United States
Environmental Protection
Agency

Office of Prevention, Pesticides
and Toxic Substances
(7505C)

Pesticide Fact Sheet

Name of Chemical: Tolylfluanid
Reason for Issuance: Import Tolerance
Date Issued: September 2002

1. DESCRIPTION OF CHEMICAL

Generic Name:	(1,1-dichloro-N-[(dimethylamino)-sulfonyl]-1-fluoro-N-(4-methylphenyl)methanesulfenamide
Common Name:	Tolylfluanid
Trade Names:	Euparen M
EPA PC Code:	309200
Chemical Abstracts Service (CAS) Number:	731-27-1
Year of Initial Tolerance:	2002
Year of Initial Registration:	Not applicable. No U.S. registration (Import tolerance only).
Pesticide Type:	Fungicide
Chemical Family:	Phenylsulfamide fungicides (dichlofluanid)

Producer: Technical grade and formulated Tolylfluanid are produced by Bayer AG in Germany for use outside the United States. No production of Tolylfluanid containing products occurs in the U.S.

2. USE PATTERNS AND FORMULATIONS

NOT REGISTERED FOR USE IN THE U.S.. The following use pattern is registered in the European Union:

Application Sites:	Apples, Grapes, Hops and Tomatoes (imported only).
Types of Formulations:	Nominally 98.1% technical product.
Types and Methods of Application:	Ground and aerial applications using standard commercial sprayer.
Application Rates:	0.89 - 2.7 lb AI/acres), applied a maximum of fifteen (15) times/season at intervals of 5-7 days with a pre-harvest interval (PHI) ranging between 3 and 35 days.
Carrier:	Water

3. SCIENCE FINDINGS

Summary Science Statements

Technical grade tolylfluanid, a colorless powder, has low acute oral toxicity in rats (LD_{50} in males and females >5000 mg/kg; Toxicity Category IV).

Chemical Characteristics

Property	Technical
Physical State	Solid (powder)
Color	Colorless
Odor	No characteristic odor
Melting Point	93±0.2°C
Density	1.520±0.004 g/cc
Solubility (Water)	0.90 mg/L

Vapor Pressure (at 25/C)	3.0E10-6 torr
Octanol/Water Partition Coefficient	log Pow = 3.93 (21°C)
pH	???

Toxicology Characteristics

Toxicity - General:

The skeletal system (bones and teeth), liver and thyroid were identified as target organs in the animal studies.

Carcinogenicity:

Tolylfluanid is classified as "Likely to be carcinogenic to humans" based on the following weight- of-the-evidence considerations:

1) Tolylfluanid induced follicular cell thyroid tumors in high-dose male and female rats and were reproducible;
2) The weight of the evidence does not suggest that tolylfluanid is mutagenic. Although *in vitro* and *in vivo* mutagenicity assays found gene mutations and chromosomal aberrations in mammalian cells, the weight-of-the-evidence does not support the mutagenic mode of action for the induction of thyroid tumors in rats.
3) Data are not adequate to support an alternative mode of action for the thyroid tumor induction.

Developmental and Reproductive Toxicity:

In the rat developmental study, there is neither quantitative nor qualitative evidence of increased susceptibility following in utero exposures in the prenatal developmental toxicity study in rats. Although there is qualitative evidence of susceptibility in the rabbit prenatal toxicity study and in the 2-generation reproduction study in rats, the Agency did not identify any residual uncertainties after establishing toxicity endpoints. For the rabbit developmental toxicity study, the Hazard Identification Assessment Review Committee (HIARC) characterized the degree of concern for the effects observed in this study as low, noting that total resorptions were only affected in one dam at the highest dose tested. Additionally, with respect to the malformations and variations, the incidences were low and while biologically significant, were not statistically significant or outside the range of historical controls. Regarding the reproduction study, the HIARC characterized the degree of concern for the effects observed in this study as low to moderate, noting that clear NOAELs and LOAELs are identified for

the effects of concern and the dose-response well-characterized.

