) and all population subgroups. The most highly exposed population subgroup is children 1-6 years old at 14% of the cPAD. The cancer risk estimate for the general U.S. population is 1.2×10^{-6}. For cancer dietary risk estimates, HED is generally concerned with cancer risks that exceed 1×10^{-6}. However, several conservative assumptions were included in the assessment (including ARs at levels higher than recommended tolerances to include all residues of concern; see Section 4.2.2.3 of this risk assessment). With additional refinements to the dietary exposure assessment (i.e., country-specific % import consumption data and/or monitoring data (including metabolites of concern), HED expects the estimated cancer risk to be below HED's level of concern for the general U.S. population.

Drinking Water Exposure Estimates

As this petition is for tolerances for imported commodities only, a drinking water exposure assessment was not conducted.

Aggregate Exposure Scenarios and Risk Conclusions

As this petition is for tolerances for imported commodities only, residential and drinking water exposure assessments were not conducted. Therefore, acute, chronic and cancer aggregate exposure risk assessments were not conducted.

Recommendation for Tolerances

Provided a revised Section F is submitted and a successful Agency PMV of the analytical method is reported as outlined in Section 8.0 of this risk assessment, the residue chemistry and toxicology databases support the establishment of the permanent tolerances for residues of tolylfluanid *per se* in/on the following imported RACs:

Grape	11 ppm
Hop, dried cones	30 ppm
Tomato	2.0 ppm
Apple	5.0 ppm

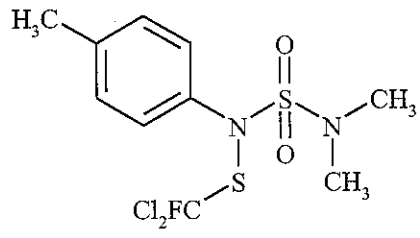
Note to RD: Language should be added to 40 CFR 180.xxx specifying that "There are no U.S. registrations for grape; hop, dried cones; tomato; and apple as of *[date of Federal Register publication]*."

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

2.1 Identification of Active Ingredient

Registrant:	Bayer Corporation and Bayer AG
Common name:	Tolylfluanid
Pesticide Type:	Fungicide
Chemical Class:	Phenylsulfamide fungicides (dichlofluanid)
Target Pests:	*Botrytis cinerea*, powdery and downy mildew, scab, early and late blight, and storage diseases such as *gleosporium*, *nectria*, and *monilia* in apples, grapes, hops, and tomatoes.
Mode of Action:	Multi-acting
Formulation:	Wettable powder (WP) and dry flowable (DF) formulations
% ai:	50
Trade Name:	Euparen M
EPA Reg No.	N/A
CAS Number:	731-27-1
PC Code:	309200
Chemical name:	(1,1-dichloro-N-[(dimethylamino)-sulfonyl]-1-fluoro-N-(4-methylphenyl)methanesulfenamide
Empirical Formula:	$C_{10}H_{13}C_{l2}FN_2O_2S_2$
Molecular Weight:	347.3

2.2 Structural Formula



Tolylfluanid

See Attachment 1 for structures of all metabolites mentioned in this risk assessment.

2.3 Physical and Chemical Properties

The following data for tolylfluanid were provided in the RD product chemistry reviews dated 29-OCT-1999 (Memo, S. Mathur; D258887) and 14-Nov-2001 (Memo, H. Podall; D276798) (note that all property values are given at 25 °C unless noted otherwise):

Appearance:	colorless, crystalline powder
Vapor Pressure:	$3.0E10^{-6}$ torr
Water Solubility:	0.90 mg/L
Partition Coefficient (Octanol/Water):	log P_{ow} = 3.93 (21 °C)
Melting Point:	93±0.2 °C
Relative Density:	1.520±0.004 g/cc
Other Registrations:	None

Tolylfluanid is a solid at room temperature with a low vapor pressure; thus, any losses due to volatilization/sublimation are expected to be minimal.

3.0 HAZARD CHARACTERIZATION

The existing toxicological database for tolylfluanid supports the establishment of permanent tolerances for residues of tolylfluanid in/on imported apples, grapes, hops and tomatoes. There are no data gaps *per se*. However, HIARC recommended the following confirmatory data:

- A comparative thyroid assay due to concern for thyroid tumors in chronic rat studies and elevated thyroid-stimulating hormone in subchronic and special studies in rats.

In addition, the CARC recommended the following confirmatory data:

- A bone marrow cytogenetic assay in order to reach definitive conclusions regarding the clastogenic potential of tolylfluanid in whole animal somatic cells.

3.1 Hazard Profile

Tolylfluanid has low acute toxicity via the oral and dermal routes. It is a severe inhalation toxicant and eye irritant. Tolylfluanid is not a skin irritant or sensitizer. The skeletal system (bones and teeth) was the primary target organ of tolylfluanid toxicity in the chronic rat and mouse studies. The liver was identified as the target organ in the developmental and reproduction studies. The thyroid was identified as the target organ in the subchronic and chronic rat studies. The rat and dog appear to be equally sensitive to the effects of tolylfluanid. The mouse is less sensitive than the rat and dog.

On May 1, 2002, the HED CARC evaluated the carcinogenic potential of tolylfluanid in accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), and classified tolylfluanid as **"likely to be carcinogenic to humans"** by the oral route, based on follicular cell thyroid tumors in high-dose male and female rats (Memo, J. Kidwell 6/10/02; TXR# 0050810). The Committee further recommended a linear low-dose extrapolation approach for the quantification of human cancer risk based on the follicular cell thyroid tumors in rats.

Tolylfluanid has been tested in *in vitro* and *in vivo* mutagenicity assays and found to induce gene mutations and chromosomal aberrations in mammalian cells. However, this mutagenic activity was not expressed in *in vivo* tests for gene mutations or chromosomal aberrations. In addition, there was no indication of DNA reactivity *in vitro* or *in vivo*. Therefore, the overall weight of the evidence does not support a mutagenic mode of action for the induction of follicular cell thyroid tumors in rats. The CARC, however, recommended conducting a bone marrow cytogenetic assay in order to reach definitive conclusions regarding the clastogenic potential of tolylfluanid in whole animal somatic cells. For more information, see the HED CARC document (TXR# 0050810).

No developmental toxicity was seen in rats at the limit dose (1000 mg/kg/day). Developmental toxicity was seen in the rabbit in the form of decreased fetal survival, increased malformations and variations at maternally toxic doses (75 mg/kg/day; HDT). In the 2-generation reproduction toxicity study, the NOAEL for the parental toxicity of 7.5 mg/kg was based on decreased body weights, body weight gains and liver weights seen at 57.5 mg/kg in the P females. Reproductive toxicity (reduced mean litter size) was also observed at this dose.

In the rat metabolism study, tolylfluanid was readily absorbed and rapidly hydrolyzed within 48 hours. Pretreatment, dose level and sex had no bearing on the absorption and excretion of tolylfluanid. Approximately 86-100% of the dose was recovered in 48 hours, with 56-80% of the dose being excreted in urine, 12-36% in the feces, and ≤0.48% found in the carcass. Urinary metabolites common to both sexes were 4-dimethylaminosulfonylamino-benzoic acid (RNH 0166; 46-78%), and 4-methylamino-benzoic acid (RNH 0416; 3-6%). Fecal compounds identified were unchanged tolylfluanid (1-19%), dimethylaminosulfotoluidid (DMST; 5-8%), RNH0166 (3-12%) and 4-methylamino-benzoic acid (RNH 0416; < 1%). The data indicate that tolylfluanid hydrolyzes to DMST, which is then transformed to the major metabolite RNH0166. RNH0166 can be further demethylated to the minor metabolite, RNH 0416. The position of the label showed different metabolic profiles. In the [dichlorofluoromethyl-^{14}C]-tolylfluanid labeled

study, the major urinary metabolite was thiazolidine-2-thione-4carbonic acid (TTCA). This metabolite resulted from cleavage of the side chain and accounted for 73-74% and 50-63%, respectively, by iv and oral routes. In the benzene-labeled study, the major metabolite was RNH0166, which accounted for 90% of urinary metabolic activity and 70% of fecal radioactivity. The structures of the aforementioned metabolites can be found in Attachment 1 of the risk assessment.

Table 1. Acute Toxicity Data on Tolylfluanid Technical.

Guideline No.	Study Type	MRID	Results	Tox Category
81-1	Acute Oral	45302604	LD_{50} > 5000 mg/kg	IV
81-2	Acute Dermal	45302611	LD_{50} > 5000 mg/kg	IV
81-3	Acute Inhalation	45302610	LC_{50} > 0.163 mg/L	II
81-4	Primary Eye Irritation	45148601	Severe irritant	II
81-5	Primary Skin Irritation	45148601	No irritation	IV
81-6	Dermal Sensitization	45336210	Skin sensitizer	N/A

Table 2. Toxicity Profile of Tolylfluanid Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity rodents (rat)	44241006, 44285806 & 45302614 (1995) **Acceptable/guideline** 0, 300, 1650, or 9000 ppm M : 0, 20.1, 108.0, or 638.9 mg/kg/day F: 0, 23.0, 131.0, or 736.1 mg/kg/day	NOAEL = 20.1 mg/kg/day (M) LOAEL = 108 mg/kg/day, based on changes in clinical blood chemistry associated with the liver and thyroid (M). NOAEL = 131 mg/kg/day (F) LOAEL = 736.1 mg/kg/day, based on changes in clinical blood chemistry associated with the liver and thyroid and decreased body weights (F).
870.3150 90-Day oral toxicity in nonrodents (dog)	44247601 (1974) **Unacceptable/guideline** 0, 400, 1000 or 3000 ppm M: 0, 8.24, 25.0 or 69.4 mg/kg/day F: 0, 8.00, 23.1 or 67.2 mg/kg/day	NOAEL = 23.1/25 mg/kg/day (F/M) LOAEL = 67.2/69.4 (F/M) mg/kg/day, based on decreased body weight gains and changes in liver structure and function in both sexes .
870.3200 21/28-Day dermal toxicity (rat)	N/A[1]	N/A
870.3250 90-Day dermal toxicity	NA	NA
870.3465 90-Day inhalation toxicity	NA	NA

