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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: February 7, 2006

MEMORANDUM

SUBJECT: 1,2,4-Triazole, Triazole Alanine, Triazole Acetic Acid: Human Health Aggregate Risk Assessment in Support of Reregistration and Registration Actions for Triazole-derivative Fungicide Compounds.
Risk Assessment Type: Single Chemical Aggregate
PC Code: 600074 – 1,2,4-Triazole
600011 – Triazole Alanine
600082 – Triazole Acetic Acid
DP Number: 322215

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1.0 Executive Summary

The Office of Pesticide Program's Health Effects Division (HED) has conducted aggregate human health risk assessments for 1,2,4-triazole and triazole conjugates (triazole alanine and triazole acetic acid). These assessments include evaluation of risks for various population subgroups, including those comprised of infants and children. 1,2,4-Triazole and its conjugates are common metabolites to the class of compounds know as the triazoles (a.k.a. triazole-derivative fungicides, T-D fungicides, conazoles). These compounds all have a triazole ring with nitrogen atoms at the 1, 2, and 4 positions. In 2000, the Agency delayed granting registration of any new triazole pesticides or new uses of already registered triazole pesticides pending resolution of a number of toxicological, occupational/residential, and dietary exposure concerns, and issued data call ins for a number of studies. At this time sufficient data are available to support a risk assessment for these metabolites. Based on the toxicological information available at this time, HED has conducted two assessments: one for 1,2,4-triazole (1,2,4-T) and one for combined exposure to triazole alanine (TA) and triazole acetic acid (TAA). Both assessments are highly conservative, screening-level evaluations in terms of the hazards associated with these compounds (e.g., use of the maximum combination of uncertainty factors) and potential dietary and non-dietary exposures (i.e., high-end estimates of both dietary and non-dietary exposures).

Triazole alanine and triazole acetic acid residues are primarily associated with plant commodities whereas 1,2,4-triazole is associated with rats and livestock, with lesser amounts being found in plants. All three metabolites may occur in the environment, with their relative proportions depending on a variety of environmental conditions. The degree of formation of these metabolites in plants, animals, and the environment is highly dependent on the properties of the various parent triazole pesticides.

Available studies indicate that 1,2,4-triazole affects the central and peripheral nervous systems, reproductive tissues of both sexes, and the hematological system. Developmental and reproductive effects have been noted for this compound. Based on the available metabolism data from rats and livestock, 1,2,4-triazole may form in humans following exposure to parent triazole compounds. In estimating exposures, HED has included direct exposure to residues of 1,2,4-triazole as well as indirect exposure via exposure to parent triazole pesticides and subsequent conversion to 1,2,4-triazole. Triazole-derivative fungicides (T-D fungicides) have registered or requested uses for a number of food commodities as well as registered and proposed uses for turf and ornamental plantings. HED has assessed potential dietary and non-dietary exposures. The assessments are based on health-protective assumptions regarding the toxicology of and exposure to 1,2,4-triazole. For all individual exposure pathways as well as for aggregate exposure, risk estimates fall below HED's level of concern for all population subgroups.

Relative to triazole alanine, fewer studies are available depicting the toxicological effects of the triazole conjugates. For purposes of this risk assessment, HED has assumed that the triazole conjugates are all toxicologically equivalent to triazole alanine. The available studies found developmental skeletal effects, decreased body weight and body weight gain, and decreased leukocytes and triglycerides. The triazole conjugates are generally not found in animal metabolism studies; therefore, HED has only assessed the direct exposure to these compounds. Furthermore, residues of TA and TAA are formed, and remain, within plant structures, making

them unavailable for dermal or hand-to-mouth exposures. Therefore, HED has assessed exposure to the triazole conjugates for the dietary pathway only. Exposure estimates for the triazole conjugates indicate that risk associated with these compounds is below HED's level of concern. The exposure estimates are based on health-protective assumptions regarding residues of the triazole conjugates.

Based on the available information and on conservative estimates of hazard and exposure, there are no human health risk issues associated with 1,2,4-triazole or its metabolites that would preclude re-registration of the triazole-derivative fungicides registered to date or conditional registration of the triazole-derivative fungicide uses that have been proposed as of September 1, 2005. HED recommends that resolution of the following issues be a condition of registration for new uses and new active ingredients.

- Chemistry:
  - Final two-year storage stability study with 1,2,4-triazole;
  - Resolution of concerns regarding the prevalence of conjugated residues of TA and the ability of the analytical method to quantify them.
- Toxicology:
  - Free triazole:
    - Developmental neurotoxicity study in rats;
    - Chronic toxicity/oncogenicity study in male rats and female mice [This study, included in the original data call-in, has not been submitted. A previous waiver request for this study was denied; a new waiver request submitted in August, 2005, is under review];
    - Acute neurotoxicity study in rats [This study, included in the original data call-in, was placed in reserve pending the results of the combined subchronic/neurotoxicity study, in response to a previous waiver request. A new waiver request for this study was submitted in August 2005, and is under review.];
  - Triazole alanine:
    - Developmental toxicity study in rabbits;
    - Chronic toxicity study in rats, conducted according to current guidelines that include neurobehavioral assessments, with additional neuropathology evaluations conducted according to the neurotoxicity guidelines;
  - Triazole acetic acid:
    - Developmental toxicity study in rabbits;
    - Combined 90-day feeding/neurotoxicity study in rats;
- Occupational/Residential Assessment:
  - None. HED has agreed to waive previous requirements for dislodgeable foliar and turf-transferable residue studies.

New uses for triazole pesticides should also be examined in terms of potential residues of 1,2,4-triazole and its conjugates. This assessment may require revision if new uses are for sites not already addressed by the current list of registered or proposed uses, if the formation of the metabolites exceeds the estimates used herein, or if required toxicity data raise concerns not addressed by the current risk assessment.

Preface and General Information

This document addresses human health risks associated with metabolites that are common to the class of compounds know as triazoles. These compounds all contain a triazole ring with nitrogen atoms at the 1,2, and 4 positions (Figure 1.1). The HED has identified 1,2,4-triazole (1,2,4-T) and its conjugates, triazole alanine (TA), triazole acetic acid (TAA), triazole pyruvic acid, and triazole lactic acid as compounds with potentially significant toxicological properties. The occurrence of triazole pyruvic acid and triazole lactic acid in metabolism studies is low; therefore, those two metabolites have not been explicitly included in this risk assessment. In 2000 the Agency delayed granting the registration of any new triazole-derivative fungicides (T-D fungicides) or new uses of registered T-D fungicides pending resolution of issues regarding toxicology, dietary exposure, and non-dietary exposure. At this time, the HED has enough information to proceed with risk assessments for these compounds, conditional on submission of additional toxicological and residue chemistry data as discussed in Sections 10 and 17.

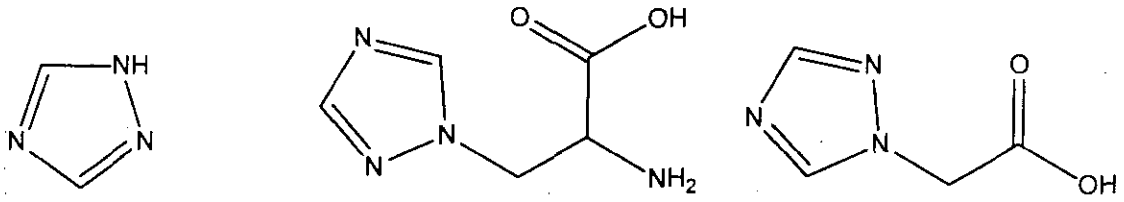
This risk assessment is intended to serve as a support document for registration and reregistration activities of the triazole-derivative fungicides. There are large number of new active ingredients and new uses that are pending for this class of compounds due to the five-year period that has elapsed since the Agency noted 1,2,4-triazole and its conjugates as residues of concern. This assessment takes into consideration the compounds and use sites that are being evaluated for reregistration, as well as the new compounds and new use sites that have been submitted to the Agency (as of 9/1/05). OPP is expecting to receive a significant number of additional new active ingredient and new use requests. HED has designed the assessments presented herein to be extremely conservative so that the assumptions associated with the risk estimates will remain valid for the majority of these expected requests. Reexamination of the risk estimates for 1,2,4-triazole, triazole alanine, and triazole acetic acid will be required:

- For crops or use sites that have not been included in the current established/requested set of uses (e.g., potatoes)
- Upon review of metabolic information for a new compound or a new use showing formation of 1,2,4-triazole, triazole alanine, triazole acetic acid, and/or labile conjugates that exceeds the maxima assumed in this assessment.
- Upon review of the required toxicology data for 1,2,4-triazole and its conjugates as discussed below.

In examining exposure to 1,2,4-triazole, HED has considered both direct exposure to this compound and indirect exposure resulting from the *in-vivo* formation of 1,2,4-triazole following exposure to parent triazole-derivative compounds. At this time, the degree to which the pharamcokinetics (PK) and pharamacodynamics (PD) of exogenous 1,2,4-triazole are the same as the PK and PD of 1,2,4-triazole formed following *in vivo* metabolism is unknown. Specifically, this analysis assumes that the target tissue, the dose at the target tissue, and timing of exposure and toxic effect are similar between the exogenous and internally generated forms of 1,2,4-triazole. As the purpose of the current risk assessment is to provide high-end, screening level risk estimates, HED has made the conservative assumption that the direct and indirect exposures can occur simultaneously and are toxicologically equivalent.

2.0 Chemical Profile

Following application of a triazole-derivative fungicide, biological and/or chemical processes may cause the triazole ring to be released from the parent compound. In rats and livestock, 1,2,4-triazole is relatively stable and is the terminal form of the triazole ring. In plants, the 1,2,4-triazole molecule may become conjugated to serine. The resulting compound, triazole alanine, may be oxidized to form triazole acetic acid. Triazole alanine and triazole acetic acid are the primary terminal forms of the triazole ring in plants, though some 1,2,4-triazole may remain. All three compounds were identified in environmental fate studies and there is evidence that in the environment there is significant conversion between all three forms. The degree of formation of any given form of the triazole ring is highly dependent on the nature and properties of the parent compound. Although other triazole conjugates such as triazole lactic acid and triazole pyruvate have been observed in plant metabolism studies, HED has concluded that TA and TAA are the predominant conjugates that need to be included in the dietary risk assessment.



1,2,4-Triazole	Triazole Alanine	Triazole Acetic Acid
(a.ka. 1,2,4-T; free triazole)	(a.ka. TA)	(a.k.a. TAA)
CAS No. 288-88-0	CAS No. 86362-20-1	CAS No. 28711-29-7
PC Code: 600074	PC Code: 600011	PC Code: 600082
Molecular wgt.: 69.07	Molecular wgt.: 156.15	Molecular wgt.: 127.10

Figure 1.1. Chemical structures for 1,2,4-triazole, triazole alanine, and triazole acetic acid

Based on the currently available toxicology data, the toxicological effects of 1,2,4-T are sufficiently different from those of the conjugates (TA, TAA) that it is appropriate to consider their risks separately. As such, this document consists of two risk assessments, one for 1,2,4-T (Sections 4 – 10) and one for combined residues of TA and TAA (Sections 11 – 17).

We note that in conducting these assessments we have used maximum metabolic conversion factors and have not made an effort to maintain mass balance with respect to residues of 1,2,4-T versus TA/TAA. As a result, a summation of the residue estimates used in these assessments results in a total residue estimate that may be greater than physically possible based on conservation of mass.

2.1 Summary of Registered/Proposed Uses Considered in These Assessments

At this time, there are 13 registered triazole-derivative fungicides with 53 uses on foods and 11 uses on non-foods (i.e., ornamental plants, turf, etc.). Additionally, the Agency has been petitioned to establish registrations for 14 triazole-derivative fungicides with 69 food uses and 4 non-food uses. This risk assessment addresses all registered and requested uses as of September 1, 2005. These uses are summarized in Table 2.1.

Table 2.1. Summary of Triazole-derivative Fungicides and Uses Addressed in these Risk Assessments.

Sorted by Active Ingredient		Sorted by Use Site	
Active Ingredient	Use Site	Use Site	Active Ingredient
Bitertanol	Banana	Almond	Fenbuconazole
Bromuconazole	Banana		Myclobutanil
	Ornamentals		Propiconazole
	Turf	Apple	Difenoconazole
Cyproconazole	Coffee	Artichoke	Myclobutanil
	Soybean		Triadimefon
	Turf	Asparagus	Myclobutanil
Difenoconazole	Apple		Tebuconazole
	Banana		Triadimefon
	Barley	Banana	Bitertanol
	Canola		Bromuconazole
	Grape		Difenoconazole
	Sweet Corn		Epoxiconazole
	Wheat		Fenbuconazole
Epoxiconazole	Banana		Hexaconazole
Fenbuconazole	Almond		Metconazole
	Banana		Myclobutanil
	Blueberry		Propiconazole
	Citrus Fruit Group		Tebuconazole
	Cranberry		Tetraconazole
	Grape		Triadimenol
	Ornamentals	Barley	Difenoconazole
	Peanut		Prothioconazole
	Pecan		Tebuconazole
	Pome Fruit Group		Triticonazole
	Stone Fruit Group	Berry Group	Propiconazole
	Sugarbeat	Blueberry	Fenbuconazole
	Turf	Bulb Vegetable Group	Propiconazole
	Wheat		Tebuconazole
Flusilazole	Soybean	Caneberry	Myclobutanil
Hexaconazole	Banana		Triadimefon
Ipconazole	Cucurbit Vegetable Group	Canola	Difenoconazole
	Ornamentals		Prothioconazole
	Sweet Corn	Carrot	Propiconazole
	Turf	Celery	Propiconazole
Metconazole	Banana	Cereal Grain Group	Propiconazole
	Soybean		Triadimenol
Myclobutanil	Almond	Citrus Fruit Group	Fenbuconazole
	Artichoke		Propiconazole
	Asparagus	Coffee	Cyproconazole
	Banana		Tebuconazole

Table 2.1. Summary of Triazole-derivative Fungicides and Uses Addressed in these Risk Assessments.

Sorted by Active Ingredient		Sorted by Use Site	
Active Ingredient	Use Site	Use Site	Active Ingredient
	Caneberry		Triadimefon
	Cotton	Corn	Propiconazole
	Cucurbit Vegetable Group		Tebuconazole
	Currant/Gooseberry		Triadimenol
	Grape	Cotton	Myclobutanil
	Hops		Tebuconazole
	Mayhaw		Triadimenol
	Ornamentals	Cranberry	Fenbuconazole
	Peppermint/Spearmint		Propiconazole
	Peppers	Cucurbit Vegetable Group	Ipconazole
	Pome Fruit Group		Myclobutanil
	Snap Bean		Tebuconazole
	Stone Fruit Group	Currant/Gooseberry	Myclobutanil
	Strawberry		Propiconazole
	Sugar Beet	Dry Bean and Pea Group	Prothioconazole
	Tomato		Tebuconazole
	Turf	Grape	Difenoconazole
Paclobutrazol	Ornamentals		Fenbuconazole
	Turf		Myclobutanil
Propiconazole	Almond		Tebuconazole
	Banana		Triadimefon
	Berry Group	Grass Grown for Seed	Propiconazole
	Bulb Vegetable Group		Tebuconazole
	Carrot	Hops	Myclobutanil
	Celery		Tebuconazole
	Cereal Grain Group	Lychee	Tebuconazole
	Citrus Fruit Group	Mango	Tebuconazole
	Corn	Mayhaw	Myclobutanil
	Cranberry		Triadimefon
	Currant/Gooseberry	Oats	Tebuconazole
	Grass Grown for Seed	Okra	Tebuconazole
	Ornamentals	Ornamentals	Bromuconazole
	Peanut		Fenbuconazole
	Pecan		Ipconazole
	Pineapple		Myclobutanil
	Pistachio		Paclobutrazole
	Sorghum		Propiconazole
	Soybean		Tebuconazole
	Stone Fruit Group		Triadimefon
	Strawberry	Peanut	Fenbuconazole
	Sugar Beet		Propiconazole
	Sugarcane		Prothioconazole

Table 2.1. Summary of Triazole-derivative Fungicides and Uses Addressed in these Risk Assessments.