Neurotoxicity:

In neurotoxicity studies, tolylfluanid did not affect brain weights, gross pathology, histopathology or neuropathology. 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.

Metabolism:

Tolylfluanid was readily absorbed and rapidly hydrolyzed within 48 hours. Pretreatment, dose level, and sex had no bearing on the absorption and excretion. 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. Position of the label showed different metabolic profiles. With [dichlorofluoromethyl-^{14}C]-tolylfluanid labeling, the major urinary metabolite was thiazolidine-2-thione-4carbonic acid resulting from cleavage of the side chain and accounted for 73 - 74% and 50 - 63% of the dose, respectively when administered by intravenous and oral routes.

Subchronic, Chronic, and Other Toxicity of Tolylfluanid Technical

Guideline No.	Study Type	Results
870.3100	90-Day oral toxicity rodents (rat)	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)	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.
870.3700a	Prenatal developmental in rodents (rat)	**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

Subchronic, Chronic, and Other Toxicity of Tolylfluanid Technical		
Guideline No.	**Study Type**	**Results**
870.3700a	Prenatal developmental in rodents (rat)	**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)	**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)	**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)	**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

Subchronic, Chronic, and Other Toxicity of Tolylfluanid Technical		
Guideline No.	**Study Type**	**Results**
870.3800	2-Generation Reproduction and fertility effects (rat)	**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.
870.3800	2-Generation Reproduction and fertility effects (rat)	**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)	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)	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)	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)	NOAEL = 12.5 mg/kg/day LOAEL = 62.5 mg/kg/day (M), based on decreased body weight gains.

Subchronic, Chronic, and Other Toxicity of Tolylfluanid Technical		
Guideline No.	**Study Type**	**Results**
870.5100	Bacterial gene mutation assay **Technical**	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**	**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.
870.5100	Bacterial gene mutation assay **Metabolite - WAK 6550**	**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**	**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**	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**	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.**

Subchronic, Chronic, and Other Toxicity of Tolylfluanid Technical		
Guideline No.	**Study Type**	**Results**
870.5300	*In vitro* mammalian cell gene mutation assay **Metabolite - WAK 6698**	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**	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.
870.5300	*In vitro* mammalian cell gene mutation assay **Technical**	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**	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**	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.

Subchronic, Chronic, and Other Toxicity of Tolylfluanid Technical		
Guideline No.	**Study Type**	**Results**
870.5375	*In vitro* mammalian chromosome aberration test **Technical**	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**	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. **Tolylfluanid 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**	No mortality or clinical signs were observed at either dose. **No statistically significant increases in the frequency of chromosomal aberrations in spermatogonia were observed.**
870.5380	*In vivo* mammalian spermatogonia chromosomal aberration test **Technical**	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**	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.

Subchronic, Chronic, and Other Toxicity of Tolylfluanid Technical		
Guideline No.	**Study Type**	**Results**
870.5385	Mammalian bone marrow chromosomal aberration test **Technical**	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**	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**	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**	Mortality at 500 mg/kg and above. Tolylfluanid did not induce sister chromatid exchange at any dose level. Positive control cyclophosphamide responded appropriately.
870.5500	Other Genotoxic Effects UDS in mammalian cells **Technical**	**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)	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)	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.

Subchronic, Chronic, and Other Toxicity of Tolylfluanid Technical		
Guideline No.	**Study Type**	**Results**
870.7485	Metabolism and pharmacokinetics (rat)	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).
870.7485	Metabolism and pharmacokinetics (rat)	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).
	Non-guideline - Rat Thyroid function	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.

Subchronic, Chronic, and Other Toxicity of Tolylfluanid Technical		
Guideline No.	**Study Type**	**Results**
	Non-guideline - mice *In vitro* investigation of TTCA goitrogenic properties **Metabolite**	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	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.