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3700a Prenatal developmental in rodents (rat)	44285801 & 45302617 (1995) **Acceptable/guideline** F: 0, 100, 300, or 1000 mg/kg/day	**Maternal** NOAEL not determined LOAEL = 100 mg/kg/day, based on decreased body weight gains and food consumption. **Developmental** NOAEL = 1000 mg/kg/day (HDT) LOAEL > 1000 mg/kg/day
870.3700a Prenatal developmental in rodents (rat)	44241029 (1976) **Acceptable/guideline** F: 0, 100, 300, or 1000 mg/kg/day	**Maternal** NOAEL = 100 mg/kg/day LOAEL = 300 mg/kg/day, based on dose-related decreased body weight gains during the dosing interval. **Developmental** NOAEL > 1000 mg/kg/day (HDT) LOAEL not identified
870.3700b Prenatal developmental in nonrodents (rabbit)	44241022, 44241021, 44241023, & 45302618 (1991) **Acceptable/guideline** F: 0, 10, 25, or 70 mg/kg/day	**Maternal** NOAEL = 25 mg/kg/day LOAEL = 70 mg/kg/day, based on evidence of hepatotoxicity (increased GLDH and triglyceride levels and gross and microscopic liver pathology) and decreased food consumption and equivocal decreases in body weight gain. **Developmental** NOAEL = 25 mg/kg/day LOAEL= 70 mg/kg/day, based on increased malformations (arthrogryposis of front extremities and small orbital cavity/folded retina) and variations (floating rib and accelerated ossification.
870.3800 2-Generation Reproduction and fertility effects (rat)	44241030 & 45302620 (1995) **Acceptable/guideline** 0, 100, 700, or 4,900 ppm (equivalent to 0, 7.9 - 10.5, 57.5 - 78.0, or 449.0 - 619.0 mg/kg/day)	**Parental/Systemic** NOAEL = 7.9 - 10.5 mg/kg/day LOAEL = 57.5 - 78.0 mg/kg/day, based on decreased body weights, body weight gains, and liver weights in the P females. **Reproductive** NOAEL = 7.9 - 10.5 mg/kg/day LOAEL = 57.5 - 78.0 mg/kg/day , based on reduced litter size **Offspring** NOAEL = 7.9 - 10.5 mg/kg/day LOAEL = 57.5 - 78.0 mg/kg/day, based on decreased pup weights, increased pup deaths and related pup viability indices.
870.3800 2-Generation Reproduction and fertility effects (rat)	44285803 & 44285804 (1991) **Unacceptable/guideline** 0, or 180 ppm (equivalent to 0, or 15.9 - 21.5 mg/kg/day)	**Parental/Systemic** NOAEL not established LOAEL = 15.9 - 21.5 mg/kg/day, based on hardened crania of P generation animals. **Reproductive** NOAEL not established LOAEL = 15.9 - 21.5 mg/kg/day, based on increased clinical signs of toxicity. **Offspring** NOAEL > 15.9 - 21.5 mg/kg/day (HDT) LOAEL not established
870.3800 2-Generation Reproduction and fertility effects (rat)	44285802 & 45302621 (1989) **Acceptable/guideline** 0, 300, 1200, or 4800 ppm (equivalent to 0, 20.1 - 26.3, 83.4 - 109.5, or 335.6 - 492.4 mg/kg/day)	**Parental/Systemic** NOAEL = 20.1 - 26.3 mg/kg/day LOAEL = 83.4 - 109.5 mg/kg/day, based on decreased body weights and body weight gains. **Reproductive** NOAEL = 83.4 - 109.5 mg/kg/day LOAEL = 335.6 - 492.4 mg/kg/day, based on decreased mean litter size **Offspring** NOAEL = 20.1 - 26.3 mg/kg/day LOAEL = 83.4 - 109.5 mg/kg/day, based on decreased pup weights.

Guideline No./ *Study Type*	MRID No. (year)/ Classification /Doses	Results
870.3800 2-Generation Reproduction and fertility effects (rat)	45272701 (1980) **Acceptable/guideline** 0, 300, 1500, or 7500 ppm (equivalent to 0, 15, 75, or 375 mg/kg/day)	**Parental/Systemic** NOAEL = 75 mg/kg/day LOAEL = 375 mg/kg/day, based on decreased body weights and body weight gains for both generations. **Reproductive** NOAEL > 375 mg/kg/day (HDT) LOAEL not established **Offspring** NOAEL = 75 mg/kg/day LOAEL = 375 mg/kg/day, based on decreased survival and reduced body weights during lactation.
870.4300 Combined chronic toxicity/carcinogenicity rodents (rat)	44241027 & 45302632 (1996) **Acceptable/guideline** 0, 60, 300, 1500, or 7500 ppm M: 0, 3.6, 18.1, 90.1, or 504.2 mg/kg/day F: 0, 4.2, 21.1, 105.2, or 584.4 mg/kg/day	NOAEL = 18.1/21.1 mg/kg/day [M/F] LOAEL = 90.1/105.2 mg/kg/day (M/F), based on skeletal changes. **Evidence of thyroid follicular cell adenomas and/or carcinomas in high dose males and females.**
870.4300 Combined chronic toxicity/carcinogenicity rodents (rat)	44247602,44967801, 45634401&45634402 (1982) **Acceptable/guideline** 0, 300, 1500, or 7500 ppm M: 0, 20, 80, or 430 mg/kg/day F: 0, 20, 110, or 580 mg/kg/day	NOAEL = 20/20 mg/kg/day [M/F] LOAEL = 80/110 mg/kg/day (M/F), based on bone hyperostosis in males and females. **Evidence of thyroid follicular cell adenomas and/or carcinomas in high dose males and females.**
870.4200 Carcinogenicity rodents (mouse)	44241028 & 45302627 (1996) **Acceptable/guideline** 0, 60, 300, 1500, or 7500 ppm M: 0, 15.3, 76.3, 375.8, or 2307.6 mg/kg/day F: 0, 24.5, 123.9, 610.8, or 2962.8 mg/kg/day	NOAEL = 76.3/123.9 mg/kg/day [M/F] LOAEL = 375.8/610.8 mg/kg/day [M/F], based on skeletal, liver and kidney changes. **No evidence of carcinogenicity.**
870.4100b Chronic toxicity (dog)	44241026 (1986) **Acceptable/guideline** *M & F: 0, 2.5, or 12.5 mg/kg/day for 52* weeks, or at 62.5 mg/kg/day for 33 weeks followed by 125 mg/kg/day for 19 weeks	NOAEL = 12.5 mg/kg/day LOAEL = 62.5 mg/kg/day (M), based on decreased body *weight gains.*
870.5100 Bacterial gene mutation assay **Technical**	MRID 44241015 (1994) **Acceptable/guideline** *S. typhimurium* strains were exposed at concentrations from 1.25 to 5,000 μg/plate and were evaluated for mutagenicity at 5 - 160 μg/plate + S9 and at 1.25 to 40 μg/plate in the absence of S9.	Tolylfluanid was cytotoxic to all strains at ≥ 8 μg/plate ± S9 and precipitated from solutions in all strains at 5000 μg/plate ± S9. **There were no reproducible, dose-related differences in the number of revertant colonies in any strain or dose over the background.** Positive controls induced appropriate response.
870.5100 Bacterial gene mutation assay **Metabolite - WAK 5815**	MRID 44241016 (1994) **Acceptable/guideline** *S. typhimurium* strains were exposed at concentrations from 16 to 5,000 μg/plate + or - S9	**There was no evidence of toxicity or significant increase in mutant colonies over background in any of strains tested in either the initial or repeat mutagenicity assays.** Positive controls induced appropriate response.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.5100 Bacterial gene mutation assay **Metabolite - WAK 6550**	44241017 (1995) **Acceptable/guideline** *S. typhimurium* strains were exposed at concentrations from 16 to 5,000 μg/plate + or - S9	**There were no reproducible, dose-related differences in the number of revertant colonies in any strain or dose over the background.** Positive controls induced appropriate response.
870.5100 Bacterial gene mutation assay **Metabolite - WAK 6676**	44241018 (1995) **Acceptable/guideline** *S. typhimurium* strains were exposed at concentrations from 16 to 5,000 μg/plate + or - S9	**There was no evidence of toxicity or significant increase in the mutant colonies over background in any strain tested.** Positive controls induced the appropriate responses in the corresponding strains and in the solvent controls were consistent with the expected ranges of revertant colonies for the strains used.
870.5100 Bacterial gene mutation assay **Metabolite - WAK 6698**	44241019 (1995) **Acceptable/guideline** *S. typhimurium* strains were exposed at concentrations from 16 to 5,000 μg/plate + or - S9	Metabolite was cytotoxic at doses ≥ 158 μg/plate in the initial assay and 1,581 μg/plate in the repeat assay. **There was no evidence of a significant increase in mutant colonies over background in any strains tested in the initial or repeat mutagenicity assays.** Positive controls induced appropriate response.
870.5100 Bacterial gene mutation assay **Technical**	44241024 (1984) **Unacceptable/guideline** *Saccharomyces cerevisiae* strains S138 was tested at concentrations of 1 - 12.5, 10 - 50, or 50 - 200 μg/mL +S9 and 1 - 12.5, 10 - 100, or 10 - 50 μg/mL -S9. Strains S211∝ was tested at 1 - 12.5, 10 - 50, or 30 - 80 μg/mL +S9 and 1 - 12.5 μg/mL -S9.	Tolylfluanid was tested to cytotoxic concentrations. **Tolylfluanid showed no evidence of inducing methionine revertants in *Saccharomyces cerevisiae* strains ± S9. However, one of the tests (S211∝) was inadequate or inconsistent. Further, in the S9 activated assays, the positive controls did not elicit an adequate response, negating the test with S9 for both strains.**
870.5300 *In vitro* mammalian cell gene mutation assay **Metabolite - WAK 6698**	44241004 (1995) **Acceptable/guideline** Dose: 1.95 to 1,000 μg/mL ± S9.	The compound was tested up to cytotoxic concentrations in two independent assays (± S9). In the initial test concentrations ranged from 50 to 1,000 μg/mL ± S9. In the repeat assay concentrations ranged from 100 to 800 μg/mL - S9 and 200 to 700 μg/mL + S9. **Tolylfluanid metabolite was negative for inducing forward mutations at the TK locus in mouse L5178Y ± S9.** Positive control methyl methanosulfonate and 3-methylcholanthrene induced appropriate responses.
870.5300 *In vitro* mammalian cell gene mutation assay **Technical**	44241005 **Acceptable/guideline** CHO cells exposed at concentrations from 3.0 to 30.0 μg/mL + S9 and from 0.5 to 6.0 μg/mL - S9.	These dose levels were selected based on a preliminary cytotoxicity study conducted at 0.5 to 250 μg/mL ± S9. **Tolylfluanid has been judged to be non-mutagenic ± S9.** Positive controls induced appropriate response ± S9.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.5300 *In vitro* mammalian cell gene mutation assay **Technical**	44241008 & 45302707 (1987) **Acceptable/guideline** CH V79 cells at concentrations from 300 to 3,000 ng/mL + S9 and from 4.0 to 40.0 ng/mL - S9.	Cultures were tested to cytotoxic concentrations. **Tolylfluanid has been judged to be non-mutagenic ± S9.** Positive controls induced appropriate response ± S9.
870.5300 *In vitro* mammalian cell gene mutation assay **Technical**	44241025 (1985) **Acceptable/guideline** Mouse lymphoma cells (L5178Y TK +/-) exposed at concentrations ranging from 25 to 600 ng/mL -S9 and 50 - 12,500 ng/mL +S9.	The compound was tested up to cytotoxic concentrations (± S9). **Tolylfluanid was positive for inducing forward mutations at the TK locus in mouse L5178Y ± S9.** Positive control ethylmethane sulfonate and 3-methylcholanthrene induced appropriate responses. Colony sizing was not performed.
Mouse spot test **Technical**	44241014 (1988) **Acceptable/non-guideline**	F1 pups from female C57B1/6J mice exposed by oral gavage to tolylfluanid (98.4%) at concentration of 0, 1750, 3,500 and 7,000 mg/kg did not show difference in incidence in relative spots between the treated and controls. Systemic toxicity was observed in dams at all doses. Mortality was observed at all doses; however treatment did not affect reproductive parameters nor there was difference in litter size. Positive controls showed a clear increase in spots in the progeny.
870.5375 *In vitro* mammalian chromosome aberration test **Technical**	44241020 (1996) **Acceptable/guideline** Chinese hamster V79 cells exposed at concentrations of 0.1, 0.5, and 1.0 μg/mL - S9 and 2, 10, and 20 μg/mL +S9.	The test was conducted up to cytotoxic levels ± S9. **Tolylfluanid was weakly clastogenic in Chinese hamster V79 cells in the presence of S9 activation.** Positive control Mitomycin and cyclophosphamide induced appropriate responses.
870.5375 *In vitro* mammalian chromosome aberration test **Technical**	44241012 & 45302712 (1984) **Acceptable/guideline** Primary human lymphocytes exposed at 0.1 to 10.0 μg/mL ± S9.	Cytotoxicity was observed at concentrations 1 to 10 μg/mL - S9 and 5 to 10 μg/mL +S9. Over the ranges tested clastogenic effects included increased incidences of metaphases with aberrations including gaps, metaphases excluding gaps, metaphases with exchanges, and metaphases with polyploidy were observed. **Tolyfluanid is clastogenic both in the presence and in the absence of S9 activation.** Positive control Mitomycin and endoxan induced appropriate responses.
870.5380 *In vivo* mammalian spermatogonia chromosomal aberration test **Technical**	44241011 (1984) **Unacceptable/guideline** Male Chinese hamsters exposed at doses of 250 or 500 mg/kg/day	No mortality or clinical signs were observed at either dose. **No statistically significant increases in the frequency of chromosomal aberrations in spermatogonia were observed.**