Sorted by Active Ingredient		Sorted by Use Site	
Active Ingredient	Use Site	Use Site	Active Ingredient
	Turf		Tebuconazole
	Wild Rice		Tetraconazole
Prothioconazole	Barley	Pecan	Fenbuconazole
	Canola		Propiconazole
	Dry Bean and Pea Group	Peppermint/Spearmint	Myclobutanil
	Peanut	Peppers	Myclobutanil
	Rice	Pineapple	Propiconazole
	Soybean		Triadimefon
	Wheat	Pistachio	Propiconazole
Tebuconazole	Asparagus		Tebuconazole
	Banana	Pome Fruit Group	Fenbuconazole
	Barley		Myclobutanil
	Bulb Vegetable Group		Tebuconazole
	Coffee		Triadimefon
	Corn	Rice	Prothioconazole
	Cotton	Snap Bean	Myclobutanil
	Cucurbit Vegetable Group	Sorghum	Propiconazole
	Dry Bean and Pea Group		Triadimenol
	Grape	Soybean	Cyproconazole
	Grass Grown for Seed		Flusilazole
	Hops		Metconazole
	Lychee		Propiconazole
	Mango		Prothioconazole
	Oats		Tebuconazole
	Okra		Tetraconazole
	Ornamentals	Stone Fruit Group	Fenbuconazole
	Peanut		Myclobutanil
	Pistachio		Propiconazole
	Pome Fruit Group		Tebuconazole
	Soybean	Strawberry	Myclobutanil
	Stone Fruit Group		Propiconazole
	Sunflower	Sugar Beet	Myclobutanil
	Tree Nuts Group		Propiconazole
	Turf		Tetraconazole
	Turnip		Fenbuconazole
	Wheat	Sugarcane	Propiconazole
Tetraconazole	Banana	Sunflower	Tebuconazole
	Peanut	Sweet Corn	Difenoconazole
	Soybean		Ipconazole
	Sugar Beet	Tomato	Myclobutanil
	Turf	Tree Nuts Group	Tebuconazole
Triadimefon	Artichoke	Turf	Bromuconazole

Table 2.1. Summary of Triazole-derivative Fungicides and Uses Addressed in these Risk Assessments.			
Sorted by Active Ingredient		Sorted by Use Site	
Active Ingredient	Use Site	Use Site	Active Ingredient
	Asparagus		Cyproconazole
	Caneberry		Fenbuconazole
	Coffee		Ipconazole
	Grape		Myclobutanil
	Mayhaw		Paclobutrazole
	Ornamentals		Propiconazole
	Pineapple		Tebuconazole
	Pome Fruit Group		Tetraconazole
	Turf		Triadimefon
Triadimenol	Banana		Triticonazole
	Cereal Grain Group	Turnip	Tebuconazole
	Corn	Wheat	Difenoconazole
	Cotton		Fenbuconazole
	Sorghum		Prothioconazole
Triticonazole	Barley		Tebuconazole
	Turf		Triticonazole
	Wheat	Wild Rice	Propiconazole

3.0 Metabolism Assessment

3.1 Comparative Metabolic Profile

1,2,4-Triazole; triazole alanine; and triazole acetic acid are common metabolites to the class of compounds known as triazoles. In plants, 1,2,4-T is rapidly conjugated with serine to form TA. The TA can then be oxidized to form TAA. The extent to which 1,2,4-T, TA, and/or TAA forms in a given plant or animal is primarily dependent on the parent triazole-derivative fungicide. Across the various parent compounds, maximum formation of 1,2 4-T in plants ranges from 0% of the total radioactive residue (TRR) to 17% TRR, with the majority of compounds yielding 1,2,4-T at around 5-10% TRR. In rats, goats, and hens, maximum 1,2,4-T formation ranges from 0 to 77% TRR. Formation of 1,2,4-T in the rat is less than 20% TRR for the majority (approximately 80%) of the triazole-derivative fungicides for which data are available. Formation of TA ranges from 0 to 89% TRR in plants. Triazole acetic acid formation in plants ranges from 0 to 76% TRR. Triazole alanine and triazole acetic acid have generally not been found to be significant metabolites in rats, lactating goats, or laying hens. The exception to this appears to be fenbuconazole. In studies with radio-labeled fenbuconazole fed to goats and hens, TA formation ranges from 0 to 35% TRR; formation of TA from fenbuconazole was not noted in the rat metabolism studies. There is evidence from toxicological studies that there can be limited reduction of TA to 1,2,4-T following oral exposure to TA.

In environmental fate studies, all three forms of triazole (1,2,4-T, TA, and TAA) have been found and there is evidence that the three can inter-convert in soil and aquatic systems. At this time, there are not reliable data available for making general descriptions about the relative rates of formation of these compounds or any steady-state equilibria that may occur.

1,2,4-Triazole

4.0 Hazard Characterization/Assessment

4.1 Hazard Characterization

1,2,4-triazole (free triazole) is a metabolite common to a number of triazole-derivative pesticides, and is found in both mammalian (rat) and plant metabolism studies. Although for most pesticides, mammals convert only a small proportion to free triazole (less than 25%), two compounds (tetraconazole and flusilazole) demonstrate relatively high conversion (68-77%) in rat metabolism studies. As a plant metabolite, and given the wide use of triazole-derivative pesticides (used as fungicides on many crops as well as on turf) free triazole is found in a variety of food commodities, including animal byproducts. 1,2,4-triazole appears to be relatively stable in the environment, and may be found in rotational crops as well as in water.

The available toxicology database for 1,2,4-triazole consists of 2 developmental toxicity studies (in rats and rabbits), a reproductive toxicity study (in rats), a combined subchronic/neurotoxicity study (in rats), and 28- and 90-day toxicity studies in mice. Two additional non-guideline studies in rats (a 30-day gavage study and an unacceptable 90-day subchronic study) provide limited additional information. No reliable data are available for dogs (an incomplete study examining ocular toxicity only was submitted, but included very limited procedural information), and no chronic or oncogenicity studies have been submitted. Although limited chronic toxicity data (chronic toxicity/oncogenicity studies in male rats and female mice) were called in by RD in 2002 (see TXR #0052011), these studies have not been conducted and a new request to waive those studies has been recently submitted (August 2005). HED has not yet completed an evaluation of the request and, to date, the data requirement remains. A previous waiver request, submitted by USTTF in March 2003 [DP Barcode 289197], was reviewed by an HED peer review committee in June 2003, and was denied [see attached memorandum, August 5, 2003, K. Raffaele to Bob Tomerlin, TXR#0052012].

Available unacceptable metabolism studies indicate that 1,2,4-triazole is rapidly absorbed after oral administration and widely distributed in all evaluated tissues. Excretion occurs mostly via the urine, largely as unchanged parent (80-95%), although biliary canulation results suggest the possibility of some enterohepatic recirculation. With an estimated half-life of 8-10 hours, excretion is largely completed within 48 hours of administration of a single dose.

Limited acute toxicity data for 1,2,4-triazole are available, but no complete guideline studies have been submitted (Table 4.1). Available acute data indicate that 1,2,4-triazole is slightly toxic by the oral route (Category III, with oral LD50 values ranging from 666 mg/kg in rabbits to 3650 mg/kg in mice) and slightly to moderately toxic by the dermal route (dermal LD50s were less than 2000 mg/kg in rabbits, and 3000-4000 mg/kg in rats). Limited available information indicates that 1,2,4-triazole is slightly irritating or non-irritating to the skin, but severely irritating to the eye. Based on the limited acute toxicity data, as well as the available developmental toxicity data (see below), it appears that rabbits may be substantially more susceptible to 1,2,4-triazole than are rats or mice.

In spite of the limitations of the available database, a number of target organs and critical effects have been identified. 1,2,4-triazole targets the nervous system, both central and peripheral, as brain lesions (most notably in the cerebellum) were seen in both rats and mice, and peripheral nerve degeneration was also seen in the subchronic neurotoxicity study in rats. In addition, brain weight decreases were seen in several studies, including in the offspring in the reproductive toxicity study. In the subchronic/neurotoxicity study, there is evidence that effects progress over time, with an increase in incidence of clinical signs (including tremors and muscle fasciculations) during weeks 8 and 13 that were not seen during earlier evaluations. Effects were also seen on reproductive organs in both sexes, most notably ovaries (in rats) and testes (in rats and mice), in both the reproductive toxicity and subchronic toxicity studies. Hematological changes, including slightly decreased hemoglobin and/or hematocrit, have also been seen in multiple studies and species (in rats at doses of 33 mg/kg/day and above, and in mice at doses of 487 mg/kg/day and above). Studies depicting the effects of chronic exposure to free triazole or its conjugates are not currently available. A request to waive chronic/oncogenicity studies has been received by the Agency and is currently under review.

1,2,4-triazole also causes developmental toxicity in both rats and rabbits, including malformations, at doses similar to those inducing maternal toxicity (decreased body weight gain in rats and clinical signs and mortality in rabbits). Developmental toxicity was also seen in the reproductive toxicity study, with offspring showing adverse effects on multiple endpoints (including decreased brain and body weight) at doses lower than those at which effects were seen in parents. In addition, reproductive toxicity was seen in both sexes: at the highest dose (3000 ppm), only two F1 litters (one pup/litter) were produced, and neither survived to adulthood.

No data are available to directly evaluate the potential for carcinogenicity of 1,2,4-triazole. Available mutagenicity data are limited (salmonella assays submitted by the USTTF and a Russian literature report (MRID 45284011) of chromosomal aberrations in rat marrow cells), but negative. A large number of parent triazole-derivative pesticides have been classified as carcinogens (most also non-mutagenic), but the relevance of that finding to expected effects of free triazole may be limited. The types of tumors associated with exposure to the parent chemicals are most commonly hepatocellular adenomas/carcinomas in mice. Other tumor types vary considerably (including liver tumors, thyroid tumors, ovarian tumors, testicular tumors, and bladder tumors). None of the tumor types are clearly associated with the proportion of free triazole formed in available rat metabolism studies. The previous HED peer review committee concluded that it was not possible to predict toxicity of free triazole based on toxicity seen with parent compounds: these conclusions and their rationale are discussed in the memoranda from those meetings (see TXR Nos. 0052011 and 0052012, attached). This conclusion is supported by the recently submitted subchronic and reproductive toxicity studies for free triazole, identifying effects not consistently seen in toxicity studies with parent compound (including pathologic lesions in the nervous system and reproductive failure seen at the high dose in the reproductive toxicity study).

Table 4.1. Acute Toxicity Profile – 1,2,4-Triazole. Note that values on this table are based on submitted summary data; full study reports are not available.

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral [rat]	45284004, 45284001	LD_{50} = 1648-3080 mg/kg	III
870.1100	Acute oral [mice]	45284001	LD_{50} = 3650 mg/kg	III
870.1100	Acute oral [rabbit]	45324301	LD_{50} = 666 mg/kg	III
870.1200	Acute dermal [rat]	45284004	LD_{50} = 3129-4200 mg/kg	III
870.1200	Acute dermal [rabbit]	45324301, 45284006	LD_{50} = <2000 mg/kg	II
870.1300	Acute inhalation [mice]	45284011	LC_{50} 4 h =2200 mg/m^3	
870.1300	Acute inhalation [rats]	45284011	LC_{50} 4 h = 2050 mg/m^3	
870.2400	Acute eye irritation [rabbit]	45284004, 45324301, 45284006	severe	
870.2500	Acute dermal irritation [rabbit]	45284004, 45324301, 45284006	not irritating to slightly irritating	IV
870.2600	Skin sensitization [species]		No studies available	unknown

TABLE 4.2 Toxicity Profile for 1,2,4 triazole.

Gdln	Study Type/ *Classification*	*MRID Number*	*Doses*	*Results*
870.3050	*28-Day oral toxicity in mice Acceptable/ non-guideline*	46467301	0, 50,250, 500, 2000 ppm **M:** 9, 47, 90, 356 mkd **F:** 12, 60, 120, 479 mkd	**NOAEL:** 90 mg/kg/day **LOAEL:** 356 mg/kg/day (male) based on testicular degeneration
870.3100	90-Day oral toxicity in mice *Acceptable/ guideline*	46467302	0, 500, 1000, 3000, 6000 ppm **M:** 80, 161, 487, 988 mkd **F:** 105, 215, 663, 1346 mkd	**NOAEL:** 80 mg/kg/day **LOAEL:** 161 mg/kg/day based on ↓testicular wt and microscopic testicular changes At 487 mg/kg/day, also tremors, ↓brain wt, slight hematology changes. At 988 mg/kg/day, also cerebellar degeneration.
870.3050	30-Day oral toxicity in rats - gavage *Acceptable/ non-guideline*	45537401	0, 8, 57, 400 mg/kg/day	**NOAEL:** <8 mg/kg/day **LOAEL:** 8 mg/kg/day based on ↓adrenal wt At 57 mg/kg/day, also slight hematology changes. At 400 mg/kg/day, also clinical signs (staggering, tremors, hunched) ↓BW
870.3100	90-Day oral toxicity in rats *Unacceptable*	45284007	0, 100, 500, 2500 ppm **M:** 8, 38, 212 mg/kg/day **F:** 10, 54, 267 mg/kg/day	**NOAEL:** 38 mg/kg/day **LOAEL:** 212 mg/kg/day based on ↓BW, convulsions, fatty infiltration of liver in males
870.3100 870.6200	90-Day oral toxicity/ neurotoxicity in rats. *Acceptable/ guideline*	46467303	0, 250, 500, 3000, 1000/ 4000 ppm **M:** 16, 33, 183, 210 mkd **F:** 19, 41, 234, 275 mkd	**NOAEL:** 16 mg/kg/day **LOAEL:** 33 mg/kg/day (male) based on ↓TSH Also at 183 mg/kg/day and above: ↓BW, tremors and other FOB, ↓brain wt, neuropath in peripheral nerves and brain (most prominently cerebellum); also slight ↓hematology, sl ↑CL.
870.3150	90-day oral toxicity study in nonrodents	---	---	No study available

TABLE 4.2 Toxicity Profile for 1,2,4 triazole.

Gdln	Study Type/ *Classification*	*MRID Number*	*Doses*	*Results*
870.3200	21/28-Day dermal toxicity (species)	---	---	No study available
870.3250	90-Day dermal toxicity (species)	---	---	No study available
870.3465	90-Day inhalation toxicity (species)	---	---	No study available
870.3700	Developmental toxicity in rats *Acceptable/ guideline*	45223401 45223402	0, 100, 200 mg/kg/day 0, 10, 30, 100 mg/kg/day	**Maternal NOAEL:** 30 mg/kg/day **Maternal LOAEL**: 100 mg/kg/day based on ↓BW gain **Developmental NOAEL**: 30 mg/kg/day **Developmental LOAEL:** 100 mg/kg/day based on ↓fetal BW, skeletal variations, undescended testes Also at 200, increased resorptions and decreased number of viable fetuses, cleft palate, hydronephrosis, increased incidence of major malformations
870.3700	Developmental toxicity in rabbits *Acceptable/ guideline*	46492903	0, 5, 15, 30, 45 mg/kg/day	**Maternal NOAEL:** 30 mg/kg/day **Maternal LOAEL**: 45 mg/kg/day based on mortality and clinical signs (↓motor activity, head tilt, lacrimation, drooping eyelids, diarrhea, salivation) **Developmental NOAEL**: 30 mg/kg/day **Developmental LOAEL:** 45 mg/kg/day based on ↓fetal wt and urinary tract malformations
870.3800	Reproduction and fertility effects *Acceptable*	46467304	0, 250, 500, 3000 ppm **M:** 15, 31, 189 mkd **F:** 18, 36, 218 mkd	**Parental NOAEL:** <15 mg/kg/day **Parental LOAEL**: 15 mg/kg/day (male) based on ↓BW and BWG in F1 males, ↓spleen weight in F1 females At 218 mg/kg/day: cerebellar lesions, ↓brain weight, ↓thyroid weight, **Offspring NOAEL:** <19 mg/kg/day **Offspring LOAEL:** 19 mg/kg/day based on ↓BW, BWG and brain wt in F2 pups, ↓spleen weight in F2 female pups. **Repro NOAEL**: 15 mg/kg/day **Repro LOAEL**: 31 mg/kg/day based on abnormal sperm and ↓# of CL in F1 females At 218 mg/kg/day, reproductive failure (no viable offspring), ↑CL in F0 parental females
870.4100a	Chronic toxicity (rodent)	---	---	No study available
870.4100b	Chronic toxicity (dog)	---	---	No study available
870.4200	Carcinogenicity (rat)	---	---	No study available
870.4300	Carcinogenicity (mouse)	---	---	No study available
870.[ ]	Gene Mutation	---	---	See attached summaries

TABLE 4.2 Toxicity Profile for 1,2,4 triazole.