Toxicological Endpoints

The dose at which no adverse effects are observed (the NOAEL) from the toxicology study identified as appropriate for use in risk assessment is used to estimate the toxicological level of concern (LOC). However, the lowest dose at which adverse effects of concern are identified (the LOAEL) is sometimes used for risk assessment if no NOAEL was achieved in the toxicology study selected. An uncertainty factor (UF) is applied to reflect uncertainties inherent in the extrapolation from laboratory animal data to humans and in the variations in sensitivity among members of the human population as well as other unknowns. An UF of 100 is routinely used, 10X to account for interspecies differences and 10X for intra species differences.

For dietary risk assessment (other than cancer) the Agency uses the UF to calculate an acute or chronic reference dose (acute RfD or chronic RfD) where the RfD is equal to the NOAEL divided by the appropriate UF (RfD = NOAEL/UF). Where an additional safety factor is retained due to concerns

unique to the FQPA, this additional factor is applied to the RfD by dividing the RfD by such additional factor. The acute or chronic Population Adjusted Dose (aPAD or cPAD) is a modification of the RfD to accommodate this type of FQPA Safety Factor.

For non-dietary risk assessments (other than cancer) the UF is used to determine the LOC. For example, when 100 is the appropriate UF (10X to account for interspecies differences and 10X for intraspecies differences) the LOC is 100. To estimate risk, a ratio of the NOAEL to exposures (margin of exposure (MOE) = NOAEL/exposure) is calculated and compared to the LOC.

The linear default risk methodology (Q*) is the primary method currently used by the Agency to quantify carcinogenic risk. The Q* approach assumes that any amount of exposure will lead to some degree of cancer risk. A Q* is calculated and used to estimate risk which represents a probability of occurrence of additional cancer cases (*e.g.*, risk is expressed as 1 x 10^{-6} or one in a million). Under certain specific circumstances, MOE calculations will be used for the carcinogenic risk assessment. In this non-linear approach, a "point of departure" is identified below which carcinogenic effects are not expected. The point of departure is typically a NOAEL based on an endpoint related to cancer effects though it may be a different value derived from the dose response curve. To estimate risk, a ratio of the point of departure to exposure (MOE_{cancer} = point of departure/exposures) is calculated.

Human Exposures and Risks

A summary of toxicological dose and endpoints for tolylfluanid for use in dietary exposure assessment is provided in the table below:

EXPOSURE SCENARIO	DOSE (mg/kg bw/day)	ENDPOINT/ STUDY	RATIONALE
Dietary Risk Assessments			
Acute Dietary females 13-50 years of age	NOAEL = 25 mg/kg/day UF = 300 FQPA = 1x	LOAEL = 70 mg/kg/day from the rabbit prenatal developmental toxicity study.	Based on increased malformations (arthrogryposis of front extremities and small orbital cavity/folded retina) and variations (floating ribs and accelerated ossification).
		acute RfD = aPAD = 0.083 mg/kg/day for females 13-50 years old **acute RfD = aPAD = 0.17 mg/kg/day for the general U.S. population, including infants and children**	

EXPOSURE SCENARIO	DOSE (mg/kg bw/day)	ENDPOINT/ STUDY	RATIONALE
Acute Dietary general population including infants and children	NOAEL = 50 mg/kg/day UF = 300 FQPA = 1x	LOAEL = 150 mg/kg/day from the rat acute oral neurotoxicity study.	Based on FOB effects (pilorection, decreased activity, gait abnormalities, decreased body temperature and/or decreased rearing).
Chronic Dietary all populations	NOAEL= 7.9 mg/kg/day UF = 300 FQPA = 1x	LOAEL = 57.5 mg/kg/day from the rat 2-generation reproduction study.	Based on decreased body weights, body weight gains and liver weights.
		chronic RfD = cPAD = 0.026 mg/kg/day	
Cancer Classification and Method of Quantification			
Classification			Likely to be carcinogenic to humans**.**
Basis for Classification			This classification is based on thyroid tumors in high-dose male and female rats.
Q_1* (mg/kg bw/day)$^{-1}$ =1.59 x 10-^{3} based upon male rat thyroid adenomas and/or carcinomas combined.			