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.5380 *In vivo* mammalian spermatogonia chromosomal aberration test **Technical**	44241032 & 45302713 (1988) **Unacceptable/guideline** Male NMRI mice dosed at 500 or 1,500 mg/kg/day	Clinical signs of toxicity and cytotoxicity to target cells were seen at 5,000 mg/kg/day. **Tolylfluanid did not induce chromosomal aberrations in spermatogonia at any dose.** Positive controls did not produce strong positive results. Therefore, sensitivity of assay is questionable and the findings of the study are equivocal.
870.5385 Mammalian bone marrow chromosomal aberration test **Technical**	44241033 (1990) **Unacceptable/guideline** Chinese hamsters dosed at a single oral dose of 4,000 mg/kg/day	3/10 animals died but exhibited no clinical signs. No cytotoxicity was observed at the dose tested. Positive controls induced appropriate response. Inadequate sampling time and no indication of test material present at target site; therefore, data not valid for regulatory purposes.
870.5385 Mammalian bone marrow chromosomal aberration test **Technical**	44241010 & 45302716 (1990) **Unacceptable/guideline** Chinese hamsters dosed at a single oral dose of 4,000 mg/kg/day	3/10 of 10 animals died but no clinical signs of toxicity were observed at the dose tested. Test results were erratic. Positive controls induced appropriate response. Inadequate study since test samples were not analyzed and doses were not high enough to produce toxicity.
870.5395 Mammalian erythrocyte micronucleus assay **Technical**	44241009 (1980) **Unacceptable/guideline** NMRI mice were administered split doses of 250 or 500 mg/kg in 1% Cremophor by oral intubation.	No clinical signs of toxicity was observed and was not toxic to the target tissue. **Treatment with tolylfluanid did not induce micronucleated polychromatic erythrocytes.** Inadequate methods and methodology.
870.5450 Dominant lethal assay - mice **Technical**	44241013 (1986) **Unacceptable but upgradable with receipt of positive control data** Male NMRI mice were orally exposed at doses of 4,000 or 8,000 mg/kg and mated sequentially to female mice	Did not induce variations in any dominant lethal parameters nor any reduced fertility. Inadequate study. No positive control data.
870.5915 *In vivo* Sister chromatid exchange assay **Technical**	44241031 & 45302722 (1988) **Acceptable/guideline** Male and female NMRI mice dosed at 0, 500, 1670, or 5000 mg/kg	Mortality at 500 mg/kg and above. Tolylfluanid did not induce sister chromatid exchange at any dose level. Positive control cyclophosphamide responded appropriately.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.5500 Other Genotoxic Effects UDS in mammalian cells **Technical**	44241003 (1995) **Acceptable/guideline** 0, 2.5, 5.0, 10.0, 12.5, 15.0, 17.5, or 20 µg/ml	**Tolylfluanid did not induce UDS up to 15.0 µg/mL.** The 17.5 and 20 µg/mL doses were highly toxic. The positive control 2-acetylaminofluorene responded appropriately.
870.6200a Acute neurotoxicity screening battery (rat)	45302723 & 45302725 (1994) **Acceptable/guideline** Dose (mg/kg): 0, 500, 1000 or 2000 (♂&♀) and 0, 50, or 150 (♀)	NOAEL = 50 mg/kg in females LOAEL = 150 mg/kg/day based on FOB effects and decreased motor and locomotor activity in females. NOAEL = 2000 mg/kg/day (M) - Limit Dose LOAEL - not established (M).
870.6200b Subchronic neurotoxicity screening battery (rat)	44241007, & 45302724 - 45302726 (1995) **Acceptable/guideline** Dose (mg/kg): M: 0, 20, 109, or 620 F: 0, 25, 134, or 771	NOAEL = 25 mg/kg (F) LOAEL = 134 mg/kg based on decreased mean body weights in females. No treatment-related neurotoxicological effects were observed at any treatment level.
870.6300 Developmental neurotoxicity	NA	NA
870.7485 Metabolism and pharmacokinetics (rat)	41819014 & 44285805 (1991) **Acceptable/guideline** M & F: 2 or 100 mg/kg single oral dose, -single gavage dose of 2 mg/kg for 14 days followed by labeled 2 mg/kg	In a metabolism study in rats, tolylfluanid was administered in single doses of 2 or 100 mg /kg of body weight, was readily absorbed and rapidly hydrolyzed within 48 hours. Absorption and excretion were independent of dose, sex and pretreatment. About 86 - 100% of the dose was recovered in 48 hours, with 56 - 80% of the dose being excreted in urine, 12 - 36% in the feces, and ≤ 0.48% found in the carcass. Urinary metabolite common to both sexes were dimethylaminosulfonylamino-benzoic acid (RNH 0166; 46 - 78%), and 4-methylamino-benzoic acid (RNH 0416; 3 - 6%). Fecal compounds identified were unchanged tolylfluanid (1 - 19%), dimethylaminosulfotoluidid (DMST; 5 - 8%), RNH 0166 (3 - 12%) and RNH 0416 (< 1%). The data indicate that tolylfluanid hydrolyzed to DMST, which is then transformed to the major metabolite RNH 0166, which can be further demethylated to the minor metabolite, RNH 0416 (MRID No. 44285805).

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485 Metabolism and pharmacokinetics (rat)	45302728 - 45302732 (1977 - 1988) ^{14}C-tolylfluanid labeled on the benzene ring or [dichlorofluoromethyl-^{14}C]-tolylfluanid were administered intravenously (10 or 20 mg/kg), intraduodenally (0.5 mg/kg), or orally (0.1, 5, or 20 mg/kg) to groups of male Wistar rats. **Biokinetics study** male and female rats were given [phenyl-UL-^{14}C]-tolyfluanid in a single oral doses of 2 or 20 mg/kg, or 14-day repeat doses of 2 mg/kg.	Series of metabolism studies showed that metabolic profile dependent upon label position. With [dichlorofluoromethyl-^{14}C]-tolylfluanid labeling major urinary metabolite was thiazolidine-2-thione-4carbonic acid resulting from cleavage of the side chain and accounted for 73 - 74% and 50 - 63%, respectively by iv and oral routes. Benzene ring label resulted in metabolite 4-(dimethylamino-sulfonylamino) benzoic acid which accounted for 90% of urinary metabolic activity and 70% of fecal radioactivity. The study with single oral dose of 2 or 20 mg/kg/day also supported the results of the main study (MRID No.44285805).
870.7600 Dermal penetration	NA	NA
Non-guideline - Rat Thyroid function	45302615 (1988) **Acceptable/nonguideline** 0,300, 1500, or 7500 ppm M:0, 20.6, 119.3, or 677.9 mg/kg/day F: 0, 22.1, 118.8, or 752.4 mg/kg/day	Thyroid-stimulating hormone levels significantly increased (168 - 425%) in high-dose males and females. Slightly increased T3 levels in males rats above 119.3 mg/kg/day.
Non-guideline - mice *In vitro* investigation of TTCA goitrogenic properties **Metabolite**	45302634 (1995) **Acceptable/nonguideline**	Tolylfluanid's metabolite TTCA was shown to reversibly inhibit thyroid peroxidase (TPO)-mediated reactions involved with the initial stages of thyroid hormone synthesis. This was shown by the dose-dependent decrease in formation of reactive iodine; the interference of the nonenzymatic and TPO-mediated iodination of L-tyrosine, and by TPO-mediated metabolism of TTCA. In the latter reaction, TTCA did not interfere with tyrosine iodination when the concentration in the reaction mixture fell below a certain concentration. Therefore, TTCA, unlike tolylfluanid, behaves as a goitrogenic compound with a potency approximately equal to propylthiouracil (PTU), a known thionamide inhibitor of initial thyroid hormone synthesis.
Non-guideline - rat ^{32}P-Postlabelling assay	45336212 (1997) **Acceptable/nonguideline** 0, 1500 or 7500 ppm for 21 days in males	In a ^{32}P-postlabelling assay for detection of adduct formation in lung, thyroid, and liver DNA in rats revealed that there was no evidence of DNA adduct formation in the liver, lung, or thyroid of rats exposed to Tolylfluanid. Positive control 2-Acetylaminofluorene (2-AAF) (liver, lung, and thyroid DNA adducts), benzidine (lung DNA adducts), 2-Thiourea (lung and thyroid DNA adducts), and dibenz[a,h]anthracene (DBA) (DNA adducts in the lungs) produced appropriate results.