Gdln	Study Type/ *Classification*	*MRID Number*	*Doses*	*Results*
870.[ ]	Cytogenetics	---	---	No study available
870.[ ]	Other Effects	---	---	No study available
870.6200a	Acute neurotoxicity screening battery	---	---	No study available
870.6200b	Subchronic neurotoxicity screening battery	---	---	See combined subchronic/neurotoxicity study (above)
870.6300	Developmental neurotoxicity	---	---	No study available
870.7485	Metabolism and pharmacokinetics - rat *Unacceptable/ guideline*	45284018	intraduodenal 1 mg/kg *i.v.* 0.1 - 100 mg/kg oral 0.4 - 866 mg/kg	Oral absorption of 80-95%. Excreted in urine (80-95%) and feces (<15%), biliary excretion of 10% with enterohepatic recirculation. Unchanged triazole accounted for ~95% of radioactivity.
870.7600	Dermal penetration (species)	---	---	No study available
Special studies	---	---	---	See Attachment 3

4.2 FQPA Hazard Considerations

4.2.1 Adequacy of the Toxicity Data Base

The available toxicity data base, including developmental toxicity studies in two species, a rat 2-generation reproductive toxicity study, and a subchronic/neurotoxicity study in rats, is adequate to evaluate the potential for increased toxicity in infants and children.

4.2.2 Evidence of Neurotoxicity

The available toxicity data base includes substantial evidence that exposure to 1,2,4-triazole causes neurotoxicity, including: neuropathological lesions in the brain (seen in the 90-day subchronic toxicity studies in both mice and rats, and in the reproductive toxicity study in rats [at doses of 183 mg/kg/day and above]); neuropathological lesions in the peripheral nervous system (seen in the subchronic neurotoxicity study in rats at doses similar to those causing brain lesions); and decreases in brain weight in several studies in both rats and mice (including decreases in brain weight of offspring in the reproductive toxicity study at doses not causing similar effects in F0 parents [see below]). In addition, effects indicating potential neurotoxicity were seen in the FOB and motor activity evaluations in the subchronic neurotoxicity study in rats (including tremors, muscle fasciculations, decreased arousal, decreased rearing, and decreased motor activity [at doses similar to those causing brain lesions]), and in the developmental toxicity study in rabbits (decreased motor activity, excessive salivation, hyperpnea, lacrimation, and head tilt [seen in does at doses of 45 mg/kg/day and above]).

4.2.3 Developmental Toxicity Studies

There is evidence of developmental toxicity in available studies in rats and rabbits. In rats, reduced fetal body weight, an increased incidence of runts, an increase in skeletal variations and an increase in incidence of undescended testes were seen at the LOAEL of 100 mg/kg/day, a dose also causing decreased body weight gain in dams. At 200 mg/kg/day in rats, there was an increase in malformations, including cleft palate and hydronephrosis, accompanied by an increase in post-implantation loss. In rabbits, there was a decrease in fetal weight and an increase in incidence of urinary tract malformations at doses causing severe effects in does (weight loss, multiple clinical signs, and increased mortality). The dose-response in rabbits appears to be very steep, with no effects seen at 30 mg/kg/day, and mortality seen at 45 mg/kg/day (only 15 mg/kg/day higher). In summary, there was no increase in quantitative severity in either species. There was an increase in qualitative sensitivity (more severe effects) in rats, but not in rabbits.

4.2.4 Reproductive Toxicity Study

There is evidence of increased offspring sensitivity, both quantitative and qualitative, in the reproductive toxicity study in rats. In adult (F1) male offspring, decreases in body weight and brain weight were seen at doses of 15-16 mg/kg/day and 36 mg/kg/day, respectively. Similar effects were seen in parental (F0) animals only at the highest dose of 189 mg/kg/day. Similarly, decreased brain weight and body weight were seen at (parental) doses of 18.9 mg/kg/day in F2 pups, doses below those causing similar effects in F0 animals (189 mg/kg/day). Decreases in corpora lutea were seen in F1 females at 36 mg/kg/day; similar effects were not seen in F0 females (increases in corpora lutea were seen at the high dose of 218 mg/kg/day; no changes were seen in mid-dose F0 females).

4.2.5 Additional Information from Literature Sources

None.

4.2.6 Pre-and/or Postnatal Toxicity

Toxicity was seen in offspring in all studies in which they were evaluated. Pre-natal findings include malformations as well as decreases in body weight. Findings in the reproductive toxicity study included effects on multiple organ systems, including decreases in body and brain weight and changes in reproductive organs (including testes and ovaries). It is not possible to determine whether the effects seen in the reproductive toxicity study were due to pre- or post-natal exposure.

4.2.6.1 Determination of Susceptibility

Available data indicate evidence of increased qualitative sensitivity in the rat developmental toxicity study (malformations seen at doses causing only decreased body weight gain in dams), and of quantitative sensitivity in the rat reproductive toxicity study (similar effects seen at lower

doses in offspring). No increase in qualitative or quantitative sensitivity was seen in the rabbit, with malformations occurring at doses causing severe maternal toxicity.

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

Although a developmental neurotoxicity study is unavailable, available data (including nervous system lesions seen in adults and decreased brain weight in offspring) raise concern regarding developmental effects on the nervous system. In an attempt to address this concern, additional brain evaluations, including morphometric measures in weanlings, were performed in the available reproductive toxicity study. Although no effects were seen in either the qualitative or quantitative evaluations performed in pups, similar evaluations were not conducted in adult animals, in spite of evidence (decreases in brain weight in F1 adults) of persistent effects on the central nervous system. It is also important to note that the highest dose evaluated in offspring, approximately 32 mg/kg/day, was substantially lower than that causing nervous system lesions in adults not developmentally dosed (approximately 183 mg/kg/day in males in the subchronic/neurotoxicity study and 189 mg/kg/day in F0 parents in the reproductive toxicity study). Although lesions were found in the peripheral nervous system (PNS) in adults in the subchronic neurotoxicity study, there has been no evaluation of PNS tissues in offspring. In addition, behavioral evaluations of pups are not available; in the subchronic/neurotoxicity study in adult rats, behavioral effects were detected during FOB and motor activity evaluations that were not seen in routine clinical observations. It is possible similar effects could occur in offspring during development, that would not have been detected in the reproductive toxicity study. Although the toxicity seen in offspring in the reproductive toxicity study indicates that offspring were exposed, the degree of lactational transfer, and thus the relative exposure of pups and adults, is unknown.

In addition to the nervous system lesions, 1,2,4-triazole also appears to impact the function of the endocrine system, based on reproductive failure at the high dose and delays in sexual maturation seen in the reproductive toxicity study, and on lesions in reproductive organs and changes in corpora lutea counts seen in various studies in rats and/or mice.

The HED Risk Assessment Review Committee (RARC) found the residual concern for the above-described effects to be low, since the endpoint of concern (effects in the offspring at the LOAEL in the reproductive toxicity study) is being used as the basis for the current risk assessment, and the appropriate uncertainty factors are being used to account for the residual uncertainty (RARC Meeting 10/4/05; see below).

4.3 Recommendation for a Developmental Neurotoxicity Study

The triazole toxicology team determined that a Developmental Neurotoxicity study is <u>required</u> based on multiple nervous system and endocrine-related findings in available studies, including effects seen in offspring at doses not causing toxicity in F0 parental animals.

4.3.1 Evidence that supports requiring a Developmental Neurotoxicity study

Pathological lesions of the nervous system have been seen in all evaluated species, in multiple studies:

- Cerebellar lesions in the 90-day study in mice at 487/663 and 988/1346 mg/kg/day (males/females).
- Brain and peripheral nervous system lesions and behavioral effects in rats at 183/234 and 210/275 mg/kg/day in the subchronic/neurotoxicity study.
- Decreases in brain weight and cerebellar lesions in both sexes of F0 adults in the rat reproductive toxicity study at 188/218 mg/kg/day (M/F).
- Decreases in brain weight in adult offspring and weanlings in the rat reproductive toxicity study at doses of 16/19 and 33/41 mg/kg/day (M/F).
- Slight increases in incidence of retinal degeneration in the 90-day subchronic/neurotoxicity study in rats, at 183/234 and 210/275 mg/kg/day (M/F).
- Possible changes in lens biochemistry were seen in an ocular toxicity study in dogs.

Clinical signs, indicative of neurobehavioral effects have been seen in multiple studies:

- Effects were seen during FOB evaluations (including tremors, muscle fasciculations, and decreases in rearing) and motor activity evaluations in the subchronic/neurotoxicity study in rats, at 183/234 and 210/275 mg/kg/day (M/F).
- Clinical signs, including gait and postural changes, tremors, and slight convulsions, were seen in two older rat toxicity studies (30-day gavage and 90-day dietary).
- Clinical signs indicative of neurotoxicity were seen in does in the rabbit developmental toxicity study.

Possible endocrine-mediated effects have been seen in multiple studies and species:

- Testicular changes in mice (28- and 90-day mouse studies), sperm abnormalities in rats (reproductive toxicity study), decreases in testes weight in old rat 30- and 90-day toxicity studies.
- Ovarian changes in rats (90-day subchronic rat and reproductive toxicity study in rats).
- Delays in sexual maturation in rat reproductive toxicity study.
- Reproductive failure at high dose in rat reproductive study (only two litters produced, with no pups surviving lactation).
- Increased incidence of undescended testicle in rat developmental toxicity study.
- Dose-related decreases in TSH at 33 mg/kg/day and above in male rats in the subchronic/neurotoxicity study.

4.3.2 Evidence that supports not requiring a Developmental Neurotoxicity study

- No effects were seen in morphometric evaluation of weanling rats in the reproductive toxicity study.

- No CNS malformations were seen in available developmental toxicity studies in rats and rabbits.

4.3.2.1 Rationale for the UF_{DB} (when a DNT is recommended)

Based on the evidence described in Section 4.3.1 regarding the concern for neurotoxic effects in developing offspring, as well as other data gaps (lack of chronic studies, oncogenicity studies, non-rodent toxicity studies), the triazole toxicology team determined that a database UF should be set at 10x. The need for this factor will be re-evaluated upon receipt of the additional required toxicology data (see Section 10.1). A larger factor will be used for some endpoints due to failure to identify a NOAEL in the reproductive toxicity study (see below).

4.4 Hazard Identification and Toxicity Endpoint Selection

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

Study Selected: Developmental Toxicity study in rabbits
MRID Number: MRID 46492903
Dose and Endpoint for Establishing aRfD: 30 mg/kg/day, based on urinary tract malformations seen at the LOAEL of 45 mg/kg/day
Uncertainty Factor(s): UF=1000 (10x for inter-species variability, 10x for intra-species variability, and 10x for data gaps and FQPA concerns)
Comments about Study/Endpoint/Uncertainty Factor: Identified developmental toxicity suitable for this exposure duration. Although changes in birth weight and in weanling brain weight were seen in offspring from the reproductive toxicity study, these were seen at the LOAEL in the F2 generation only, and thus are unlikely to occur following a single exposure.

Acute RfD = 30 mg/kg/day (NOAEL) ÷ 1000 (UF) = 0.03 mg/kg/day

4.4.2 Acute Reference Dose (aRfD) - General Population

Study Selected: Developmental Toxicity study in rabbits
MRID Number: MRID 46492903
Dose and Endpoint for Establishing aRfD: NOAEL=30 mg/kg/day, based on clinical signs and mortality in does seen at the LOAEL of 45 mg/kg/day,
Uncertainty Factor(s): UF=1000 (10x for inter-species variability, 10x for intra-species variability, and 10x for data gaps and FQPA concerns)
Comments about Study/Endpoint/Uncertainty Factor: Effects in does were seen starting on Gestation Day 6 or 7, and are therefore suitable for this exposure duration.

Acute RfD = 30 mg/kg/day (NOAEL) ÷ 1000 (UF) = 0.03 mg/kg/day

4.4.3 Chronic Reference Dose (cRfD)

Study Selected: Reproductive toxicity study in rats (MRID 46467304)
MRID Number: MRID 46467304
Dose and Endpoint for Establishing cRfD: LOAEL=15 mg/kg/day, based on decreased body weight and body weight gain in F1 males, decreased body weight, body weight gain, and brain

weight in F2 pups. A NOAEL was not established for this study (NOAEL=less than 15 mg/kg/day).

Uncertainty Factor(s): UF=3000 (10x for intraspecies, 10x for interspecies, 10x for data gaps (lack of DNT, chronic studies, oncogenicity studies, non-rodent toxicity studies), 3x for extrapolation from LOAEL to NOAEL).

Comments about Study/Endpoint/Uncertainty Factor: Longest duration study available, with lowest effect level, in available database.

Chronic RfD = 15 mg/kg/day (LOAEL) ÷ 3000 (UF) = 0.005 mg/kg/day

4.4.4 Incidental Oral Exposure (Short-Term)

Study Selected: Developmental Toxicity study in rabbits
MRID Number: MRID 46492903
Dose and Endpoint: NOAEL=30 mg/kg/day, based on clinical signs and mortality in does seen at the LOAEL of 45 mg/kg/day,
Uncertainty Factor(s): UF=1000 (10x for inter-species variability, 10x for intra-species variability, and 10x for data gaps and FQPA concerns)

Comments about Study/Endpoint/MOE: Duration appropriate for this time frame (up to 28 days). MOE=1000 (10x for intraspecies, 10x for interspecies, 10x for data gaps and FQPA concerns).

4.4.5 Incidental Oral Exposure (Intermediate-Term)

Study Selected: Reproductive toxicity study in rats
MRID Number: 46467304
Dose and Endpoint: LOAEL=15 mg/kg/day, based on decreased body weight and body weight gain in F1 males, decreased body weight, body weight gain, and brain weight in F2 pups. A NOAEL was not established in this study (less than 15 mg/kg/day).

Comments about Study/Endpoint/MOE: Duration appropriate for this time frame (28 days to 6 months). MOE=3000 (10x for intraspecies, 10x for interspecies, 10x for data gaps (lack of DNT, chronic studies, oncogenicity studies, non-rodent toxicity studies), 3x for extrapolation from LOAEL to NOAEL).

4.4.6 Dermal Absorption

No data are available regarding dermal absorption of 1,2,4-triazole, therefore if direct dermal exposure to 1,2,4-triazole is anticipated, a default assumption of 100% dermal absorption should be used. For evaluation of risk from estimated exposure to 1,2,4-triazole occurring as a result of metabolism following dermal exposure to parent conazole compounds, dermal absorption estimates for parent compounds should be used.