FQPA Safety Factor Considerations:

The Agency has concluded that while no special safety factors specific to the Food Quality Protection Act (FQPA) of 1996 are necessary to ensure the safety of infants and children, an additional database uncertainty factor of 3X (in addition to the traditional 10X for inter-species and 10X for intra-specific variability) should be applied due to a concern for elevated thyroid stimulating hormones in subchronic and special studies in rats. The HIARC concluded that an 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.

Acute Dietary Exposure Analysis

An acute dietary risk assessment was conducted for the proposed tolylfluanid food uses based on the following assumptions:

1. No import consumption data were used in the assessment (i.e., the assessment assumes that all acute dietary exposure from the proposed commodities is from imported commodities).
2. 100 % crop treated was assumed for these imported commodities: all imported grapes, apples, hops and tomatoes were assumed to have been treated with tolylfluanid and to have tolylfluanid residues at the level of the tolerance.

To assess acute dietary exposures to females 13-50 years old, the Agency selected the no observed adverse effect level (NOAEL) of 25 mg/kg/day. Dietary exposures to females 13-50 years old utilize 20% of the acute population adjusted dose (aPAD). To assess acute dietary exposures to the U.S. population, including infants and children, the Agency selected the NOAEL of 50 mg/kg/day. Dietary exposures to the U.S. population utilize 31% of the aPAD for the U.S. population. Exposures for the most highly exposed subpopulation, infants less than 1 year old, utilize 100% of the aPAD. While the risk cup would appear to be full, if assumptions reflecting the percent of each crop imported into the U.S. were incorporated into the assessment, the percentage of the aPAD utilized would drop significantly.

Chronic Dietary Exposure Analysis

A chronic dietary risk assessment was conducted for the proposed tolylfluanid food uses based on the following assumptions:

1. 100 % crop treated was assumed for these imported commodities: all imported grapes, apples, hops and tomatoes were assumed to have been treated with tolylfluanid and to have tolylfluanid residues at the level of the tolerance.
2. The calculated anticipated residues for tolylfluanid and additional metabolites of concern which are not in tolerance expression) are based on field trial data, submitted by the registrant to support tolerances. Field trial residue data are generally considered by the Agency 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).

To assess chronic dietary exposures, the Agency selected the NOAEL of 7.9 mg/kg/day. Exposures for the most highly exposed subpopulation, children ages 1-6 years old, utilize 14% of the chronic population adjusted dose (cPAD).

Cancer Dietary Exposure Analysis

A dietary cancer risk assessment was conducted for the proposed tolylfluanid food uses based on the following assumptions:

1. 100 % crop treated was assumed for these imported commodities: all imported grapes, apples, hops and tomatoes were assumed to have been treated with tolylfluanid and to have tolylfluanid residues at the level of the tolerance.
2. The calculated anticipated residues for tolylfluanid and additional metabolites of concern which are not in tolerance expression) are based on field trial data, submitted by the registrant to support tolerances. Field trial residue data are generally considered by the Agency 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 lifetime risk of developing cancer from tolylfluanid exposure is determined for the U.S. population (total) only. The estimated exposure to tolylfluanid is 0.000780 mg/kg bw/day. Applying the Q_1* of 1.59 x 10-3 $(mg/kg\ bw/day)^{-1}$ to the exposure value results in a cancer risk estimate of 1.2 x 10-6 for the general U.S. population. Additional refinement, such as country-specific percent import consumption data), would reduce the estimated cancer risk significantly.

Mechanism of Pesticidal Action

Tolylfluanid belongs to the phenylsulfamide fungicide family and is registered for use in the European Union for use in/on apples, grapes and tomatoes.

4. SUMMARY OF REGULATORY POSITION AND RATIONALE

The available data provide adequate information to support the tolerance for tolylfluanid residues in/on imported apples, grapes, hops and tomatoes. However, the Agency has recommended that the registrant submit the following studies:

1. 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. and

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

5. **CONTACT PERSON AT EPA**

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