[1] NA = Not Applicable.

3.2 FQPA Considerations

On 6/17/02, the FQPA SFC recommended a **UF_{DB} of 3x be applied to the acute and chronic RfDs** in order to address the data requirement for the comparative thyroid assay (adult versus young animals) (Memo, B. Tarplee, 8/1/02; TXR NO. 0051023). The FQPA SFC based this recommendation on the following:

> The consensus of the FQPA Safety Factor Committee was that an additional traditional UF is needed until the comparative data are available and demonstrate that the young are not more sensitive with regard to thyroid effects. The committee agreed that a **database uncertainty factor of 3X** is adequate in this case since the thyroid hormone changes were observed at a dose level more than 3-fold higher than the dose levels (based on developmental and reproductive toxicity) used as the basis for endpoints for risk assessment.

Taking into account the recommendation regarding the data deficiency, the FQPA SFC recommends that no **Special FQPA safety factor** is necessary to protect the safety of infants and children in assessing tolylfluanid exposure and risks. The FQPA SFC based this recommendation on the following:

> The toxicology database for Tolylfluanid contains acceptable guideline developmental and reproduction studies as well as acute and subchronic neurotoxicity studies. HIARC concluded that there is no quantitative or qualitative evidence of increased susceptibility following *in utero* exposure in the prenatal developmental study in rats. Although there is qualitative evidence of increased susceptibility in the prenatal developmental study in rabbits and in the 2-generation reproduction study in rats, the HIARC did not identify any residual uncertainties after establishing toxicity endpoints and traditional UFs to be used in the risk assessment of tolylfluanid. The RfDs established are protective of pre-/postnatal toxicity following acute and chronic exposures.

A summary of the FQPA safety factors chosen for tolylfluanid is provided in Table 3.

Table 3. Summary of FQPA Safety Factors for Tolylfluanid.

	LOAEL to NOAEL (UF_L)	**Subchronic to Chronic (UF_S)**	**Incomplete Database (UF_{DB})**	**Special FQPA Safety Factor (Hazard and Exposure)**
Magnitude of Factor	1X	1X	**3X**	**1X**
Rationale for the Factor	No LOAEL to NOAEL extrapolations performed	No subchronic to Chronic extrapolations performed	**Lack of comparative thyroid assay (adult versus young animals)**	**No residual uncertainties regarding pre- or post-natal toxicity or completeness of the toxicity or exposure databases**
Endpoints to which the Factor is Applied	Not Applicable	Not Applicable	**All dietary exposure scenarios**	**Not Applicable**

3.3 Dose-Response Assessment

This petition is for tolerances for imported commodities only. Therefore, since there is no concern for incidental oral, dermal or inhalation exposure for all durations, HIARC did not select endpoints for these scenarios.

Acute Dietary Endpoint (Females 13-50 years old): The rabbit developmental study was used to select the endpoint for establishing the acute RfD of 0.083 mg/kg/day. The developmental NOAEL of 25 mg/kg/day was based on increased malformations (arthrogryposis of front extremities and small orbital cavity/folded retina) and variations (floating rib and accelerated ossification) seen at 70 mg/kg/day (LOAEL). The endpoint, increased malformations and variations, is presumed to occur following a single exposure and is applicable only to females 13 - 50 years old. A 300-fold UF (3x UF_{DB}; 10x for interspecies extrapolation and 10x for intraspecies variation) was incorporated into the acute RfD for females 13-50 years old. The FQPA SFC determined that a special FQPA safety factor of 1x is applicable for acute dietary risk assessment for females 13-50 years old. Thus, the aPAD is 0.083 mg/kg/day.

Acute Dietary Endpoint (General U.S. Population, Including Infants and Children): Two complimentary acute rat oral neurotoxicity studies were used to select the endpoint for establishing the acute RfD of 0.17 mg/kg/day. The NOAEL of 50 mg/kg/day was based on FOB effects and decreased motor and locomotor activity seen at 150 mg/kg/day (LOAEL). The decreased motor and locomotor activity and FOB effects were seen after a single exposure and is appropriate for this risk assessment. A 300-fold UF (3x UF_{DB}; 10x for interspecies extrapolation and 10x for intraspecies variation) was incorporated into the acute RfD for females 13-50 years old. The FQPA SFC determined that a special FQPA safety factor of 1x is applicable for acute dietary risk assessment for the general U.S. population. Thus, the aPAD is 0.17 mg/kg/day.

Chronic Dietary Endpoint: The 2-generation rat reproduction study was used to select the endpoint for establishing the chronic RfD of 0.026 mg/kg/day. The parental toxicity NOAEL of 7.9 mg/kg/day was based on decreased body weights, body weight gains and liver weights observed at 57.5 mg/kg/day (LOAEL). This study has the lowest NOAEL in the database and is of appropriate duration for this exposure scenario. A 300-fold UF (3x UF_{DB}; 10x for interspecies extrapolation and 10x for intraspecies variation) was incorporated into the chronic RfD. The FQPA SFC determined that a special FQPA safety factor of 1x is applicable for chronic dietary risk assessment. Thus, the cPAD is 0.026 mg/kg/day.

Carcinogenicity: On May 1, 2002, the HED CARC evaluated the carcinogenic potential of tolylfluanid in accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), and classified tolylfluanid as **"likely to be carcinogenic to humans"** by the oral route, based on follicular cell thyroid tumors in high-dose male and female rats. The Committee further recommended a linear low-dose extrapolation approach for the quantification of human cancer risk based on the follicular cell thyroid tumors in rats. The unit risk, Q_1^*, of tolylfluanid based upon male rat thyroid adenomas and/or carcinomas combined tumor rates is 1.59×10^{-3} in human equivalents (Memo, L. Brunsman 6/12/02; TXR# 0050791).

Recommendation for Aggregate Exposure Risk Assessments: There are no residential uses. As this petition is for tolerances for imported commodities only, endpoints for dermal and inhalation exposures were not selected. Therefore, aggregate exposure risk assessment is not applicable.

The doses and toxicological endpoints selected for the dietary exposure scenarios are summarized in Table 4.

Table 4. Summary of Toxicological Dose and Endpoints for Tolylfluanid for Use in Human Health Risk Assessment[1].

Exposure Scenario	Dose (mg/kg/day) UF /MOE	Hazard Based Special FQPA Safety Factor	Endpoint for Risk Assessment
Dietary Risk Assessments			
Acute Dietary females 13-50 years of age	NOAEL = 25 UF = 300 **Acute RfD = aPAD =** 0.083 mg/kg/day	1x	Prenatal Developmental Toxicity/Rabbit LOAEL = 70 mg/kg/day based on increased malformations (arthrogryposis of front extremities and small orbital cavity/folded retina) and variations (floating ribs and accelerated ossification).
Acute Dietary general population including infants and children	NOAEL = 50 UF = 300 **Acute RfD = aPAD =** 0.17 mg/kg/day	1x	Acute Oral Neurotoxicity/Rat LOAEL = 150 mg/kg/day based on FOB effects (pilorection, decreased activity, gait abnormalities, decreased body temperature and/or decreased rearing).
Chronic Dietary all populations	NOAEL= 7.9 UF = 300 **Chronic RfD = cPAD =** 0.026 mg/kg/day	1x	2-Generation Reproduction/Rat LOAEL = 57.5 mg/kg/day based on decreased body weights, body weight gains and liver weights.
Cancer	**Classification: "likely to be carcinogenic to humans"** by the oral route, based on thyroid tumors in high-dose male and female rats. The Committee further recommended a linear low-dose extrapolation approach for the quantification of human cancer risk based on the thyroid tumors in rats. Q_1^* = 1.59 x 10^{-3} based upon male rat thyroid adenomas and/or carcinomas combined.		

[1] UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose.

3.4 Endocrine Disruption

EPA is required under the Federal Food Drug and Cosmetic Act (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 the recommendations of its Endocrine Disruptor Screening and

Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases 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 has 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).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, tolylfluanid may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Proposed Uses

Tolylfluanid is currently registered for use on apples, grapes and tomatoes in several European countries. The use patterns vary depending on crop and country. The application rate ranges from 0.89 to 2.7 lb. ai/A; the number of applications per season ranges from 2 to 15; the retreatment interval (RTI) ranges from 5 to 7 days; and the preharvest interval (PHI) ranges from 3 to 35 days. Applications can be made using ground and aerial equipment; however, aerial applications are not common in Europe. Tolylfluanid is registered for use on tomatoes in greenhouses in Belgium and the Netherlands.

Apples: Apples may be treated up to 15 times/season with tolylfluanid (DF and WP) at 1.0 lb. ai/A or up to 3 times/season at 1.3 lb. ai/A. The RTI is 10 days and the PHI is 7 days.

Grapes: Grapes may be treated 2 to 8 times/seasons with tolylfluanid (DF and WP) at application rates ranging from 1.3 to 1.8 lb. ai/A, depending on the region. The RTI ranges from 7 to 10 days and the PHI from 14 to 35 days, depending on the country.

Tomatoes: Tomatoes may be treated 3 to 4 times/season with tolylfluanid (DF and WP) at 1.1 lb. ai/A or 6 times/season at 1.3 lb. ai/A. The RTI ranges from 5 to 10 days and the PHI from 3 to 7 days, depending on the region.

Hops: Hops may be treated a maximum of 6 times/season (3 will be recommended) with tolylfluanid (DF and WP) at 2.7 lb. ai/A. The RTI and PHI are 10 and 14 days, respectively.

Label Deficiencies: The petitioners have provided translated end-use product labels and a summary of tolylfluanid uses registered in Europe for use on apples, grapes, hops, and tomatoes. The proposed use directions are adequate and are supported by the submitted residue data.

4.2 Dietary Exposure/Risk Pathway

The residue chemistry data submitted in support of the tolerances for residues of tolylfluanid in/on imported apples, grapes, hops and tomatoes were reviewed in the HED memorandum dated 8/14/02 (Memo in progress, J. Tyler; D237220).