4.4.7 Dermal and Inhalation Exposure (Short-Term)

Study Selected: Developmental Toxicity study in rabbits
MRID Number: MRID 46492903
Dose and Endpoint: NOAEL=30 mg/kg/day, based on clinical signs and mortality in does seen at the LOAEL of 45 mg/kg/day,
Uncertainty Factor(s): UF=1000 (10x for inter-species variability, 10x for intra-species variability, and 10x for data gaps and FQPA concerns)

Comments about Study/Endpoint/MOE: Duration appropriate for this time frame (up to 28 days). MOE=1000 (10x for intraspecies, 10x for interspecies, 10x for data gaps and FQPA concerns).

4.4.8 Dermal and Inhalation Exposure (Intermediate- and Long-Term)

Study Selected: Reproductive toxicity study in rats
MRID Number: 46467304
Dose and Endpoint: LOAEL=15 mg/kg/day, based on decreased body weight and body weight gain in F1 males, decreased body weight, body weight gain, and brain weight in F2 pups. NOAEL was not established in this study (less than 15 mg/kg/day).

Comments about Study/Endpoint/MOE: Duration appropriate for this time frame (28 days to lifetime). No longer-term study is available. MOE=3000 (10x for intraspecies, 10x for interspecies, 10x for data gaps (lack of DNT, chronic studies, oncogenicity studies, non-rodent toxicity studies), 3x for extrapolation from LOAEL to NOAEL)

4.4.9 Margins of Exposure and Levels of Concern

The levels of concern (LOC) for residential and occupational risk assessment are as follows:

Table 4.3. Summary of Levels of Concern for Residential and Occupational Risk Assessments for 1,2,4-triazole.

Route of Exposure	Duration of Exposure		
	Short-Term (1-30 Days)	Intermediate-Term (1-6 Months)	Long-Term (>6 Months)
Occupational Exposure			
Dermal	1000	3000	3000
Inhalation	1000	3000	3000
Residential Exposure			
Incidental Oral	1000	3000	3000
Dermal	1000	3000	3000
Inhalation	1000	3000	3000

4.4.10 Recommendation for Aggregate Exposure Risk Assessments

For a given duration of exposure, the same study and endpoint is being used for all exposure pathways; therefore, HED is assuming that the toxicological effects following exposure via those routes are the same. Exposure from all routes should be aggregated.

4.4.11 Classification of Carcinogenic Potential

There are no available cancer bioassay studies on 1,2,4-triazole. 1,2,4-triazole and its conjugate (triazole alanine), however, are not mutagenic. The mutagenicity data on the parent triazole fungicides (i.e., the conazoles) indicate that this class of compounds also generally lacks genotoxic potential. Some parent triazole fungicides have been shown to be carcinogenic in rodents, in particular some have produced mouse liver tumors while other have produced rat thyroid tumors, and a few produced both tumor types. Other tumor types noted with several individual triazoles include ovarian tumors, testicular tumors, and bladder tumors. For the last several years, the EPA's National Health and Environmental Effects Research Laboratory (NHEERL) has been conducting research on the potential mode of carcinogenic action underlying the rodent hepatic and thyroid follicular cell tumor responses found for the parent triazole fungicides. The NHEERL cancer mechanistic studies on fluconazole, myclobutanil, propiconazole, and triadimefon are just beginning to appear in the scientific literature (Sun et al., 2004; Wolf et al., 2005; Allen et al., 2005; Goetz et al., 2005; Hester et al., 2005; Ren et al., 2005; Ward et al., 2005). NHEERL used both traditional toxicology endpoints and DNA microarrays to profile gene expression in their investigations on potential modes of carcinogenic action. This recent evidence indicates that the parent triazole compounds appear to result in a tumor response subsequent to perturbation of liver metabolism, specifically xenobiotic and fatty acid metabolic pathways. Some of the altered pathways are regulated by CAR, PXR, and other nuclear receptors. In addition the thyroid response appears to be secondary to perturbation of thyroid homeostasis. Thus, the conazoles appear to drive a tumor response secondary to epigenetic effects and not from direct interaction with the DNA. An epigenetic mode of action would be consistent with a nonlinear process.

The toxicity profile of 1,2,4-triazole is not similar to those of related conazole pesticides showing a high rate of metabolic conversion to 1,2,4-triazole (see Appendix). Unlike the conazoles currently being studied by NHEERL, 1,2,4-triazole did not alter thyroid hormones and did not cause any of the pre-neoplastic changes in liver or thyroid typically observed following subchronic exposures. There were decreases in liver weights reported in the 30-day and 2-generation reproductive rat studies but these effects were not associated with preneoplastic changes. Also, a decrease in serum TSH was reported in a subchronic neurotoxicity study which is inconsistent with the mode of thyroid carcinogenic action which requires increased circulating TSH and subsequent thyroid follicular cell hyperplasia. The available toxicity studies on 1,2,4-triazole indicate that the nervous system and reproductive tissue are primary targets and thus those toxicities should be considered in the risk assessment.

In summary, because a chronic cancer study is not available, it is recommended that a margin of exposure or RfD approach based on the most sensitive toxicity endpoint with the inclusion of a database uncertainty factor to account for the absence of chronic toxicity studies should be used. This approach should be adequately protective of human health and would be consistent with the recently reported cancer-related findings for a series of triazole-derivative fungicides.

4.5 Special FQPA Safety Factor

Based on the hazard data, the RARC recommended the special FQPA SF be reduced to 1x because there are low residual concerns and no residual uncertainties with regard to pre- and/or postnatal toxicity. The 1,2,4-triazole risk assessment team evaluated the quality of the exposure data and, based on these data, recommended that the special FQPA SF be reduced to 1x. The recommendation is based on the following:

- The dietary exposure assessment is based on 100% CT information for all food commodities and conservatively estimated anticipated residue levels. Estimates for drinking water were generated by models and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations. By using these screening-level assessments, dietary exposures/risks will not be underestimated.

- The residential exposure assessment is based on high-end assumptions regarding incidental oral and dermal exposures to 1,2,4-T.

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

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (females 13-49)	NOAEL = 30 mg/kg UF=1000 **Acute RfD**= 0.03 mg/kg	FQPA SF = 1 **aPAD** = acute RfD / FQPA SF = 0.03 mg/kg/day	**Developmental Toxicity study in rabbits** LOAEL=45 mg/kg based on urinary tract malformations in fetuses
Acute Dietary (general population)	NOAEL = 30 mg/kg UF=1000 **Acute RfD**= 0.03 mg/kg	FQPA SF = 1 **aPAD** = acute RfD / FQPA SF = 0.03 mg/kg/day	**Developmental Toxicity study in rabbits** LOAEL=45 mg/kg based on clinical signs and mortality in does starting on Gestation Day 6 or 7
Chronic Dietary (all populations)	LOAEL = 15 mg/kg/day UF =3000 **Chronic RfD** = 0.005 mg/kg/day	FQPA SF =1 **cPAD** = chronic RfD / FQPA SF =0.005 mg/kg/day	**Reproductive Toxicity study in rats** LOAEL = 15 mg/kg/day based on decreased body weight in adult males, decreased body weight and brain weight in offspring
Incidental Oral Short-term (1-30 days)	NOAEL = 30 mg/kg/day	FQPA SF =1 LOC=1000	**Developmental Toxicity study in rabbits** LOAEL=45 mg/kg/day based on clinical signs and mortality in does starting on Gestation Day 6 or 7

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

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Incidental Oral Intermediate- or Long-term (30 days to 6 months)	LOAEL = 15 mg/kg/day	FQPA SF =1 LOC=3000	**Reproductive Toxicity study in rats** LOAEL = 15 mg/kg/day based on decreased body weight in adult males, decreased body weight and brain weight in offspring
Dermal Short-term (1-30 days)	NOAEL = 30 mg/kg/day	LOC=1000	**Developmental Toxicity study in rabbits** LOAEL=45 mg/kg/day based on clinical signs and mortality in does starting on Gestation Day 6 or 7
Dermal Intermediate- or Long-term (30 days to 6 months)	LOAEL = 15 mg/kg/day	LOC=3000	**Reproductive Toxicity study in rats** LOAEL = 15 mg/kg/day based on decreased body weight in adult males, decreased body weight and brain weight in offspring
Inhalation Short-term (1 - 30 days)	NOAEL = 30 mg/kg/day	LOC=1000	**Developmental Toxicity study in rabbits** LOAEL = 45 mg/kg/day based on clinical signs and mortality in does starting on Gestation Day 6 or 7
Inhalation Intermediate- or Long-term (30 days to 6 months)	LOAEL = 15 mg/kg/day	LOC=3000	**Reproductive Toxicity study in rats** LOAEL = 15 mg/kg/day based on decreased body weight in adult males, decreased body weight and brain weight in offspring
Cancer (oral, dermal, inhalation)	**Classification:** Not determined. Evaluate by RfD approach.		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable
* Refer to Section 4.5

4.6 Endocrine disruption

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

wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

Effects were observed in tests which indicated potential estrogen, androgen, and/or thyroid mediated toxicity.

- Testicular changes in mice (28- and 90-day mouse studies), sperm abnormalities in rats (reproductive toxicity study), decreases in testes weight in old rat 30- and 90-day toxicity studies.
- Ovarian changes in rats (90-day subchronic rat and reproductive toxicity study in rats).
- Delays in sexual maturation in rat reproductive toxicity study.
- Reproductive failure at high dose in rat reproductive study (only two litters produced, with no pups surviving lactation).
- Increased incidence of undescended testicle in rat developmental toxicity study.
- Dose-related decreases in TSH at 33 mg/kg/day and above in male rats in the subchronic/neurotoxicity study.

When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, 1,2,4-triazole may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

5.0 Public Health Data

No incidents involving 1,2,4-triazole were found from a search of the Incident Data System (1992 to present), the Poison Control Center Data (1993-2003), California (1982-2003, or NIOSH (1998-2003).

6.0 Exposure Characterization/Assessment

6.1 Dietary Exposure/Risk Pathway

(M. Doherty, DP 322238, 11/1/05)

6.1.1 Residue Profile

6.1.1.1 Residues in Food

Exposure to 1,2,4-triazole may occur through direct or indirect means. For purposes of this assessment, direct exposure is defined as exposure to residues of 1,2,4-triazole, *per se*. Indirect exposure to 1,2,4-triazole may occur when there is exposure to a triazole-derivative fungicide. Indirect exposure is defined as exposure to 1,2,4-triazole that occurs from exposure to a triazole fungicide and subsequent metabolic conversion of the parent compound to 1,2,4-triazole within the human system. For assessing direct and indirect dietary exposure, residue levels of 1,2,4-triazole were estimated from parent triazole-derivative fungicide tolerances. For each food/parent fungicide tolerance combination, a residue estimate was calculated by multiplying the tolerance by a metabolic conversion factor and by a molecular weight conversion factor. Direct-exposure residue levels used the metabolic factors from plant metabolism studies for crop

commodities and from livestock metabolism studies for livestock commodities. Indirect-exposure residue levels used metabolic factors from rat metabolism studies. For some compounds metabolic conversion factors were not readily available and the maximum factors from the entire class of compounds were used (20% for plants, 77% for livestock).

Through a joint effort by the U.S. Triazole Task Force (USTTF) and USDA's Pesticide Data Program (PDP), monitoring data depicting residues of 1,2,4-triazole are available for apples, peaches, wheat flour, bananas, eggs, peanut butter, soybeans, finished water, strawberry, milk, grapes, and tomato. Most of the monitoring data for 1,2,4-triazole were reported as being below the level of quantification.

The following rules were used to select residues for the dietary exposure analysis:

1. If no monitoring data were available for the crop, or from a representative commodity, the calculated residue value was used.
2. If the monitoring dataset contains values that are greater than the LOQ, the monitoring data were used.
3. If the monitoring data are all less than the reported LOQ and the calculated residue value is less than ½ LOQ, the calculated residue values were used.
4. If the monitoring data are less than the reported LOQ and the calculated residue value is greater than the LOQ, a value of ½ LOQ was used.
5. Average residue estimates from the indirect exposure pathway were added to either the maximum direct residue estimate for acute assessments or the average direct residue estimate for chronic assessments.

For the indirect-exposure part of the analysis, average indirect-residue estimates were used for both the acute and chronic assessments. The average value was selected due to the fact that this indirect exposure is addressed, at least in part, by the toxicology studies and risk assessment for the various triazole-derivative parent fungicides. A summary of the values used in the assessments and their sources is shown in Table 6.1. Field trial studies for some triazole-derivative fungicides include analyses for 1,2,4-triazole. These data could be used to refine the exposure and risk estimates; however, due to timing issues, resource constraints, and the various stages of review of the submissions, they were not considered for these assessments.

1,2,4-Triazole is not currently listed in 40 CFR Section 180, nor is it included in the tolerance expression for any triazole-derivative fungicide. Due to the multiple potential sources of 1,2,4-triazole and its occurrence in the environment, HED believes that 1,2,4-triazole is not an appropriate analyte for tolerance-enforcement purposes and is not recommending that tolerances for this compound be established.

Table 6.1. Summary of Direct and Indirect Residue Estimates Used to Assess Dietary Exposure to 1,2,4-Triazole.

Item	Dietary Model Input, ppm [1]		Direct Exposure [2]									Average Indirect Residue Estimate, ppm [6]
			Selected Residue Estimate, ppm [3]				Calculated Data, ppm [4]		Monitoring Data, ppm [5]			
	Acute	Chronic	Acute	Acute Source	Chronic	Chronic Source	Max.	Avg.	LOQ	Max.	Avg.	
Pome Fruit (Apple)	0.0253	0.0253	0.0100	1/2 LOQ	0.0100	1/2 LOQ	0.0470	0.0182	0.02000	0.02000	0.02000	0.0153
Artichoke	0.0753	0.0655	0.0478	Max. Calc'd	0.0380	Avg. Calc'd	0.0478	0.0380	---	---	---	0.0275
Asparagus	0.0099	0.0056	0.0071	Max. Calc'd	0.0028	Avg. Calc'd	0.0071	0.0028	---	---	---	0.0028
Banana	0.0238	0.0238	0.0050	1/2 LOQ	0.0050	1/2 LOQ	0.1913	0.0279	0.01000	0.00315	0.00036	0.0188
Dry Bean	0.0230	0.0137	0.0202	Max. Calc'd	0.0109	Avg. Calc'd	0.0202	0.0109	---	---	---	0.0028
Succulent Bean	0.0568	0.0291	0.0478	Max. Calc'd	0.0201	Avg. Calc'd	0.0478	0.0201	---	---	---	0.0090
Blueberry	0.0462	0.0321	0.0404	Max. Calc'd	0.0263	Avg. Calc'd	0.0404	0.0263	---	---	---	0.0058
Caneberry	0.1495	0.1305	0.0957	Max. Calc'd	0.0767	Avg. Calc'd	0.0957	0.0767	---	---	---	0.0538
Canola	0.0100	0.0082	0.0040	Max. Calc'd	0.0022	Avg. Calc'd	0.0040	0.0022	---	---	---	0.0060
Carrot	0.0101	0.0101	0.0081	Max. Calc'd	0.0081	Avg. Calc'd	0.0081	0.0081	---	---	---	0.0020
Leafy Petioles	0.2523	0.2523	0.2018	Max. Calc'd	0.2018	Avg. Calc'd	0.2018	0.2018	---	---	---	0.0505
Barley	0.0055	0.0043	0.0040	Max. Calc'd	0.0028	Avg. Calc'd	0.0040	0.0028	---	---	---	0.0015
Oats	0.0056	0.0046	0.0040	Max. Calc'd	0.0030	Avg. Calc'd	0.0040	0.0030	---	---	---	0.0016
Rice	0.3073	0.1236	0.2826	Max. Calc'd	0.0989	Avg. Calc'd	0.2826	0.0989	---	---	---	0.0247
Rye	0.0058	0.0050	0.0040	Max. Calc'd	0.0032	Avg. Calc'd	0.0040	0.0032	---	---	---	0.0018
Wheat	0.0053	0.0040	0.0040	Max. Calc'd	0.0027	Avg. Calc'd	0.0040	0.0027	---	---	---	0.0013
Wheat Flour	0.0053	0.0040	0.0040	Max. Calc'd	0.0027	Avg. Calc'd	0.0040	0.0027	0.01000	0.01000	0.01000	0.0013
Wild Rice	0.0252	0.0252	0.0202	Max. Calc'd	0.0202	Avg. Calc'd	0.0202	0.0202	---	---	---	0.0050
Citrus Group	0.0436	0.0436	0.0410	Max. Calc'd	0.0410	Avg. Calc'd	0.0410	0.0410	---	---	---	0.0026
Coffee	0.0411	0.0005	0.0410	Max. Calc'd	0.0004	Avg. Calc'd	0.0410	0.0004	---	---	---	0.0001
Field Corn	0.0052	0.0035	0.0040	Max. Calc'd	0.0023	Avg. Calc'd	0.0040	0.0023	---	---	---	0.0012
Sweet Corn	0.0051	0.0033	0.0040	Max. Calc'd	0.0022	Avg. Calc'd	0.0040	0.0022	---	---	---	0.0011
Cotton	0.0965	0.0300	0.0898	Max. Calc'd	0.0233	Avg. Calc'd	0.0898	0.0233	---	---	---	0.0067
Cranberry	0.0460	0.0266	0.0404	Max. Calc'd	0.0210	Avg. Calc'd	0.0404	0.0210	---	---	---	0.0056
Cucurbits	0.0126	0.0100	0.0096	Max. Calc'd	0.0070	Avg. Calc'd	0.0096	0.0070	---	---	---	0.0030
Curant	0.1844	0.1328	0.1435	Max. Calc'd	0.0919	Avg. Calc'd	0.1435	0.0919	---	---	---	0.0409
Elderberry	0.0505	0.0505	0.0404	Max. Calc'd	0.0404	Avg. Calc'd	0.0404	0.0404	---	---	---	0.0101
Grape	0.0500	0.0337	0.0213	Max. Mon.	0.0050	Avg. Mon.	0.2244	0.0727	0.01000	0.02130	0.00150	0.0287

Table 6.1. Summary of Direct and Indirect Residue Estimates Used to Assess Dietary Exposure to 1,2,4-Triazole.

Item	Dietary Model Input, ppm [1]		Direct Exposure [2]									Average Indirect Residue Estimate, ppm [6]
			Selected Residue Estimate, ppm [3]				Calculated Data, ppm [4]		Monitoring Data, ppm [5]			
	Acute	Chronic	Acute	Acute Source	Chronic	Chronic Source	Max.	Avg.	LOQ	Max.	Avg.	
Raisin	0.5932	0.5132	0.4800	Max. Calc'd	0.4000	Avg. Calc'd	0.4800	0.4000	---	---	---	0.1132
Hops	1.5278	1.5278	1.3460	Max. Calc'd	1.3460	Avg. Calc'd	1.3460	1.3460	---	---	---	0.1818
Lychee	0.0855	0.0855	0.0673	Max. Calc'd	0.0673	Avg. Calc'd	0.0673	0.0673	---	---	---	0.0182
Mango	0.0114	0.0114	0.0090	Max. Calc'd	0.0090	Avg. Calc'd	0.0090	0.0090	---	---	---	0.0024
Mayhaw	0.0419	0.0419	0.0335	Max. Calc'd	0.0335	Avg. Calc'd	0.0335	0.0335	---	---	---	0.0084
Bulb Vegetables	0.0142	0.0104	0.0121	Max. Calc'd	0.0083	Avg. Calc'd	0.0121	0.0083	---	---	---	0.0021
Green Onion	0.3350	0.3350	0.3229	Max. Calc'd	0.3229	Avg. Calc'd	0.3229	0.3229	---	---	---	0.0121
Okra	0.0570	0.0570	0.0449	Max. Calc'd	0.0449	Avg. Calc'd	0.0449	0.0449	---	---	---	0.0121
Peanut	0.0097	0.0053	0.0081	Max. Calc'd	0.0037	Avg. Calc'd	0.0081	0.0037	---	---	---	0.0016
Peanut Butter	0.0779	0.0266	0.0763	Max. Mon.	0.0250	Avg. Mon.	0.0081	0.0037	0.01000	0.07630	0.02500	0.0016
Peppers	0.0717	0.0717	0.0478	Max. Calc'd	0.0478	Avg. Calc'd	0.0478	0.0478	---	---	---	0.0239
Peppermint	0.2153	0.2153	0.1435	Max. Calc'd	0.1435	Avg. Calc'd	0.1435	0.1435	---	---	---	0.0718
Pineapple	0.2192	0.1507	0.1411	Max. Calc'd	0.0726	Avg. Calc'd	0.1411	0.0726	---	---	---	0.0781
Sorghum	0.0094	0.0056	0.0081	Max. Calc'd	0.0043	Avg. Calc'd	0.0081	0.0043	---	---	---	0.0013
Soybean	0.0145	0.0145	0.0050	1/2 LOQ	0.0050	1/2 LOQ	0.0807	0.0290	0.01000	0.00290	0.00060	0.0095
Spearmint	0.2153	0.2153	0.1435	Max. Calc'd	0.1435	Avg. Calc'd	0.1435	0.1435	---	---	---	0.0718
Stone Fruit-no cherry	0.1158	0.0858	0.0957	Max. Calc'd	0.0657	Avg. Calc'd	0.0957	0.0657	0.21000	0.21000	0.21000	0.0201
Cherry	0.2863	0.1824	0.2392	Max. Calc'd	0.1353	Avg. Calc'd	0.2392	0.1353	---	---	---	0.0471
Strawberry	0.0315	0.0315	0.0180	1/2 LOQ	0.0180	1/2 LOQ	0.0605	0.0422	0.03600	0.03600	0.03600	0.0135
Sugar Beet	0.0152	0.0092	0.0121	Max. Calc'd	0.0061	Avg. Calc'd	0.0121	0.0061	---	---	---	0.0031
Sugar Beet Molasses	0.1520	0.0920	0.1210	Max. Calc'd	0.0610	Avg. Calc'd	0.1210	0.0610	---	---	---	0.0310
Sunflower	0.0028	0.0028	0.0022	Max. Calc'd	0.0022	Avg. Calc'd	0.0022	0.0022	---	---	---	0.0006
Tomato	0.0122	0.0122	0.0050	1/2 LOQ	0.0050	1/2 LOQ	0.0144	0.0144	0.01000	0.01000	0.01000	0.0072
Turnip	0.0228	0.0228	0.0180	Max. Calc'd	0.0180	Avg. Calc'd	0.0180	0.0180	---	---	---	0.0048
Turnip Greens	0.3638	0.3638	0.3590	Max. Calc'd	0.3590	Avg. Calc'd	0.3590	0.3590	---	---	---	0.0048
Tree Nuts	0.0048	0.0039	0.0040	Max. Calc'd	0.0031	Avg. Calc'd	0.0040	0.0031	---	---	---	0.0008
Almond	0.0186	0.0120	0.0164	Max. Calc'd	0.0098	Avg. Calc'd	0.0164	0.0098	---	---	---	0.0022
Pecan	0.0049	0.0049	0.0041	Max. Calc'd	0.0041	Avg. Calc'd	0.0041	0.0041	---	---	---	0.0008
Pistachio	0.0048	0.0039	0.0040	Max. Calc'd	0.0031	Avg. Calc'd	0.0040	0.0031	---	---	---	0.0008

Table 6.1. Summary of Direct and Indirect Residue Estimates Used to Assess Dietary Exposure to 1,2,4-Triazole.

Item	Dietary Model Input, ppm [1]		Direct Exposure [2]									Average Indirect Residue Estimate, ppm [6]
			Selected Residue Estimate, ppm [3]				Calculated Data, ppm [4]		Monitoring Data, ppm [5]			
	Acute	Chronic	Acute	Acute Source	Chronic	Chronic Source	Max.	Avg.	LOQ	Max.	Avg.	
Poultry Meat	0.0073	0.0051	0.0045	Max. Calc'd	0.0023	Avg. Calc'd	0.0045	0.0023	---	---	---	0.0028
Poultry Fat	0.0064	0.0038	0.0045	Max. Calc'd	0.0019	Avg. Calc'd	0.0045	0.0019	---	---	---	0.0019
Poultry Meat Byprod.	0.0063	0.0036	0.0045	Max. Calc'd	0.0018	Avg. Calc'd	0.0045	0.0018	---	---	---	0.0018
Poultry Liver	0.0073	0.0056	0.0045	Max. Calc'd	0.0028	Avg. Calc'd	0.0045	0.0028	---	---	---	0.0028
Egg	0.0073	0.0056	0.0045	Max. Calc'd	0.0028	Avg. Calc'd	0.0045	0.0028	0.01000	0.00370	0.00050	0.0028
Cattle Meat	0.0644	0.0254	0.0517	Max. Calc'd	0.0127	Avg. Calc'd	0.0517	0.0127	---	---	---	0.0127
Cattle Fat	0.0644	0.0323	0.0517	Max. Calc'd	0.0196	Avg. Calc'd	0.0517	0.0196	---	---	---	0.0127
Cattle Meat Byprod.	0.0644	0.0253	0.0517	Max. Calc'd	0.0126	Avg. Calc'd	0.0517	0.0126	---	---	---	0.0127
Cattle Liver	0.6834	0.2236	0.5716	Max. Calc'd	0.1118	Avg. Calc'd	0.5716	0.1118	---	---	---	0.1118
Cattle Kidney	0.0675	0.0316	0.0517	Max. Calc'd	0.0158	Avg. Calc'd	0.0517	0.0158	---	---	---	0.0158
Milk	0.0080	0.0052	0.0053	Max. Mon.	0.0025	Avg. Mon.	0.0071	0.0027	0.00500	0.00530	0.00140	0.0027

[1] Values used in the dietary exposure assessment are a sum of the selected acute or chronic residue estimate and the average indirect residue estimate.
[2] Values used to estimate direct ingestion of residues of 1,2,4-triazole. Values were selected from calculated data or monitoring data as indicated.
[3] Residue estimates and sources selected from calculated data or monitoring data using the criteria discussed in Section 6.1.1.1.
[4] Maximum or average residue estimates based on parent triazole-derivative fungicide tolerances after compensating for metabolic and molecular weight factors.
[5] Residue data for 1,2,4-triazole from USDA Pesticide Data Program or U.S. Triazole Task Force monitoring data.
[6] Average indirect residue estimates based on parent triazole-derivative fungicide tolerances after compensating for rat metabolic and molecular weight factors.

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6.1.1.2 Residues in Water
(I. Maher, DP 320682, In Preparation)

Residues of 1,2,4-triazole in drinking water were provided to HED by the Environmental Fate and Effects Division. The Tier II PRZM/EXAMS (surface water) and SCIGROW (groundwater) residue estimates are summarized in Table 6.2. The estimated surface water concentrations were used directly in the acute and chronic dietary exposure model. A small-scale prospective groundwater monitoring study was conducted in New Jersey for parent triadimefon (1997). In that study, the average maximum concentration (663-day mean) of 1,2,4-T in pore water at a depth of 9 ft was 0.0167 ppm. That level is significantly greater than the SCIGROW estimate. HED notes that there were no detections of 1,2,4-triazole in any of the 271 water samples analyzed by PDP. The limit of quantification for those analyses is 730 parts-per-trillion (0.73 ppb, 0.00073 ppm), more than two orders of magnitude less than the modeled surface water residue estimates.

Table 6.2. Summary of Tier II Modeled Concentrations of Triazole Metabolites in Drinking Water.

Exposure Duration	Surface Water Concentration, ppm	Groundwater Concentration, ppm
Acute	0.041	0.001
Chronic	0.011	0.001

6.1.2 Acute and Chronic Dietary Exposure and Risk

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID, Version 2.03), which uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. A separate cancer dietary assessment was not conducted. Although there is some concern regarding the carcinogenicity of 1,2,4-T, HED believes that the chronic dietary exposure assessment is sufficiently protective of any cancer-related effects.

The acute and chronic assessments include direct dietary exposure to 1,2,4-triazole as well as indirect exposure that may occur due to food-borne residues of parent triazole-derivative fungicide and the subsequent *in-vivo* conversion of parent compound to 1,2,4-trizole within the human system. For both direct and indirect exposures, residue estimates were derived from parent-compound tolerance values, taking into consideration any monitoring data that were available for 1,2,4-triazole. Both acute and chronic assessments make the conservative assumption that 100% of foods with triazole-derivative fungicide registrations (active, pending, and requested) were treated with a triazole-derivative fungicide. Both assessments are deterministic and include residue estimates for water.

Acute exposure estimates for 1,2,4-triazole range from 0.0025 to 0.0096 mg/kg/day at the 95th percentile of exposure. The maximum exposure estimate is for infants less than 1 year of age and corresponds to a risk estimate of 32% of the acute Population-adjusted Dose (aPAD). Chronic exposure estimates range from 0.0005 to 0.00196 mg/kg/day. For the chronic exposure estimates, the maximum is for children aged 1 to 2 years. The risk estimate associated with that group is 39% of the chronic PAD (cPAD). HED is generally concerned when risk estimates for any representative population subgroup exceed 100% of the PAD. The risk estimates associated with 1,2,4-triazole are below HED's level of concern. These assessments are considered to be

conservative because (1) the food residue estimates are derived from parent-compound tolerances or from high-end residues in monitoring data, (2) the residue in drinking water is based on conservatively modeled estimates, (3) all food and water in the analysis are assumed to have high-end levels of residue, and (4) the inclusion of the indirect exposure pathway is already partially addressed by the dietary exposure and risk analyses for the various parent compounds. As shown in Table 6.3, risk estimates for all population subgroups are below HED's level of concern at all presented percentiles of exposure. Based on the conservative nature of this assessment, the 95th percentile is the most appropriate for regulatory purposes.

Although these dietary exposure assessments are principally based on anticipated residues, the data, selection criteria, and assumptions that serve as the source of those residues are conservative in nature. HED has assumed that application of multiple triazole-derivative fungicides will not occur for any given crop during a single growing season. Although such a scenario is not currently prohibited via product labeling, HED believes that such practices will be unlikely due to economic and resistance-management issues. Overall, this assessment likely overestimates actual direct and indirect dietary exposure to 1,2,4-triazole. Even with the conservatisms in the dietary assessments, risk estimates for the general U.S. population and all representative population subgroups, including those of infants and children, are well below HED's level of concern. Reviewed field trial data depicting measured residues of 1,2,4-triazole in foods are likely to be available as HED progresses with evaluation of new-use and new-active-ingredient petitions. Use of these data, as well as incorporation of the entire distribution of monitoring data, will result in more realistic dietary exposure and risk estimates and may be useful if exposure and risk estimates require refinement.

Table 6.3. Dietary (Food + Water) Direct and Indirect Exposure and Risk Estimates for 1,2,4-Triazole.

Population Subgroup	aPAD, mg/kg/day	Exposure Estimate, mg/kg/day			Risk Estimate, %aPAD[a]		
		95th %ile	99th %ile	99.9th %ile	95th %ile	99th %ile	99.9th %ile
Acute							
U.S. Population (total)	0.03	0.0036	0.0060	0.0108	12	20	36
All infants (< 1 year)	0.03	**0.0096**	**0.0130**	**0.0212**	**32**	**44**	**71**
Children 1-2 yrs	0.03	0.0072	0.0107	0.0145	24	36	48
Children 3-5 yrs	0.03	0.0059	0.0085	0.0144	20	28	48
Children 6-12 yrs	0.03	0.0038	0.0055	0.0082	13	18	27
Youth 13-19 yrs	0.03	0.0027	0.0044	0.0067	9	15	22
Adults 20-49 yrs	0.03	0.0028	0.0044	0.0069	9	15	23
Adults 50+ yrs	0.03	0.0025	0.0034	0.0056	8	11	19
Females 13-49 yrs	0.03	0.0028	0.0043	0.0067	9	14	22

Chronic			
Population Subgroup	cPAD, mg/kg/day	Exposure Estimate, mg/kg/day	Risk Estimate, % cPAD[a]
U.S. Population (total)	0.005	0.00069	14
All infants (< 1 year)	0.005	0.00156	31
Children 1-2 yrs	0.005	**0.00196**	**39**
Children 3-5 yrs	0.005	0.00149	30
Children 6-12 yrs	0.005	0.00088	18
Youth 13-19 yrs	0.005	0.00054	11
Adults 20-49 yrs	0.005	0.00055	11
Adults 50+ yrs	0.005	0.00055	11
Females 13-49 yrs	0.005	0.00054	11

The values for the population with the highest risk for each type of risk assessment are bolded.
[a] Reported to 2 significant figures.