4.2.1 Residue Profile

Background

There are currently no registered or proposed uses of tolylfluanid in the U.S. The petitioners have submitted a petition for the establishment of permanent tolerances for residues of tolylfluanid, expressed as the parent *per se*, in/on the following imported RACs:

Apples	5 ppm
Grapes	5 ppm
Hops	30 ppm
Tomato	1 ppm

Nature of the Residue

Plants: The nature of the residue in apple, grape, lettuce, and strawberry is adequately understood. The submitted metabolism studies will support the tolerance petition for the proposed uses. The metabolic pathways of tolylfluanid in the above crops appear to be qualitatively similar. Metabolism is very slow in apples and lettuce. By contrast, grapes showed the most extensive metabolism, which the registrants attribute to a longer PHI. For most crops tested, the majority of radioactive residues remained on the surface of either fruits or leaves. Tolylfluanid is initially converted to DMST by cleavage of the dichlorofluorosulfenyl side chain. DMST then undergoes hydroxylation of the phenyl ring or the 4-methyl group. The resulting hydroxylated metabolites are then conjugated to form a variety of glycosidic conjugates of hydroxylated-DMST.

On 5/29/02, the results of the apple, grape, lettuce, and strawberry metabolism studies were presented to the HED Metabolism Assessment Review Committee (MARC) (Memo, J. Tyler, et.al. 5/22/02; D282891). The MARC concluded that tolylfluanid *per se* should be included in the **tolerance expression** for plants (Memo, J. Tyler 7/30/02; D282892).

The MARC determined that the residues of concern in plants for the **risk assessment** are parent and TTCA due to its goitrogenic effects, which could be related to the formation of thyroid follicular cell tumors in rats. Although the MARC expressed concerns with the toxicity of TTCA, there are no adequate plant metabolism or magnitude of the residue data available to assess the likely levels of TTCA. The plant metabolism studies identified DMST, and the glucoside conjugates of 4-hydroxymethyl-DMST, 2-hydroxyphenyl-DMST as the major metabolites. According to the proposed metabolic pathway, tolylfluanid is cleaved to form TTCA and DMST (see Attachment 2). DMST then undergoes hydroxylation of the phenyl ring or the 4-methyl group, and the resulting hydroxylated metabolites are then conjugated to form a

variety of glycosidic conjugates of hydroxylated-DMST. Therefore, upon cleavage, one molecule of the parent is expected to produce one molecule each of TTCA and DMST. The MARC recommended that the sum of DMST, and the glucoside conjugates of 4-hydroxymethyl-DMST and 2-hydroxyphenyl-DMST be used as a surrogate measure of TTCA in the risk assessment for plants. The Committee noted that the glycosidic conjugates of hydroxolated-DMST are expected to be significantly less toxic than the parent due to the absence of the dichlorofluoromethylthio side chain, which is believed to generate thiophosgene which in turn leads to TTCA. Therefore, tolylfluanid, DMST, and the glucoside conjugates of 4-hydroxymethyl-DMST, 2-hydroxyphenyl-DMST, and 3-hydroxyphenyl-DMST should be included in the risk assessment for plant commodities. The structures of the aforementioned metabolites can be found in Attachment 1 of the risk assessment.

Residues of the glucoside conjugates of 4-hydroxymethyl-DMST and 2-hydroxyphenyl-DMST were determined in the grape crop field trial study only. Therefore, the MARC recommended that the risk assessment team use the residue proportion of the glucoside conjugate to the parent compound in the grape field trial study in order to calculate the anticipated glucoside conjugate residues in apple, hop and tomato field trials.

Livestock: The submitted goat metabolism study is acceptable. Following three consecutive daily doses of [^{14}C]tolylfluanid to a lactating goat at 250 ppm (25x and 50x the maximum theoretical dietary burden (MTDB; parent and additional metabolites of concern not in tolerance expression) for beef and dairy cattle, respectively), the total radioactive residues (TRRs) were 0.036-0.066 ppm in morning milk and 0.138-0.240 ppm in evening milk collected 2-8 hours after dosing. The TRR in tissues ranged from 0.527 ppm in muscle to 37.0 ppm in kidney. The parent tolylfluanid was not detected in milk or tissues. The major metabolites identified in all matrices were RNH0166 and its glycine conjugate N-[4-(dimethylaminosulfonylamido)benzoyl]glycine (WAK 6426). In addition, DMST was a major metabolite in fat. Minor amounts of hydroxyl-, acid, and conjugated metabolites were present in all matrices. The petitioner proposes that tolylfluanid in ruminants is metabolized via cleavage of the dichlorofluorosulfenyl moiety to yield DMST, which may subsequently be de-methylated to WAK 5767. Either of these metabolites may form hydroxylated intermediates, which are subsequently oxidized to the respective acids and conjugated with glycine. The methylaminosulfonyl-phenyl portion of the molecule remains intact and no free aniline is produced.

On 5/29/02, the results of the lactating goat metabolism study were presented to the MARC (Memo, J. Tyler et.al. 5/22/02; D282891). The MARC determined that the residues of concern in livestock for the risk assessment are parent and TTCA due to its goitrogenic effects, which could be related to the formation of thyroid follicular cell tumors in rats (Memo, J. Tyler 7/30/02; D282892). Although the MARC expressed concerns with the toxicity of TTCA, there are no adequate livestock metabolism data available to assess the likely levels of TTCA. The lactating goat metabolism study identified WAK 6426 and RNH0166 as the major metabolites. According to the proposed metabolic pathway, tolylfluanid is cleaved to form TTCA and DMST (see Attachment 2). DMST may form hydroxylated intermediates, which are subsequently oxidized to the respective acids and conjugated with glycine. In a manner similar to that of the plants, one molecule of the parent is expected to produce one molecule each of TTCA and DMST. The MARC recommended that the sum of the metabolites WAK 6426 and RNH0166 be used as a

surrogate measure for TTCA in the risk assessment for livestock. The MARC concluded that tolylfluanid, and the metabolites WAK 6426 and RNH0166 should be included in the risk assessment for livestock commodities. The structures of the aforementioned metabolites can be found in Attachment 1 of the risk assessment.

There are no poultry feed items associated with any of the imported crops for which tolerances for tolylfluanid residues are proposed.

Residue Analytical Methods

Plants: The petitioners have proposed a gas chromatograph (GC)/ thermal ionization detector (TID) method designated as Method 00441 and entitled "Determination of Tolylfluanid in/on Various Raw Agricultural and Processed Commodities" for use as an enforcement method for plant commodities. The reported limits of quantitation (LOQs) for tolylfluanid and DMST were each 0.02 ppm for most matrices, 0.05 ppm for raisins and wet apple pomace, 0.5 ppm for green hop cones, and 1.0 ppm for dried hop cones. Although the method is capable of determining residues of tolylfluanid and DMST, the method validation conducted by the petitioners only analyzed for the parent compound. The validation data indicate that Method 00441 can adequately recover residues of tolylfluanid from tested plant commodities.

An independent laboratory validation (ILV) of Method 00441 was performed by ABC Laboratories (Columbia, MO). Acceptable recoveries were obtained by the laboratory; only the parent compound was determined using grape and dried hop cones as the matrices. The GC/TID method has been forwarded to the Analytical Chemistry Branch (ACB) of BEAD for a PMV (Memo, J. Tyler 12/18/01; D267306). Provided that the method is successfully validated by the Agency, HED concludes that the requirements for a plant enforcement method have been fulfilled for the purpose of permanent tolerances for residues in/on the proposed imported commodities.

Livestock The petitioners have proposed a GC/electron capture detection (ECD) method designated as Method 00435 for use as an enforcement method for livestock commodities. Apple wet pomace is the only feed commodity resulting from the proposed tolylfluanid uses. On 5/29/02, the MARC concluded that tolerances for livestock are not needed at this time. Based on the proposed uses, a residue enforcement method for livestock commodities is not necessary at this time.

Multiresidue Method (MRM)

The petitioners submitted the data concerning the recovery of tolylfluanid residues using the Food and Drug Administration (FDA) MRM protocols (PAM Vol. I) and following modified cleanup procedures. These results indicate that tolylfluanid is likely to be recovered through FDA MRM Protocols D and E. The results have been forwarded to the FDA for inclusion in the Pesticide Analytical Method Volume I (PAM I) (J. Tyler 3/27/01; D273621).

Magnitude of Residues in Plants

Apples: The geographic representation and number of apple field trials are adequate for the establishment of a tolerance for imported apples. The data indicate that residues of tolylfluanid will not exceed the proposed tolerance of 5.0 ppm in/on apples: (a) grown in *Germany* and harvested 0-21 days following the last of 15 foliar applications of the 50% WP formulation, using ground equipment, at 1.0 lb ai/A/application (equivalent to a total application rate of 15.0 lb ai/A); and (b) grown in *France, Germany, Italy, the Netherlands, and Spain* and harvested 0-14 days following the last of 3-15 foliar applications of the 50% DF formulation, using ground equipment, at 1.0-1.34 lb ai/A/application (equivalent to a total application rate of 4.02-15.0 lb ai/A). The application rates of 1.0-1.34 lb ai/A are 1x the maximum single application rates listed in the summary of proposed and registered foreign uses of tolylfluanid provided by the petitioners. Although the data indicate that residues will be less than the proposed tolerance of 5.0 ppm, HED recommends in favor of this tolerance in order to harmonize with the current Codex Maximum Residue Limit (MRL) for pome fruit. **HED notes that the correct commodity definition is "apple." A revised Section F should be submitted to include the correct commodity definition.**

Grapes: The geographic representation and number of field trials are adequate for the establishment of a tolerance for imported grapes. The data indicate that residues of tolylfluanid will not exceed 11 ppm in/on grapes: (a) grown in *Chile* and harvested 14 days following the last of 2 foliar applications of the 50% WP formulation, using ground equipment, at 1.3 lb ai/A/application (equivalent to a total application rate of 2.6 lb ai/A); (b) grown in *Southern Europe (S. France, Italy, Spain, Portugal and Greece)* and harvested 21 days following the last of 3 foliar applications of the 50% WP formulation, using ground equipment, at 1.8 lb ai/A/application (equivalent to a total application rate of 5.4 lb ai/A); and (c) grown in *Northern Europe (N. France, Germany, Italy, and Switzerland)* and harvested 35 days following the last of up to 8 foliar applications of the 50% DF formulation, using ground equipment, at 1.6 lb ai/A/application (equivalent to a total application rate of 12.8 lb ai/A). **HED notes that the correct commodity definition is "grape." A revised Section F should be submitted to include the correct commodity definition and the following tolerance:**