6.2 Residential (Non-Occupational) Exposure/Risk Pathway

(J. Arthur, DP 322240, 12/9/05)

6.2.1 Home Uses

There is a potential for exposure to 1,2,4-T for homeowners in residential settings during the application of T-D fungicide products on lawns (turf) and from subsequent contact during activities in such treated areas. As a result, risk assessments have been completed for both residential handler and postapplication scenarios.

Toddlers can be exposed directly to 1,2,4-T by ingesting soil where T-D fungicides have been applied due to environmental degradation of the parent compound to 1,2,4-T. Indirect exposure to 1,2,4-T for toddlers can occur from dermal contact and absorption of T-D fungicide residues on treated turf, with subsequent internal metabolism to 1,2,4-T. Similarly, indirect exposure also can occur through incidental ingestion of parent residues from hand-to-mouth and object-to-mouth activities on T-D fungicide-treated turf. Indirect 1,2,4-T exposure can occur for adults following direct dermal and inhalation exposure to T-D fungicides while applying these products to home lawns. Indirect exposure may also occur after application via the dermal route from subsequent contact with treated lawns. HED believes that formation of 1,2,4-T in plants will occur within the structures of the plant or result from uptake from soil. Therefore surface, dislodgable residues will not be available and direct hand-to mouth, object-to-mouth, or dermal exposure to 1,2,4-T are unlikely.

1,2,4-T exposure is determined by certain key characteristics specific to the parent T-D fungicide from which it is formed. These characteristics can be different for each parent T-D fungicide and include application rate, environmental and metabolic conversion rates, molecular weight, and dermal absorption factors. HED has based its assessment of residential exposure on the currently registered turf-use T-D fungicide that results in the highest 1,2,4-T exposure (i.e., triadimefon)

6.2.1.1 Application Scenarios

Non-occupational exposure is likely during the handling of T-D fungicides in the treatment of residential lawns. The major residential exposure scenarios are mixer/loader/applicators using a hose-end sprayer or a low-pressure hand wand.

The following assumptions and factors are specific to the residential assessment:

- Residential handler exposure scenarios are limited to short-term duration due to the episodic uses associated with homeowner products.
- Homeowner handler assessments are based on individuals wearing shorts and short-sleeved shirts.
- Homeowner handlers are expected to complete all tasks associated with the use of a pesticide product including mixing/loading, if needed, as well as the application.
- The Agency always considers the maximum application rates allowed by labels in its risk

assessments to consider what is legally possible based on the label.

- The Agency based calculations on what would reasonably be treated by homeowners such as the size of a lawn, or the size of a garden.
- A 70-kg body weight is used for adults because the toxicity endpoint is not gender-specific.

Residential handlers may be exposed dermally and by inhalation during mixing, loading and application of T-D fungicides for short-term durations. Because a common toxicity endpoint was identified for both dermal and inhalation routes, a combined risk from both routes of exposure is assessed. Results from these risk calculations for residential handlers are seen in Table 6.4 for triadimefon.

Table 6.4. Non-occupational Handler Exposure and Risk Estimates for 1,2,4-Triazole from Triadimefon Application to Turf.

Exposure Scenario	Personal Protective Equipment	Exposure Route	Applic. Rate, lb ai/A	Absorption Rate, %	Amount Treated per day, acre	Unit Exposure, mg/lb ai	Data Confidence	Daily Dose,[1] mg/kg/day	MOE[2]	Total Daily Dose, mg/kg/day	Total MOE[3]
M/L/A Liquids: hose-end sprayer	short sleeves short pants no gloves	Dermal	2.75	8	0.5	11[4]	High	0.00091	33,000	0.00093	32,000
		Inhalation		100		0.016[4]	High	0.000017	1.8E+6		
M/L/A Liquids: low-pressure hand wand	short sleeves short pants no gloves	Dermal	2.75	8	0.023 (1000 ft^2)	56[5]	Low	0.00021	140,000	0.00021	140,000
		Inhalation		100		0.0038[5]	Medium	0.00000018	1.7E+8		

[1] Daily Dose = [Application Rate * MW Ratio (0.24) * Metabolic Rate (0.22) * Absorption Rate * Amount Treated * Unit Exposure)]/Body Weight (70 kg)
[2] MOE = NOAEL/Daily Dose. The dermal and inhalation NOAEL = 30 mg/kg/day, was used for all calculations. The LOC = 1000.
[3] Total MOE = NOAEL/(dermal daily dose + inhalation daily dose)
[4] Unit exposure values taken from ORETF study (OMA004), "Mixer/Loader/Applicator: Hose-end Sprayer. Mix your own."
[5] Unit exposure values taken from ORETF study (OMA005), "Resident Mixer/loader/applicator - Handheld Pump Sprayer: Fruit Trees and Ornamentals."

Residential handler risk estimates from exposure to 1,2,4-T do not exceed HED's LOC for lawn use of triadimefon. Dermal absorption factors used in this assessment were taken from the May 2005 assessment (MRID 46553701) provided by the U.S. Triazole Task Force (USTTF).

6.2.1.2 Postapplication Scenarios

Individuals of varying ages can potentially be exposed from activities on treated turf. Potential routes of exposure include dermal and incidental ingestion (toddlers only). Residential uses of T-D fungicides may result in short-term (1 to 30 days) postapplication exposures. Available data for 1,2,4-T and various parent T-D fungicides indicates that residues of these compounds may persist long enough to warrant assessment of intermediate-term exposures (> 30 days to 180 days).

The HED Standard Operating Procedures for Residential Exposure Assessments (Draft, December 18, 1997) were used as a guideline for performing the residential postapplication assessment. Also used in the assessment were interim changes to these SOPs which were adopted by the HED Exposure Science Advisory Council regarding standard values, including, for turf transferrable residues, turf transfer coefficients and hand-to-mouth activities (Policy 11, February 22, 2001). The exposure and risk estimates for the four residential exposure scenarios are assessed for the day of application (day "0") because it is assumed that adults and toddlers could contact the lawn immediately after application. On the day of application, it was assumed that 5 percent of the application rate is available from the turf grass as transferable residue (20 percent for object-to-mouth activities).

Assessment of residential postapplication exposure was performed using the same approach as was used for handler exposure above using the T-D fungicide triadimefon.

A summary of the estimated exposures and risks, along with the algorithms used for each turf exposure scenario are presented below in Tables 6.5 – 6.8 for triadimefon.

Table 6.5. Dermal Exposure and Risk for Adults and Children from Treated Lawns (Triadimefon)									
Subgroup exposed	Application Rate, lb ai/A	Fraction of ai Available	Turf Transferrable Residue at Day "0" (ug/cm^2)[1]	Dermal Transfer Coefficient, cm^2/hr	Exposure Time, hrs/day	Absorption Factor	Body Weight, kg	Daily Dose,[2] mg/kg/day	MOE[3]
Adult	5.4	0.05	2.94	14,500	2	8%	70	0.0051	5,900
Children	5.4	0.05	2.94	5200	2	8%	15	0.0086	3,500

[1] Turf Transferrable Residue (ug/cm^2) = Application rate (lb ai/A) x Fraction of ai Available x 4.54E+8 ug/lb x 2.47E-8 A/cm^2

[2] Daily Dose = (Turf Transferrable Residue x Absorption Factor x 1E-3 mg/ug x Dermal Transfer Coefficient x Exposure Time x MW ratio (0.24) x Metab. Conv. Rate (0.22))/Body weight

[3] MOE = Dermal NOAEL (30 mg/kg/day) /Daily Dose. LOC = 1000.

Table 6.6. Oral Hand-to-mouth Exposure and Risk for Children from Treated Lawns (Triadimefon)									
Application Rate, lb ai/A	Fraction of ai Available	Turf Transferrable Residue at Day "0", (ug/cm^2)[1]	Exposure Time, hrs/day	Extraction by saliva	Hand Surface Area, cm^2/event	Frequency, events/ hr	Body Weight, kg	Daily Dose,[2] mg/kg/day	MOE[3]
5.4	0.05	2.94	2	0.5	20	20	15	0.0041	7,300

[1] Turf Transferrable Residue (ug/cm^2) = Application rate (lb ai/A) x Fraction of ai Available x 4.54E+8 ug/lb x 2.47E-8 A/cm^2

[2] Daily Dose = (Turf Transferrable Residue x Extraction by Saliva x Hand Surface Area x Frequency x 1E-3 mg/ ug x Exposure Time x MW ratio x Metab. Conv. Rate)/Body Weight.

[3] MOE = Oral NOAEL (30 mg/kg/day) /Daily Dose. LOC = 1000.

Table 6.7. Oral Object-to-mouth (Turfgrass) Exposure and Risk for Children from Treated Lawns (Triadimefon)						
Application Rate, lb ai/A	Fraction of ai Available	Grass Residue at Day "0", (ug/cm^2)[1]	Surface Area Mouthed, cm^2/day	Body Weight, kg	Daily Dose,[2] mg/kg/day	MOE[3]
5.4	0.2	11.6	25	15	0.001	30,000

[1] Grass Residue (ug/cm^2) = Application rate (lb ai/A) x Fraction of ai Available x 4.54E+8 ug/lb x 2.47E-8 A/cm^2

[2] Daily Dose = (Grass residue x Surface Area Mouthed x 1E-3 mg/ug x MW ratio (0.24) x Metab. Conv. Rate (0.22))/Body Weight.

[3] MOE = Oral NOAEL (30 mg/kg/day) /Daily Dose. LOC = 1000.

Table 6.8 Exposure and Risk for Children from Ingestion of Soil from Treated Lawns (Triadimefon)								
Application Rate, lb ai/A	Fraction of ai Available	Soil Residue at Day "0", (ug/g)[1]	1,2,4-T to Parent MW Ratio	Max. Soil Conversion Rate to 1,2,4-T, %	Ingestion Rate, mg/day	Body Weight, kg	Daily Dose,[2] mg/kg/day	MOE[3]
5.4	1	39.4	0.24	30.7	100	15	0.000019	1,600,000

[1] Soil residue (ug/g) = [Application Rate (lbs ai/A) x Fraction of ai Available x 4.54E+8 ug/lb x 2.47E-8 A/cm^2 x 0.67 cm^3/g soil]
[2] Daily Dose = [Soil residue (ug/g) x Ingestion rate (mg/day) x 1E-6 g/ug] x Soil Conversion Rate x MW ratio / [Body Weight (kg)]
[3] MOE = Oral NOAEL (30 mg/kg/day) /Daily Dose. LOC = 1000.

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The MOEs for postapplication exposure to the T-D fungicide turf product, triadimefon are all > 1000 for individual routes of exposure, and therefore do not exceed HED's level of concern. FQPA requires residential exposures that could reasonably be expected to occur on the same day be combined and compared to the appropriate toxicity endpoint. Toddler dermal and incidental ingestion by hand-to-mouth, object-to-mouth and soil ingestion activities may co-occur. When the exposure estimates from these routes are combined, the MOE is 2200. As with the individual route MOEs, the aggregate MOE does not exceed HED's LOC.

HED has considered only ingestion of soil-borne residues in assessing intermediate-term risk. Although residues of parent T-D fungicides may persist on turf (environmental half-lives are on the order of 1-3 months), the act of mowing the lawn removes residues from the lawn surface and makes them unavailable for hand-to-mouth, object-to-mouth, and dermal exposures. The exposure estimate of 0.00013 mg/kg/day from short-term soil ingestion is being used as a highly conservative estimate for intermediate-term exposure as well. Applying the intermediate-term NOAEL of 15 mg/kg/day gives a MOE of approximately 120,000, which is significantly greater than the LOC of 3000. Therefore, the estimated intermediate-term risk is below HED's level of concern.

The exposure estimates in this assessment are based on some upper-percentile (i.e., maximum application rate) and some central tendency (i.e., surface area, hand-to-mouth activity, and body weight) assumptions and are, therefore, considered to be representative of central to high-end exposures. The uncertainties associated with this assessment stem from the use of an assumed amount of pesticide available from turf, and assumptions regarding transfer of chemical residues, and hand-to-mouth activity. Dermal absorption factors used in the assessments were taken from the May 2005 assessment (MRID 46553701) provided by the USTTF.

6.2.2 Recreational Use Sites

T-D fungicides may be used on turf at recreational use sites and, therefore may result in postapplication exposure to adults and children involved in recreational activities. Exposures to adults and children from the use of T-D fungicides at recreational use sites are assumed to be the same as those assessed for residential use sites, and therefore, a separate recreational exposure assessment was not included. Results from the residential turf exposure assessment are considered upper percentile risk estimates. Therefore, it is not expected that the high-end residential exposure scenario would occur on the same day as a high-end recreational exposure scenario. Exposures from the residential and recreational scenarios are not aggregated. Rather, the residential risk estimate should serve as a high-end estimate for both residential and recreational exposure.

6.2.3 Other (Spray Drift, etc.)

While the drifting of agricultural spray applications of T-D fungicides to nearby residential settings is possible, the T-D funcgicide turf uses addressed in the above residential risk assessment are considered to be conservative, worst case scenarios, that would cover any potential 1,2,4-T risks from agricultural spraying operations.

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

6.2.4 Pharmaceutical Uses

Triazole fungicides have proved to be useful tools in combating systemic fungal infections in humans. Examples of these compounds include fluconazole, itraconazole, voriconazole, and posaconazole. The Food and Drug Administration (FDA) approves uses of pharmaceutical products under FFDCA. EPA is currently working with FDA to derive appropriate exposure assessment methodology to determine how the pharmaceutical uses of triazole fungicides should be considered in the aggregate risk assessments for 1,2,4-triazole and the triazole conjugates (triazole alanine and triazole acetic acid). A supplementary exposure analysis will be completed, and the incremental impact of exposure to pharmaceutical uses of the triazole fungicides will be considered in the Agency's reregistration decisions for propiconazole, triadimefon, and triadimenol. For additional information, please refer to the EPA memorandum to FDA regarding the pharmaceutical uses of triazole fungicides (included in the dockets for propiconazole, triadimefon, and triadimenol).

7.0 Aggregate Risk Assessments and Risk Characterization

In assessing acute and chronic risk from aggregate exposure to 1,2,4-triazole, the only scenarios appropriate for consideration are dietary exposure (all non-dietary exposures are short- to intermediate-term in duration). Water was included in the dietary exposure estimates; therefore, the acute and chronic aggregate risk estimates are the same as those presented in Section 6.1.2. Risk estimates for those durations were all less than HED's level of concern. As previously noted, the chronic risk assessment is believed to be protective of any carcinogenic effects attributable to 1,2,4-T and a separate cancer risk assessment has not been completed. Risk estimates for short- and intermediate-term aggregate exposure are presented below. Evaluation of short- and intermediate-term risk includes exposures from non-dietary sources coupled with chronic dietary exposure estimates, as an approximation of background-level exposure by the dietary route. HED notes that this approach implicitly assumes that the non-dietary and dietary exposures are constantly co-occurring during the short- or intermediate-term duration being evaluated. The approach does not take into account the temporal variability inherent in exposures from these different pathways. Triadimefon use on turf is being used to cover non-dietary exposures for all T-D fungicides.

7.1 Short-term Aggregate Risk

In assessing short-term aggregate risk, HED has combined estimates of dietary exposure (direct and indirect), dermal exposure (indirect), hand-to-mouth exposure (indirect, toddlers only), object-to-mouth exposure (indirect, toddlers only) and soil ingestion (direct, toddlers only). These short-term aggregate risk estimates are considered to be very conservative. The pathway-specific exposure estimates are derived from high-end, health-protective assumptions. In aggregating these exposure estimates, HED has made the further conservative assumption that the exposures co-occur for the duration of the exposure interval (1-30 days). The exposure estimates and resulting aggregate MOE are summarized in Table 7.1. Aggregate MOEs are greater than the LOC of 1000 for all population subgroups. Therefore, the estimated risks are not of concern.

Table 7.1. Short-term Aggregate Exposure and Risk Estimates for 1,2,4-Triazole.

Population Subgroup	Exposure Estimate, mg/kg/day							Aggregate MOE[1]
	Dietary	Dermal (M/L/A)	Dermal (Post-Applic.)	Hand-to-Mouth	Object-to-Mouth	Soil Ingestion	Aggregate	
U.S. Population (total)	0.00069	0.00183	0.0051	N/A	N/A	N/A	0.00762	3,900
All infants (< 1 year)	0.00156	N/A	0.0086	0.0041	0.0010	0.000019	0.01528	2,000
Children 1-2 yrs	0.00196	N/A	0.0086	0.0041	0.0010	0.000019	0.01568	1,900
Children 3-5 yrs	0.00149	N/A	0.0086	0.0041	0.0010	0.000019	0.01521	2,000
Children 6-12 yrs	0.00088	N/A	0.0086	N/A	N/A	N/A	0.00948	3,200
Youth 13-19 yrs	0.00054	0.00183	0.0051	N/A	N/A	N/A	0.00747	4,000
Adults 20-49 yrs	0.00055	0.00183	0.0051	N/A	N/A	N/A	0.00748	4,000
Adults 50+ yrs	0.00055	0.00183	0.0051	N/A	N/A	N/A	0.00748	4,000
Females 13-49 yrs	0.00054	0.00183	0.0051	N/A	N/A	N/A	0.00747	4,000

[1] Aggregate MOE = NOAEL (30 mg/kg/day) ÷ Aggregate Exposure Estimate (mg/kg/day). LOC = 1000.

7.2 Intermediate-term Aggregate Risk

In assessing intermediate-term aggregate risk, HED has combined dietary exposure (direct and indirect) with soil ingestion (direct, toddlers only). Other sources of non-dietary exposure have not been included. As noted in Section 6.2, many T-D fungicides are relatively stable (half-lives on the order of 1-3 months). Although residues may persist into an intermediate-term timeframe, they will not be available for hand-to-mouth, object-to-mouth, or dermal exposure. Therefore, intermediate-term aggregate risk estimates only include pathways of dietary exposure and soil ingestion. Aggregate MOEs for infants and children ages 1 to 2 years are well above the intermediate-term LOC of 3000 and, therefore, represent risks that are below HED's level of

concern. Aggregate risk estimates for older populations, where soil ingestion is not an issue, are equivalent to the dietary risk estimates presented in Section 6.1.

Table 7.2. Intermediate-term Aggregate Exposure and Risk Estimates for 1,2,4-Triazole.

Population Subgroup	Exposure Estimate, mg/kg/day			Aggregate MOE[1]
	Dietary	Soil Ingestion	Aggregate	
U.S. Population (total)	0.00069	N/A	0.00069	22,000
All infants (< 1 year)	0.00156	0.000019	0.00158	9,500
Children 1-2 yrs	0.00196	0.000019	0.00198	7,600
Children 3-5 yrs	0.00149	0.000019	0.00151	9,900
Children 6-12 yrs	0.00088	N/A	0.00088	17,000
Youth 13-19 yrs	0.00054	N/A	0.00054	28,000
Adults 20-49 yrs	0.00055	N/A	0.00055	27,000
Adults 50+ yrs	0.00055	N/A	0.00055	27,000
Females 13-49 yrs	0.00054	N/A	0.00054	28,000

[1] Aggregate MOE = NOAEL (15 mg/kg/day) ÷ Aggregate Exposure Estimate (mg/kg/day). LOC = 3000.

8.0 Cumulative Risk Characterization/Assessment

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 assessment for the triazole metabolites. Investigations into the potential cumulative effects of 1,2,4-triazole, triazole alanine and triazole acetic acid, and parent triazole-derivative fungicides are currently being undertaken by the Office of Research and Development. Additionally, EPA has not made a common mechanism of toxicity finding regarding the triazole metabolites and any other substances. For purposes of this assessment, EPA has assumed that 1,2,4-triazole and triazole alanine/triazole acetic acid do not have a common mechanism of toxicity and that the triazole metabolites do not have a common mechanism of toxicity with other substances.

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). For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for

cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

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 the triazole metabolites share a common mechanism of toxicity with any other substances. If HED identifies other substances that share a common mechanism of toxicity with the triazole metabolites, HED will perform aggregate exposure assessments on each chemical and will begin to conduct a cumulative risk assessment.

As previously noted, this assessment does take into consideration the multiple parent triazole-derivative fungicides that may lead to dietary and non-dietary exposure to the triazole metabolites.

9.0 Occupational Exposure/Risk Pathway

Occupational exposure to 1,2,4-triazole is likely to occur as a result of activities associated with a single T-D compound. The risks associated with occupational exposure to this compound are addressed in the risk assessments for the parent compounds. Those risk estimates inherently include risk associated with occupational exposure to 1,2,4-triazole. Therefore, an occupational exposure and risk assessment for 1,2,4-triazole, *per se*, is not warranted. This is unlike the case for dietary exposure where it is likely that multiple T-D fungicides simultaneously lead to 1,2,4-triazole exposure.

10.0 Data Needs and Label Requirements

10.1 Toxicology

- Developmental neurotoxicity study in rats.
- Chronic toxicity/oncogenicity study in male rats and female mice [This study, included in the original data call-in, has not been submitted. As noted above, a previous waiver request for this study was denied. A new waiver request submitted in August, 2005, is under review.]
- Acute neurotoxicity study in rats [This study, included in the original data call-in, was placed in reserve pending the results of the combined subchronic/neurotoxicity study, in response to a previous waiver request. A new waiver request for this study was submitted in August 2005, and is under review.]

10.2 Residue Chemistry

- A final two-year storage stability study with 1,2,4-triazole remains outstanding. An interim report, depicting residues following one year of storage indicates that 1,2,4-T is stable in frozen food commodities.

10.3 Occupational and Residential Exposure

- A study examining dislodgeable foliar residues of the T-D fungicide metabolites was requested. However, the USTTF has requested that the Agency waive the study, arguing that any residues of metabolites would be contained within the leaf surface and therefore not dislodgeable. The waiver request has been reviewed by HED and recommended to be granted (Jack Arthur, D319566, 12/22/05).

Triazole Alanine and Triazole Acetic Acid

11.0 Hazard Characterization/Assessment

11.1 Hazard Characterization

11.1.1 Database Summary

11.1.1.1 Studies available and considered

For triazole alanine, acute toxicity was evaluated using acute oral toxicity studies and a non-guideline acute intraperitoneal toxicity study. Subchronic studies available for hazard characterization included 14-day, 28-day, and 90-day oral toxicity studies in the rat and a 90-day oral toxicity study in the dog. No chronic studies were submitted. Developmental toxicity and two-generation reproduction studies in the rat were evaluated; a developmental toxicity study in the rabbit was not available. Multiple mutagenicity and metabolism studies were considered.

For triazole acetic acid, five acceptable studies were available for hazard characterization: an acute oral toxicity study, a non-guideline 14-day oral toxicity study in the rat, a bacterial reverse mutation assay, and two non-guideline metabolism studies.

For triazole lactic acid and triazole pyruvate, no mammalian toxicology studies were available.

11.1.1.2 Mode of action, metabolism, and toxicokinetic data

Mode of action. The parent triazole fungicides act by inhibiting sterol synthesis, particularly by preventing the 14-demethylation of the sterols. The sterols, which are similar to cholesterol in mammals, are important for fungi membrane structure and function. The mode(s) of action for mammalian toxicity associated with 1,2,4-triazole and the triazole conjugates is currently unknown.

Metabolism and toxicokinetic data. Pharmacokinetic studies showed that triazole alanine is rapidly absorbed and excreted following single oral gavage doses of 0.5, 0.56, 5, 54, 56, or 994 mg/kg, following five daily oral gavage doses of approximately 48-49 mg/kg/day, and following a single dose of 5 mg/kg by i.v. injection. Excretion occurred mostly in the urine, accounting for 81-85% to >90% of the administered radioactivity in three single oral and i.v. injection studies and ~55-63% in the multiple oral dose study at 168 hours. Much less of the radioactivity was excreted in the feces, which accounted for ~2-5% of the administered radioactivity in the single dose studies and ~11-27% in the multiple oral dose study. Volatiles accounted for <1% of the

radioactivity. Tissue residues were low in all studies, with the majority of the radiolabel found in tissues located in the liver and kidneys.

The two single oral dose triazole alanine metabolism studies are consistent, since both found high amounts of unchanged triazole alanine (72-93% of the radioactivity) recovered in the urine 24 hours after exposure to 0.56-994 mg/kg, lesser amounts of N-acetyl triazole alanine (8-30%), and a small percentage of unknown metabolites. There was no mention that triazole acetic acid or 1,2,4-triazole were detected in these urinary samples. (Note that N-acetyl triazole alanine and triazole acetic acid are structurally different.) From the fecal samples taken 24 hours following oral exposure to 56 mg/kg, a high proportion of the recovered radioactivity was unchanged triazole alanine (50%), with less N-acetyl triazole alanine identified (16%), similar to what was found in the urine. However, 30% of the radioactivity found in the fecal samples consisted of an unknown component that did not appear in the urinary samples.

In the repeated oral dose metabolism study, a large amount (63%) of the radioactivity recovered in the urine samples taken 168 hours following 5 doses of ~48-49 mg/kg/day triazole alanine was identified as unchanged triazole alanine, similar to what was seen 24 hours after a single dose. However, 30% of the urinary radioactivity was identified as triazole acetic acid, and 1.6% was identified as 1,2,4-triazole. These compounds were not seen in the single dose studies; furthermore, N-acetyl triazole alanine, which was seen in the single dose studies, was not seen in the repeated dose study. This study also showed that the same three components seen in the urine were found in the feces. However, a much larger percentage of the radioactivity recovered in the feces was identified as triazole acetic acid (69%) and 1,2,4-triazole (11%), with significantly less excreted as unchanged triazole alanine (2%). The remaining radioactivity in the feces was made up of three unknown conjugates, none of which was greater than 7%.

For triazole acetic acid, two metabolism and pharmacokinetic studies showed rapid absorption and excretion following a single oral dose of approximately 0.6, 59, or 1035 mg/kg or five daily oral doses of approximately 50-51 mg/kg/day. Excretion occurred mainly in the urine, as it did for triazole alanine, accounting for ~90-104% of the administered radiolabel in the single dose study and ~66-75% of the radiolabel in the multiple dose study at 168 hours. The feces accounted for much less of the administered radiolabel: ~1-7% in the single dose study and ~11-32% in the multiple dose study. In both studies, tissue burdens were very low. Unlike triazole alanine, the sole component identified in both the urinary and fecal extracts from these two studies was triazole acetic acid, indicating that triazole acetic acid administered to the rat is excreted intact without metabolic conversion.

11.1.1.3 Sufficiency of studies/data

Triazole alanine. The partial toxicology database available for triazole alanine is insufficient to fully characterize the hazards associated with this conjugate. However, it was possible to categorize the acute toxicity of triazole alanine, to identify effects following subchronic exposure, to begin examination of the differences in toxicity associated with longer duration of exposure and across species (i.e., rat and dog), to examine potential reproductive toxicity, to evaluate the differences in susceptibility between rodent parents and offspring, and to examine the potential of triazole alanine to cause mutagenicity.

The toxicity resulting from exposures to triazole alanine longer than 90 days was not determined because no chronic studies were available.

Interspecies differences were not fully examined because no triazole alanine studies were conducted in rabbits or mice. The lack of a developmental toxicity study in rabbits is a particularly important data gap, because mortality and clinical signs were seen in adult rabbits following a single dose of 45 mg/kg 1,2,4-triazole in a rabbit developmental study (MRID 46492903). For free triazole, the rabbit was shown to be the most sensitive species; in the absence of data to suggest otherwise, it is likely that rabbits are also more sensitive to triazole alanine.

Triazole acetic acid. The toxicology database for triazole acetic acid consists of five acceptable studies, including three non-guideline studies. In the absence of additional data, the studies on triazole acetic acid were compared to corresponding studies on triazole alanine to determine potential differences in potency between these two conjugates.

Other triazole conjugates. No mammalian toxicology studies are available for triazole lactic acid or triazole pyruvate. These compounds occur only infrequently in plant metabolism studies and have not been included in the quantitative risk assessment.

11.1.2 Toxicological Effects

11.1.2.1 Acute toxicity

Triazole alanine. The acute toxicity of triazole alanine is low, based on acute oral toxicity studies in the the rat and mouse (Category IV) and an acute intraperitoneal toxicity study in the rat (LD50 > 5000 mg/kg). Although triazole alanine was classified as Category III according to results from one acute oral toxicity study (MRID 00138119), this was because inadequate dose levels were tested. Note that although the acute toxicity of 1,2,4-triazole was greater in the rabbit than in the rat or mouse, a similar comparison of the acute toxicity of triazole alanine across species could not be made since acute rabbit studies were not submitted for the conjugate.

Triazole acetic acid. The acute toxicity of triazole acetic acid is also low, based on an acute oral toxicity study in the rat (Category IV).

Table 11.1. Acute Toxicity Profile for Triazole Alanine

Test Material [% ai]	Guideline Number	Study Type	MRID Number	Results	Toxicity Category
Triazole alanine [not specified]	870.1100	Acute oral - rat	00138119 (TXR 004766 Acc. 252132) 00133356	LD_{50} (♂+♀) > 2000 mg/kg Unacceptable/supplementary	III
Triazole alanine ["analytically pure"]	870.1100	Acute oral - rat	00138120 (TXR 004766 Acc. 252132) 00133357	LD_{50} (♂+♀) > 5000 mg/kg Acceptable/guideline	IV

Table 11.1. Acute Toxicity Profile for Triazole Alanine					
Test Material [% ai]	Guideline Number	Study Type	MRID Number	Results	Toxicity Category
Triazole alanine ["analytically pure"]	870.1100	Acute oral - mouse	00138120 (TXR 004766 Acc. 252132) 00133357	LD_{50} (♂+♀) > 5000 mg/kg Acceptable/guideline	IV
Triazole alanine [99%]	870.1100	Acute oral - dog	00138130 (TXR 004766 Acc. 252132)	Both dogs vomited a portion of the test material (5000 mg/kg) within 4 hours of dosing. No other signs were observed in the male. Slight salivation, slightly unsteady gait, and decreased food consumption and body weight were seen in the female. Unacceptable	Not determined
Triazole alanine ["analytical pure"]	Non-GDLN	Acute intraperitoneal - rat	00138120 (TXR 004766 Acc. 252132) 00133357	LD_{50} (♂+♀) > 5000 mg/kg Acceptable/non-guideline	N/A
Triazole alanine	870.1200	Acute dermal - rat	ND	ND	ND
Triazole alanine	870.1300	Acute inhalation - rat	ND	ND	ND
Triazole alanine	870.2400	Acute eye irritation - rabbit	ND	ND	ND
Triazole alanine	870.2500	Acute dermal irritation - rabbit	ND	ND	ND
Triazole alanine	870.2600	Skin sensitization - guinea pig	ND	ND	ND

ND = Study not done

Table 11.2. Acute Toxicity Profile for Triazole Acetic Acid					
Test Material [% ai]	Guideline Number	Study Type	MRID Number	Results	Toxicity Category
Triazole acetic acid [>99%]	870.1100	Acute oral - rat	45596802	LD_{50} (♂+♀) > 5000 mg/kg	IV
Triazole acetic acid	870.1200	Acute dermal - rat	ND	ND	ND
Triazole acetic acid	870.1300	Acute inhalation - rat	ND	ND	ND
Triazole acetic acid	870.2400	Acute eye irritation - rabbit	ND	ND	ND
Triazole acetic acid	870.2500	Acute dermal irritation - rabbit	ND	ND	ND
Triazole acetic acid	870.2600	Skin sensitization - guinea pig	ND	ND	ND

ND = Study not done

11.1.2.2 Subchronic, Chronic, and Other Toxicity

Triazole alanine. The toxicity of triazole alanine in the rat was examined in 14-, 28-, and 90-day oral toxicity studies, a developmental toxicity study, and a two-generation reproduction study. Of these five studies, adverse effects in adults were only observed in the 90-day feeding study.