Grape ..... 11 ppm

Hops: The geographic representation and number of field trials are adequate to set a tolerance for imported hops. The data indicate that residues of tolylfluanid will not exceed the proposed tolerance of 30 ppm in/on hops grown in *Germany* and harvested 13-14 days following the last of six applications of the 50% DF formulation, using ground equipment, at 0.892-2.68 lb ai/A/application (equivalent to a total application rate of 10.7 lb ai/A). Residues of tolylfluanid were 3.8-20.0 ppm and 2.79-27.0 ppm in/on green hop cones and dried hop cones, respectively, harvested 13-14 days (proposed PHI is 14 days) following 6 applications of the 50% DF formulation at 0.892-2.68 lb ai/A/application (0.33-1x the maximum proposed single application rate and 0.7x the maximum proposed seasonal rate). **HED notes that the correct commodity definition is "hop, dried cones." A revised Section F should be submitted to include the correct commodity definition.**

Tomatoes: The geographic representation and number of field trials are adequate for the establishment of a tolerance for imported tomatoes. The submitted tomato trials indicate that residues of tolylfluanid will not exceed a tolerance of 1.0 ppm in/on tomatoes: (a) grown in *Mexico* and harvested 3 days following the last of four applications of the 50% WP formulation, using ground equipment, at 1.34 lb ai/A/application (equivalent to a total application rate of 5.35 lb ai/A; 1x the proposed maximum seasonal rate for Latin America); (b) grown in *Spain* under greenhouse conditions and harvested 0-7 days following the last of three applications of the 50% WP formulation, using ground equipment, at 1.07-1.25 lb ai/A/application (equivalent to a total application rate of 3.57 lb ai/A); and (c) grown in *France, Germany, Italy, and Spain* and harvested 7 days following the last of 1-6 applications of the 50% DF formulation, using ground equipment, at 0.535-5.35 lb ai/A/application (equivalent to a total application rate of 2.68-6.16 lb ai/A; 0.4-0.9x the proposed maximum seasonal rate excluding the Netherlands). Although the submitted tomato trials indicate that residues of tolylfluanid will not exceed the proposed tolerance of 1.0 ppm in/on tomatoes, HED recommends that a tolerance of 2.0 ppm be established in order to harmonize with the current Codex MRL on tomato. **HED notes that the correct commodity definition is "tomato." A revised Section F should be submitted to include the correct commodity definition and the following tolerance:**

Tomato ..... 2.0 ppm

Magnitude of Residues in Processed Commodities

Apples: The submitted apple processing data are adequate and indicate that tolylfluanid does not concentrate in juice and sauce processed from treated apples. Therefore, tolerances on these commodities are not needed. The submitted data also indicate that residues of tolylfluanid concentrate 5.3-10.9x in dry pomace processed from apples bearing detectable residues. However, as dry apple pomace is no longer considered significant food/feed items (OPPTS 860.1000, Table 1), a tolerance is not needed.

The data indicate that residues of tolylfluanid concentrate 1.5-4.3x in wet pomace processed from apples bearing detectable residues. Based on the available field trial data, the highest average field trial (HAFT) residue for apples, harvested 7 days following treatment at or below the maximum proposed seasonal application rate (15.0 lb ai/A), is 2.4 ppm. Theoretically, the maximum tolylfluanid residues expected in wet apple pomace may be calculated by multiplying the HAFT residue and the average concentration factor of 2.9x. Based on the highest expected residues of 6.96 ppm, a tolerance of 7 ppm for residues of tolylfluanid in wet apple pomace is appropriate. As wet apple pomace is not likely to be imported into the U.S., setting a tolerance on this commodity is not necessary. However, it may be used as a livestock feed item overseas, and meat and meat byproducts from livestock that could potentially be fed this commodity could then be imported to the U.S. Therefore, wet apple pomace will be included in the risk assessment as a livestock feed item.

Grapes: The submitted grape processing data are adequate. The data indicate that residues of tolylfluanid do not concentrate in raisins and juice processed from grapes bearing detectable residues; no tolerances are required for the processed commodities of grapes. The submitted data also indicate that residues of tolylfluanid may concentrate in raisin waste (5.5-13x), wet pomace

(1-17x), and dry pomace (1.2-17x) processed from treated grapes. However, as grape raisin waste, and wet and dry pomace are no longer considered significant food/feed items (OPPTS 860.1000, Table 1), tolerances for these items are not required.

Tomatoes: The submitted tomato processing data are adequate. The data indicate that residues of tolylfluanid do not concentrate in paste, puree and juice processed from tomatoes bearing detectable residues. Therefore, no tolerances are required for these processed commodities of tomatoes. The submitted data indicate that residues of tolylfluanid concentrate 0.6-4.9x in wet pomace and 2.4-11.9x in dry pomace processed from tomatoes bearing detectable residues. However, as wet and dry pomace are no longer considered significant food/feed items (OPPTS 860.1000, Table 1), tolerances are not required.

Magnitude of Residues in Meat, Milk, Poultry and Eggs (MMPE)

No livestock feeding studies were submitted in this petition, and apple wet pomace is the only ruminant feed commodity resulting from the proposed uses for tolylfluanid. In a memo dated 3/27/96, HED granted a waiver request for ruminant feeding study (Memo, G. Herndon; D224125). This waiver was granted under the assumption that the residue of concern in livestock commodities would be determined to be tolylfluanid *per se*. However, the MARC determined that additional metabolites in livestock are of toxicological concern and should be included in the risk assessment. However, based on the limited use of tolylfluanid on livestock feed items, the HED Risk Assessment Review Committee (RARC) recommended that livestock commodities not be included in the dietary exposure assessment (see 4.4.2 for rationale). HED notes that if in the future tolylfluanid is proposed for use on additional livestock feed items, then ARs (parent and additional metabolites of concern not in tolerance expression) for livestock commodities may need to be included in the dietary exposure assessment.

There are no poultry feed items associated with this petition. Therefore, data pertaining to the magnitude of tolylfluanid residues in poultry commodities are not required.

Confined and Field Accumulation in Rotational Crops

No confined or field rotational crop studies were submitted with this petition. These studies are not required for the purposes of this tolerance petition.

International Harmonization of Tolerances

There are no Canadian or Mexican MRLs established for tolylfluanid residues in/on crop commodities. The Codex Alimentarius Commission has established MRLs for tolylfluanid residues in/on various commodities, including currants (black, red, and white) at 5 ppm, gherkin at 2 ppm, lettuce (head) at 1 ppm, pome fruits at 5 ppm, strawberries at 3 ppm, and tomatoes at 2 ppm. The Codex MRLs are expressed in terms of tolylfluanid *per se*. Although the submitted residue data support the proposed tolerance of 1.0 ppm on tomatoes, HED recommends this tolerance be increased to 2.0 ppm in order to harmonize with the current Codex MRL. Therefore, no compatibility issues exist with regard to the recommended U.S. tolerances discussed in this petition review.

4.2.2 Dietary Exposure Analyses

Tolylfluanid acute, chronic and cancer dietary exposure assessments were conducted using the DEEM™ software Version 7.76, which incorporates consumption data from USDA's CSFII, 1989-1992. The 1989-92 data are based on the reported consumption of more than 10,000 individuals over three consecutive days; and, therefore, represent more than 30,000 unique "person days" of data. Foods "as consumed" (i.e., apple pie) are linked to RACs and their food forms (i.e., apples-cooked/canned or wheat-flour) by recipe translation files internal to the DEEM software. Consumption data are averaged for the entire U.S. population and within population subgroups for chronic exposure assessment, but are retained as individual consumption events for acute exposure assessment.

For acute exposure assessments, individual one-day food consumption data are used on an individual-by-individual basis. The reported consumption amounts of each food item can be multiplied by a residue point estimate and summed to obtain a total daily pesticide exposure for a deterministic (Tier 1 or Tier 2) exposure assessment, or "matched" in multiple random pairings with residue values and then summed in a probabilistic (Tier 3/4) assessment. The resulting distribution of exposures is expressed as a percentage of the aPAD on both a user (i.e., those who reported eating relevant commodities/food forms) and a per-capita (i.e., those who reported eating the relevant commodities as well as those who did not) basis. In accordance with HED policy, per capita exposure and risk are reported for all tiers of analysis. However, for Tiers 1 and 2, significant differences in user vs. per capita exposure and risk are identified and noted in the risk assessment.

For chronic exposure and risk assessment, an estimate of the residue level in each food or food-form (i.e., orange or orange-juice) on the commodity residue list is multiplied by the average daily consumption estimate for that food/food form. The resulting residue consumption estimate for each food/food form is summed with the residue consumption estimates for all other food/food forms on the commodity residue list to arrive at the total estimated exposure. Exposure estimates are expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

The results of the acute, chronic and cancer assessments are listed in Table 6. HED notes that there is a degree of uncertainty in extrapolating exposures for certain population subgroups which may not be sufficiently represented in the consumption surveys (i.e., nursing infants). Therefore, risks estimated for these subpopulations were included in representative populations having sufficient numbers of survey respondents (*i.e.*, all infants or females 13-50 years old). Thus, the population subgroups listed in Table 6 include those subgroups having sufficient numbers of survey respondents in the CSFII food consumption survey.

Anticipated Residues: ARs were calculated in order to account for the metabolites of concern in plant (tolylfluanid, DMST, and the glucoside conjugates of 4-hydroxymethyl-DMST and 2-hydroxyphenyl-DMST) commodities for risk assessment purposes (See Table 5). Detailed explanation of AR calculations can be found in the HED dietary exposure assessment (Memo, J. Tyler 8/1/02; D283982).

Table 5. Summary of HED-Recommended Tolerances and ARs (Parent and additional metabolites of concern not in tolerance expression) used in Dietary Exposure Assessment.

Commodity	Recommended Tolerance	Anticipated TTR for Risk Assessment[1]	
		Acute	Chronic
Grapes	11	14	2.3
Apples	5.0	3.4	1.2
Hops	30	61	24
Tomatoes	2.0	0.92	0.36

1. TTR = Total toxic residues. For plants, the TTR includes the parent, DMST and the glucosidic conjugates of DMST (WAK 6550 and WAK 6676).

HED recently performed estimates of the acute, chronic and cancer dietary exposures and associated risks for the new fungicide tolylfluanid resulting from the proposed tolerances for residues on imported apples, grapes, hops and tomatoes (Memo, J. Tyler 8/1/02; Barcode D283982). In order to account for possible residues in imported livestock commodities, ARs (parent and additional metabolites of concern not in tolerance expression) were calculated and included in the assessment. Livestock commodities had very little affect on the acute, chronic and cancer dietary exposure estimates for the general U.S. population and all other population subgroups, especially infants and children. In all cases, apple and grape commodities were the drivers in the dietary risk estimates. However, in a meeting on 8/8/02, the HED RARC recommended that livestock commodities be removed from the acute, chronic and cancer dietary exposure assessment. The recommendation was based on the following:

> Wet apple pomace is the only livestock feed item associated with proposed uses. It is highly unlikely that domestic livestock will be fed imported wet apple pomace. Therefore, any tolylfluanid residues in livestock commodities will only be in imported meat and milk products. Very little milk is imported into the U.S.. In addition, the majority of the meat imported into the U.S. is from countries in which tolylfluanid is not registered for use on apples. Therefore, it is highly unlikely that meat and milk from livestock that have been fed tolylfluanid-treated wet apple pomace will be imported into the U.S..

Therefore, an updated acute, chronic and cancer dietary exposure assessments were conducted without livestock commodities (Memo, J. Tyler 8/13/02; D284799). No other aspects of the 8/1/02 dietary exposure assessment were changed. HED notes that if in the future tolylfluanid is proposed for use on additional livestock feed items, then ARs (parent and additional metabolites of concern not in tolerance expression) for livestock commodities may need to be included in the dietary exposure assessment.

4.2.2.1 Acute Dietary Exposure Analysis

The HIARC selected separate acute dietary endpoints for females 13-50 years old and the general U.S. population (including infants and children). Partially refined separate acute dietary exposure assessments were performed for females 13-50 years old and the general U.S. population (including infants and children), incorporating (parent and additional metabolites of concern not in tolerance expression) calculated from field trial data for all proposed tolylfluanid food uses. In addition, it was assumed that all proposed food items contain tolylfluanid residues

(i.e., 100% CT). The acute dietary exposure estimates are below HED's level of concern (<100% aPAD) at the 95th exposure percentile for females 13-50 years old (42% aPAD), the general U.S. population (31% of the aPAD) and all other population subgroups. The most highly exposed population subgroup is infants <1 year old, at 100% of the aPAD.

The acute assessment was conservative, using the following upper-end assumptions:

- No import consumption data were used in the assessment (i.e., the assessment assumes that all dietary exposure from the proposed commodities is from imported commodities).
- The calculated ARs (parent and additional metabolites of concern not in tolerance expression; see Table 5) are based on field trial data, submitted by the registrant to support tolerances. Field trial residue data are generally considered by HED as an upper-end or a worst case scenario of possible residues and are more suited to the requirements of tolerance setting, because it requires highest rates of application and shortest PHI, than to the requirements of dietary exposure assessment (when a more realistic estimate is desired).
- The method in which the ARs (parent and additional metabolites of concern not in tolerance expression) were calculated resulted in an upper-end estimate of the concentration of the residues of concern in all commodities.

For the acute assessment, apple and grape commodities (particularly apple juice and grape juice) were the major drivers. Inclusion of additional data, such as % CT/import consumption data and/or monitoring data (including metabolites of concern), could be made in order to refine the acute dietary exposure assessment.

4.2.2.2 Chronic Dietary Exposure Analysis

A partially refined, chronic dietary exposure assessment was conducted for the general U.S. population and all population subgroups (including infants and children) using ARs (parent and additional metabolites of concern not in tolerance expression) calculated from field trial data for all commodities, and % import share information provided by BEAD for apple, grapes, and tomatoes. Modified DEEM™ processing factors based on the results of processing studies were used for raisins and apple and grape juice/juice concentrates. Default DEEM™ processing factors were used for all other processed commodities. The chronic dietary exposure estimates are below HED's level of concern (<100% cPAD) for the general U.S. population (3% cPAD) and all population subgroups. The most highly exposed population subgroup is children 1-6 years old at 14% of the cPAD.

As with the acute assessment, apple and grape commodities (particularly apple and grape juices) were the drivers in the chronic assessment. Inclusion of additional data, such as country-specific % import consumption data and/or monitoring data (including metabolites of concern), could be made in order to refine the chronic dietary exposure assessment.

4.2.2.3 Cancer Dietary Exposure Analysis

A partially refined, cancer dietary exposure assessment was conducted for the general U.S. population using ARs (parent and additional metabolites of concern not in tolerance expression) calculated from field trial data for all commodities, and % import share information provided by BEAD for apple, grapes, and tomatoes. Modified DEEM™ processing factors based on the results of processing studies were used for raisins and apple and grape juice/juice concentrates. Default DEEM™ processing factors were used for all other processed commodities. The cancer risk estimate is 1.2×10^{-6} for the general U.S. population.

For cancer dietary risk estimates, HED is generally concerned with cancer risks that exceed 1×10^{-6}. However, the following conservative assumptions were used in the cancer dietary exposure assessment:

- The % import consumption information used for apples, grapes and tomato commodities assume that 100% of the imported commodities are treated with tolylfluanid.
- The calculated ARs (parent and additional metabolites of concern not in tolerance expression; see Table 5) are based on field trial data, submitted by the registrant to support tolerances. Field trial residue data are generally considered by HED as an upper-end or a worst case scenario of possible residues and are more suited to the requirements of tolerance setting, because it requires highest rates of application and shortest PHI, than to the requirements of dietary exposure assessment (when a more realistic estimate is desired).
- The method in which the ARs (parent and additional metabolites of concern not in tolerance expression) were calculated resulted in a upper-end estimate of the concentration of the residues of concern in all commodities.

As with the acute assessment, apple and grape commodities (particularly apple and grape juices) were the drivers in the cancer assessment. With additional refinements to the dietary exposure assessment (i.e., country-specific % import consumption data and/or monitoring data (including metabolites of concern)), HED expects the estimated cancer risk to be below HED's level of concern for the general U.S. population.

Table 6. Summary of Results from Acute, Chronic and Cancer DEEM™ Analyses of Tolylfluanid.

Population Subgroup	Acute Dietary[1]		Chronic Dietary[2]		Cancer Dietary Risk [3]
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD	
U.S. Population (total)	0.051973	31	0.000780	3	1.2×10^{-6}
All Infants (< 1 year old)	0.169772	100	0.003397	13	NA[4]
Children 1-6 years old	0.159553	94	0.003638	14	
Children 7-12 years old	0.063237	37	0.001029	4	
Females 13-50 years old	0.034529	20	0.000399	2	
Males 13-19 years old	0.023476	14	0.000342	1	
Males 20+ years old	0.030744	18	0.000340	1	
Seniors 55+ years old	0.033375	20	0.000333	1	

1. Acute dietary endpoint of 0.083 mg/kg/day applies to females 13-50 years old only; acute dietary endpoint of 0.17 mg/kg/day applies to the general U.S. population (including infants and children).
2. Chronic dietary endpoint of 0.026 mg/kg/day applies to general U.S. population and all population subgroups.
3. $Q_1^* = 0.00159$
4. NA = not applicable.

4.3 Water Exposure/Risk Pathway

As this petition is for tolerances for imported commodities only, a drinking water exposure assessment was not conducted.

4.4 Residential Exposure/Risk Pathway

As this petition is for tolerances for imported commodities only, a residential exposure assessment was not conducted.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

As this petition is for tolerances for imported commodities only, residential and drinking water exposure assessments were not conducted. Therefore, acute, chronic and cancer aggregate exposure risk assessments were not conducted.

6.0 CUMULATIVE RISK

FQPA (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or

other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

HED did not perform a cumulative risk assessment as part of this tolerance action for tolylfluanid because HED has not yet initiated a review to determine if there are any other chemical substances that have a mechanism of toxicity common with that of tolylfluanid. For purposes of this tolerance action, EPA has assumed that tolylfluanid does not have a common mechanism of toxicity with other substances.

On this basis, the Registrant must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether tolylfluanid shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for tolylfluanid need to be modified or revoked. If HED identifies other substances that share a common mechanism of toxicity with tolylfluanid, HED will perform aggregate exposure assessments on each chemical, and will begin to conduct a cumulative risk assessment.

HED has recently developed a framework that it proposes to use for conducting cumulative risk assessments on substances that have a common mechanism of toxicity. This guidance was issued for public comment on January 16, 2002 (67 FR 2210-2214) and is available from the OPP Website at: http://www.epa.gov/pesticides/trac/science/cumulative_guidance.pdf. In the guidance, it is stated that a cumulative risk assessment of substances that cause a common toxic effect by a common mechanism will not be conducted until an aggregate exposure assessment of each substance has been completed.

Before undertaking a cumulative risk assessment, HED will follow procedures for identifying chemicals that have a common mechanism of toxicity as set forth in the "*Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity*" (64 FR 5795-5796, February 5, 1999).

7.0 OCCUPATIONAL EXPOSURE

As this petition is for tolerances for imported commodities only, an occupational exposure assessment was not conducted.

8.0 DATA NEEDS/LABEL REQUIREMENTS

8.1 Chemistry

- Successful PMV by the Agency.
- Revised Section F to include to following:
  - *Apple*: The correct commodity definition "apple."
  - *Grape*: The correct commodity definition "grape" and a tolerance at 11 ppm.
  - *Hop*: The correct commodity definition "hop, dried cones."
  - *Tomato*: The correct commodity definition "tomato" a tolerance at 2.0 ppm.

8.2 Toxicology

There are no data gaps *per se*. However, HIARC and CARC recommended the following confirmatory data:

- A comparative thyroid assay due to concern for thyroid tumors in chronic rat studies and elevated thyroid stimulating hormone in subchronic and special studies in rat.

- A bone marrow cytogenetic assay in order to reach definitive conclusions regarding the clastogenic potential of tolylfluanid in whole animal somatic cells.

9.0 ATTACHMENTS

Attachment 1. Chemical structures of all metabolites mentioned in this risk assessment
Attachment 2. Proposed metabolic pathways of tolylfluanid in plants and animals (lactating goat and rats). Not available electronically.

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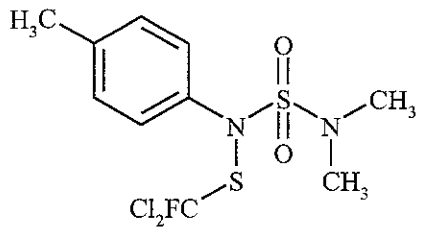
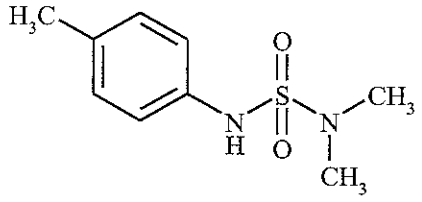
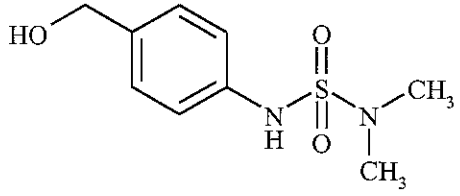
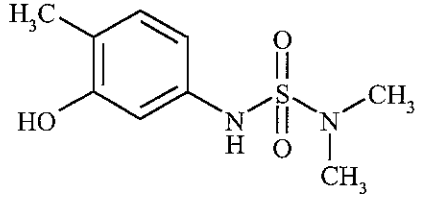
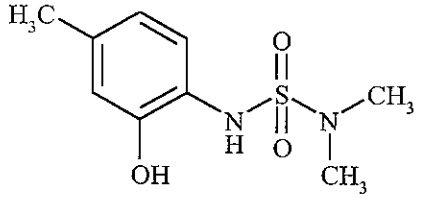
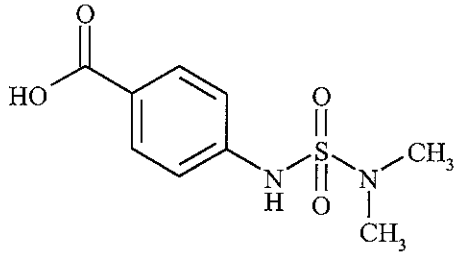
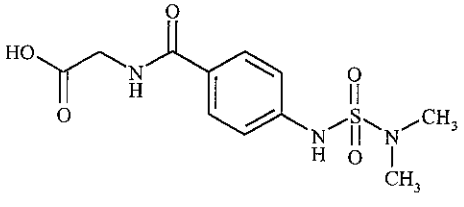
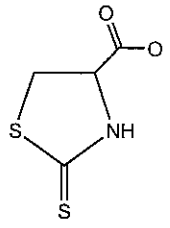
ATTACHMENT 1

Tolylfluanid	
DMST; WAK 5506 Dimethylaminosulfotoluidid	
4-Hydroxymethyl-DMST; **WAK 5818** N,N-Dimethyl-N'-[4-(hydroxymethyl)phenyl]sulfamide	
3-Hydroxyphenyl-DMST N,N-Dimethyl-N'-[3-hydroxy-4-methylphenyl]sulfamide	
2-Hydroxyphenyl-DMST (WAK 6698) N,N-Dimethyl-N'-[2-hydroxy-4-methylphenyl]sulfamide	
RNH0166 4-[[(Dimethylamino)sulfonyl]-amino]benzoic acid	
WAK 6426 N-[4-(Dimethylaminosulfonyl-amido)benzoyl]glycine	

TTCA Thiazolidine-2-thione-4-carboxylic acid	
RNH 0416 4-methylamino-benzoic acid	

ATTACHMENT 2
(not available electronically)

Figure 1: Proposed metabolic pathway of tolylfluanid in plants

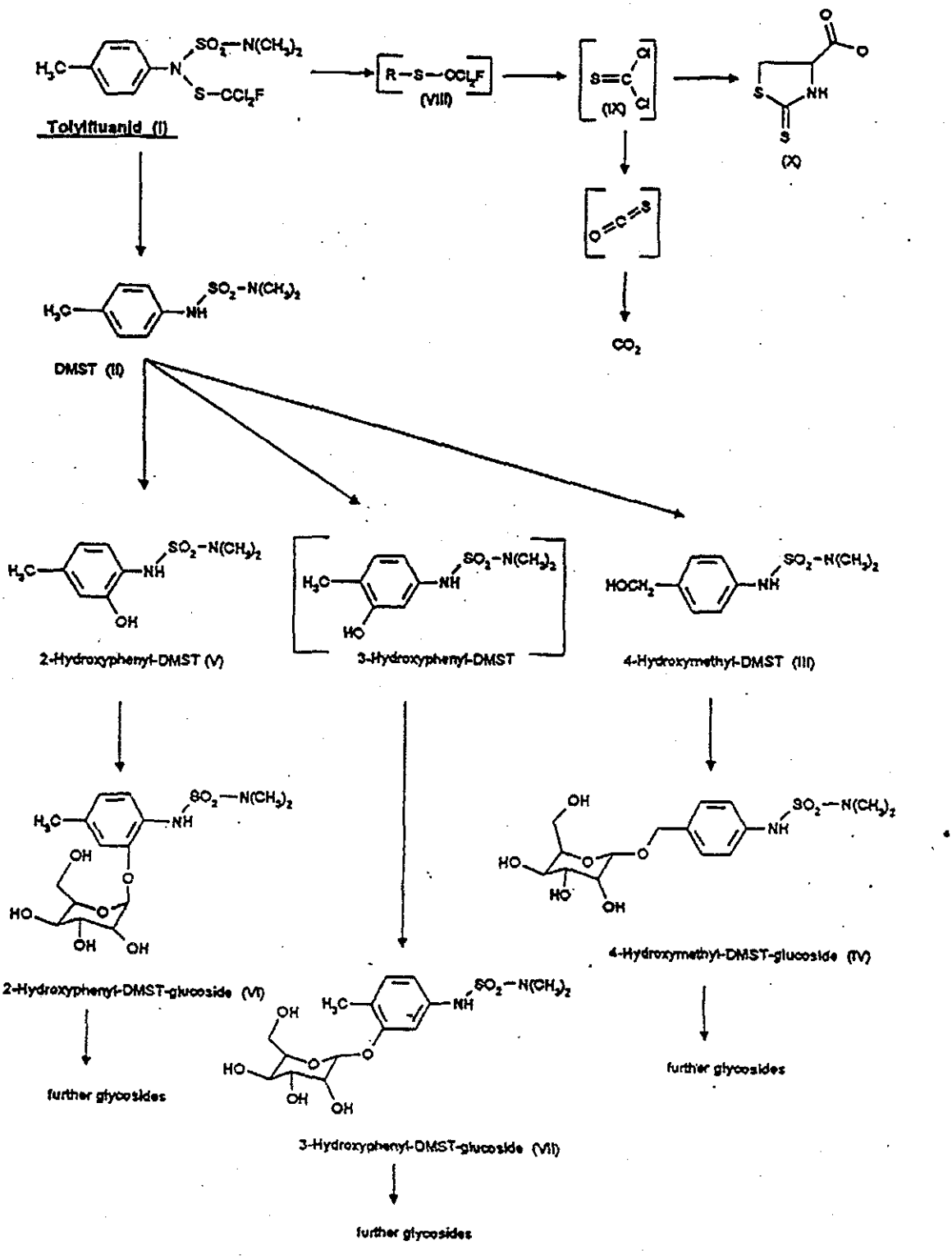
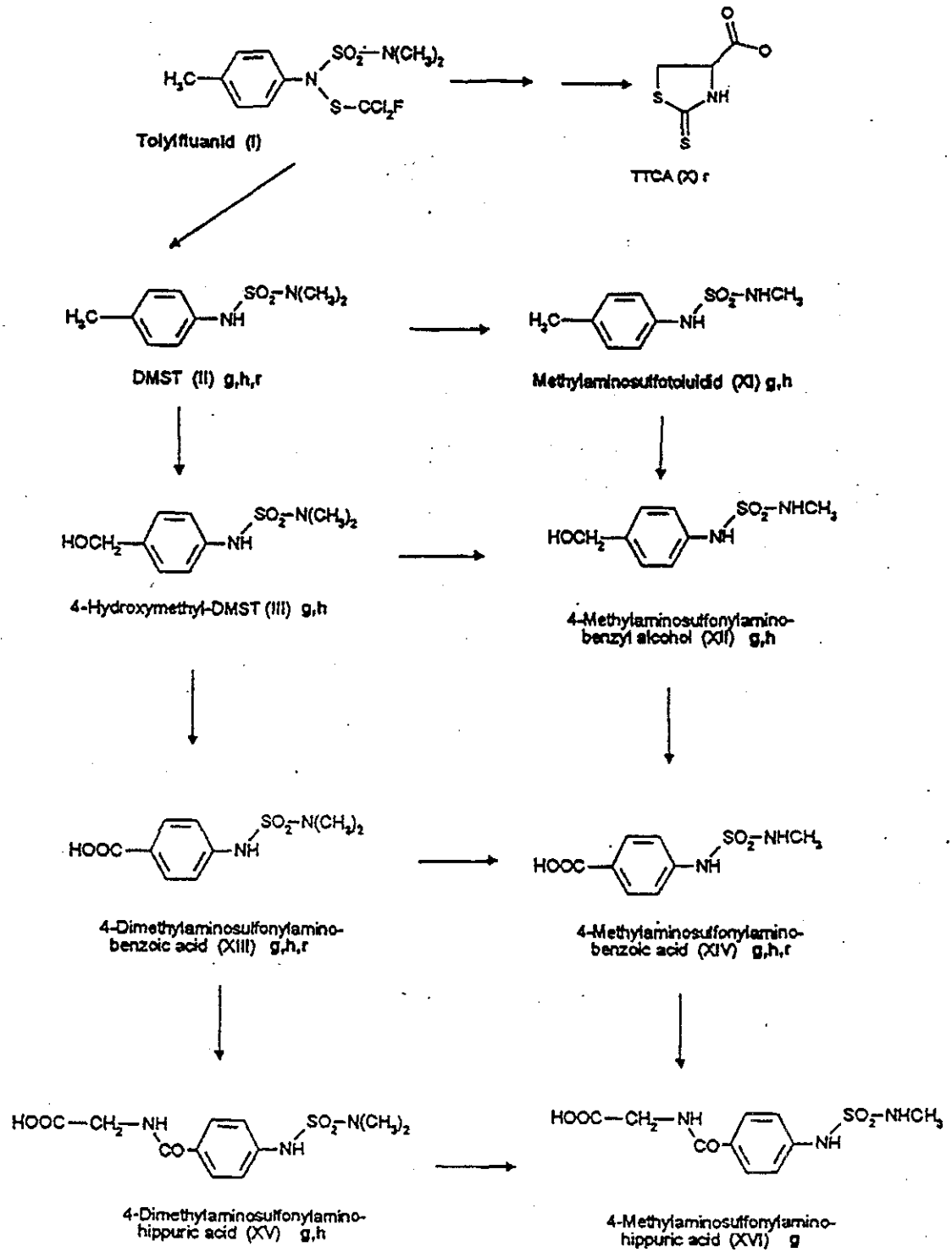


Figure 2: Proposed metabolic pathway of tolylfluanid in animals (r = rat; g = goat; h = hen)



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