These effects included decreased leukocytes in males and decreased triglycerides at the LOAEL (370/400 mg/kg/day, males/females), with decreased body weight and body weight gain (males), decreased leukocytes (both sexes), and decreased triglycerides (both sexes) observed at 1510/1680 mg/kg/day (males/females).

No treatment-related effects were seen in the 14-day drinking water study, in which male rats were exposed to triazole alanine at dose levels up to ~1500 mg/kg/day. Because hematological and clinical chemistry parameters (including those decreased in the 90-day study) were not measured in this study, it is unknown if they would be affected by two weeks exposure to triazole alanine. The decreases in body weight and body weight gain seen at the high dose in the 90-day rat study were not observed until week 3, so it is not unexpected that body weight measurements remained comparable to controls in this two week study.

No treatment-related effects were seen in the 28-day oral toxicity study, in which rats were exposed to triazole alanine via oral gavage at dose levels up to 400 mg/kg/day. This study was classified unacceptable due to the lack of analytical data on the test compound and incomplete hematological, clinical chemistry, and histopathological analyses. Leukocyte counts, which were measured in this study, were unaffected following 28 days exposure to triazole alanine by gavage (vehicle = Cremophor EL), although they were slightly decreased after one month of dietary exposure in the 90-day feeding study. Triglycerides, which were decreased in the 90-day study, were not evaluated in this study. The decreased body weights and body weight gains observed on week 3 of the 90-day study were not seen in this study, which is not unexpected given that the highest dose tested in the 28-day study was just 400 mg/kg/day vs. 1510 mg/kg/day in the 90-day study.

Systemic maternal/paternal toxicity was not seen in the developmental toxicity or two-generation reproduction studies in rats at dose levels up to ~1000 mg/kg/day. Reproductive toxicity was also not noted. Because hematology and clinical chemistry are not examined in developmental or reproduction studies, it is unknown if they were affected as in the 90-day feeding study. Changes in body weights observed in the 90-day study were not seen in either of these studies; however, the highest dose levels tested in the developmental and reproduction studies were lower than those which produced body weight effects in the 90-day study.

Differences in toxicity due to increased duration of exposure to triazole alanine could not be confirmed since treatment-related effects were only seen in the 90-day study and since hematological and clinical chemistry parameters were not measured in the shorter duration studies.

Differences between routes of exposure to triazole alanine could not be examined because dermal and inhalation studies were not available.

Differences in the toxicity of triazole alanine across mammalian species were examined by comparing the 90-day feeding studies in the rat and the dog. (Studies using the mouse or rabbit were not available. The lack of a rabbit study is a particularly important data gap because the rabbit is the most sensitive species to free triazole. Mortality and clinical signs of neurotoxicity were seen in adult rabbits following a single gavage dose of 45 mg/kg 1,2,4-triazole in a rabbit

developmental study [MRID 46492903]). As stated previously, treatment-related effects in the 90-day rat study include decreased leukocytes (males) and triglycerides (females) at the LOAEL (370/400 mg/kg/day in males/females), as well as decreased leukocytes and triglycerides in both sexes and decreased body weights and body weight gains in males at the highest dose tested (1510/1680 mg/kg/day in males). Triazole alanine is less toxic in dogs. The only treatment-related effect seen in the 90-day dog study was a 10% decrease in female food consumption near the limit dose (902 mg/kg/day), with no effects seen in males.

Increased quantitative and qualitative susceptibility of the offspring was seen in the developmental toxicity rat study, and increased quantitative susceptibility was seen in the two-generation reproduction study. In the developmental toxicity study, increased incidences of skeletal findings were seen in the offspring at the mid and high doses, while no treatment-related effects were seen in the dams up to the limit dose. These skeletal findings include unossified odontoid processes at 300 and 1000 mg/kg/day, with partially ossified transverse processes of the 7th cervical vertebra (bilateral), unossified 5th sternebra, and partially ossified 13th thoracic centrum observed only at 1000 mg/kg/day. In the reproduction study, mean litter weights were decreased approximately 10-20% for both generations at ~1000 mg/kg/day, compared to controls, but parental body weights were unaffected at all treatment levels.

No mutagenic potential was noted in the following acceptable mutagenicity studies:

1. bacterial reverse mutation assays,
2. *in vitro* mammalian cell gene mutation tests conducted in BALB/3T3 and CHO cells,
3. mammalian erythrocyte micronucleus tests conducted using mice and Chinese hamsters, and
4. bacterial DNA damage and repair tests.

An increased number of transformed colonies was seen in an *in vitro* mammalian cell gene mutation test conducted in baby hamster kidney cells (MRID 00132914); however, this study was classified unacceptable/inconclusive due to severe toxicity, excessive concentrations, and lack of information regarding test material purity. Mutagenic potential was also seen in a mammalian erythrocyte micronucleus test conducted using mice (MRID 0013912); however, this study was classified unacceptable/inconclusive because effects were seen only at 24 hours and not at 48 or 72 hours. Finally, triazole alanine inhibited protein biosynthesis in microorganisms (TXR 005841); however, this study was classifed unacceptable due to inconsistent results, a lack of individual data, not enough dose levels tested, and no explanation of incubation times used.

Triazole acetic acid. In a 14-day toxicity feeding study in rats, no treatment-related effects were observed up to the highest dose tested (788/703 mg/kg/day in males/females). No other studies are available to determine the target organs and critical effects of triazole acetic acid; to compare toxicity across species, routes of exposure, or duration of exposure; or to examine potential developmental, reproductive, or neurological toxicity. This short-term study is comparable to the 14-day oral triazole alanine study, in which no effects were seen in male rats up to 1491 mg/kg/day, and to the 28-day oral triazole alanine study, in which no effects were seen in male or female rats up to 400 mg/kg/day. However, since no effects were seen in the available short-term studies, a difference in toxicity between triazole alanine and triazole acetic acid could not be evaluated.

Mutagenicity was not seen in an acceptable/guideline bacterial reverse mutation assay using triazole acetic acid or in the available mutagenicity studies for triazole alanine. Therefore, neither compound appears mutagenic.

11.1.3 Dose-Response

For triazole alanine, greater toxicity was seen at higher doses. At the mid dose (LOAEL) in the 90-day feeding study, decreased leukocytes were seen in males only and decreased triglycerides were seen only in females (370/400 mg/kg/day, males/females). However, at the high dose, decreased leukocytes and triglycerides were each seen in both sexes, along with decreased body weight and body weight gain in males (1510/1680 mg/kg/day, males/females). In the rat developmental toxicity study, more types of skeletal findings were observed in offspring at the high dose (1000 mg/kg/day), compared to the mid dose (300 mg/kg/day).

For triazole acetic acid, dose-response could not be evaluated because no treatment-related effects were observed in the available toxicity studies.

Table 11.3. Subchronic, Chronic, and Other Toxicity Profile for Triazole Alanine

Guideline Number	Study Type/ *Classification*	*MRID Number*	*Doses*	*Results*
Non-guideline	*14-Day drinking water toxicity in rodents - rat* *Acceptable/non-guideline*	00138121 (TXR 004766 Accession # 252132) 00133358	0, 3000, 10000 ppm M: 0, 448, 1491 mg/kg/day F: not tested	NOAEL = 1491 mg/kg/day (M) LOAEL = >1491 mg/kg/day (M)
870.3050	28-Day oral toxicity in rodents - rat *Unacceptable*	00138122 (TXR 004766 Accession # 252132) 00133359	0, 25, 100, 400 mg/kg/day	NOAEL = 400 mg/kg/day (M/F) LOAEL = >400 mg/kg/day (M/F) Many of the required hematology, clinical chemistry, and microscopic pathology parameters were not examined. Dosages administered to the test animals were not analytically quantitated.

Table 11.3. Subchronic, Chronic, and Other Toxicity Profile for Triazole Alanine

Guideline Number	Study Type/ *Classification*	*MRID Number*	*Doses*	*Results*
870.3100	90-Day oral toxicity in rodents - rat *Acceptable/non-guideline*	00164107 (TXR 005532 005094)	0, 1250, 5000, 20000 ppm M: 0, 90, 370, 1510 mg/kg/day F: 0, 160, 400, 1680 mg/kg/day	NOAEL = 90/160 mg/kg/day (M/F) LOAEL = 370/400 mg/kg/day (M/F) based on decreased leukocyte counts in males and decreased triglycerides in females. At 1510/1680 mg/kg/day (M/F), decreased body weight (M), body weight gain (M), leukocytes (M&F), and triglycerides (M&F) were seen. There was no assessment of motor activity, grip strength, or sensory reactivity of the test animals. There was no indication of how often fresh batches of food containing the test material were given to the animals.
870.3100	90-Day oral toxicity in rodents - mouse	ND	ND	ND
870.3150	90-Day oral toxicity in nonrodents - dog *Acceptable/guideline*	00164106 00154946 (TXR 004469 005841 Accession # 256058)	0, 3200, 8000, 20000 ppm M: 0, 144, 322, 850 mg/kg/day F: 0, 150, 345, 902 mg/kg/day	NOAEL = 850/345 mg/kg/day (M/F) LOAEL = >850/902 mg/kg/day (M/F) based on 10% decreased food consumption in females only. No treatment-related effects were seen in males.
870.3200	21/28-Day dermal toxicity	ND	ND	ND
870.3250	90-Day dermal toxicity	ND	ND	ND
870.3465	90-Day inhalation toxicity	ND	ND	ND
870.3700	Prenatal developmental toxicity in rodents - rat *Acceptable/guideline*	00138128 (TXR 004766 & 005155 Accession # 252132) 00132915 00147889 (TXR 0005155 Accession # 252132)	0, 100, 300, 1000 mg/kg/day	Maternal NOAEL = 1000 mg/kg/day LOAEL = >1000 mg/kg/day Developmental NOAEL = 100 mg/kg/day LOAEL = 300 mg/kg/day based on increased incidence of skeletal findings (unossified odontoid process). At 1000 mg/kg/day, increased incidences of partially ossified transverse processes of the 7th cervical vertebra (bilateral), unossified 5th sternebra, and partially ossified 13th thoracic centrum were also seen.

Table 11.3. Subchronic, Chronic, and Other Toxicity Profile for Triazole Alanine				
Guideline Number	Study Type/ *Classification*	*MRID Number*	*Doses*	*Results*
870.3700	Prenatal developmental toxicity in nonrodents	ND	ND	ND
870.3800	Reproduction and fertility effects - rat *Acceptable/guideline*	00164112 (TXR 005841 & 008292 Accession # 252132) 41326803 (TXR 008292) 41326804 (TXR 008292)	0, 500, 2000, 10000 ppm M (F0/F1): 0, 50/47, 213/192, 1098/929 mg/kg/day F (F0/F1): 0, 51/49, 223/199, 1109/988 mg/kg/day	Parental/Systemic NOAEL = 929/988 mg/kg/day (M/F) LOAEL = >929/>988 mg/kg/day (M/F) Reproductive NOAEL = 929/988 mg/kg/day (M/F) LOAEL = >929/>988 mg/kg/day (M/F) Offspring NOAEL = 192/199 mg/kg/day (M/F) LOAEL = 929/988 mg/kg/day (M/F) based on reduced mean litter weights in both generations.
870.4100	Chronic toxicity	ND	ND	ND
870.4200	Carcinogenicity	ND	ND	ND
870.4300	Combined chronic toxicity/ carcinogenicity	ND	ND	ND
870.5100	Bacterial reverse mutation assay *Acceptable/guideline*	00138123 00132911 (TXR 004469 004562 004766 Accession #252132)	20, 100, 500, 2500, 12500 ug/plate for *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 (±S9)	Not mutagenic in bacteria (*Salmonella typhimurium*,±S9) under conditions of this assay.
870.5100	Bacterial reverse mutation assay *Acceptable*	00164111 (TXR 005841)	20-5000 µg/plate for *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537 (±S9).	Not mutagenic.

Table 11.3. Subchronic, Chronic, and Other Toxicity Profile for Triazole Alanine

Guideline Number	Study Type/ *Classification*	*MRID Number*	*Doses*	*Results*
870.5300	*In vitro* mammalian cell gene mutation test (Baby hamster kidney cells) *Unacceptable*	00132914 00139576 (TXR 004562 004766 Accession #252132)	-S9: 0.5, 1, 2, 4, 8 mg/ml +S9: 1, 2, 4, 8, 16 mg/ml	Inconclusive. -S9: LD_{39} = 8mg/ml (HDT). Transformation frequency was 39 vs 10 for control. An increase in number of transformed colonies. +S9: LD_{50} = 5.2 mg/ml. Transformation frequency was 28 vs 0 for the control at 16 mg/ml. Increase in number of transformed colonies, but in the presence of severe toxicity and excessive concentrations. In addition, the lack of information on the test material purity raises concerns regarding the validity of the response.
870.5300	*In vitro* mammalian cell gene mutation test (BALB/3T3 cells) *Acceptable*	00147892 (TXR 005155 Accession # 257997)	62.5, 125, 250, 500, 1000 ug/ml (±S9)	Not mutagenic. Triazole alanine did not induce cell transformations at levels up to 1000 µg/ml. The HDT of 1000 µg/ml is the highest level recommended for this test system. The increase in cell transformation frequency in the presence of S9 was not significant.
870.5300	*In vitro* mammalian cell gene mutation test (CHO cells) *Acceptable*	00164108 41326801 (TXR 005841 008292)	500, 1000, 2000, 4000, 6000, 8000, 10000 µg/ml	Not mutagenic with or without S9 activation. Viability of cells at 10000 µg/ml was 66-67% relative to control. At 10000 µg/ml, a 3-fold increase was within the accepted spontaneous range for this cell line. Stability of compound was confirmed.
870.5375	*In vitro* mammalian chromosome aberration test	ND	ND	ND
870.5395	Mammalian erythrocyte micronucleus test (mice) *Unacceptable*	00132912 00138125 00138131 (TXR 004562 004766 Accession #252131)	8000 mg/kg, single oral dose to 15 mice/sex	Inconclusive because effects were only seen at 24 hours. No clinical or cytotoxice effects. TA caused slight induction of micronuclei in bone marrow PCEs at 24 hrs, but not at 48 or 72 hrs. No data for the negative control at these two intervals.

Table 11.3. Subchronic, Chronic, and Other Toxicity Profile for Triazole Alanine				
Guideline Number	Study Type/ *Classification*	*MRID Number*	*Doses*	*Results*
870.5395	Mammalian erythrocyte micronucleus test (mice) *Acceptable/guideline*	00133361 00138124 (TXR 004562 004766 Accession # 252132)	2500 or 5000 mg/kg, by intraperitoneal injection	Not mutagenic. Under the conditions of this test, triazole alanine did not cause induction of micronuclei in mouse bone marrow PCE stem cells when administered by i.p. injection at 2500 or 5000 mg/kg. The effects of the positive control were clearly demonstrated.
870.5395	Mammalian erythrocyte micronucleus test (Chinese hamster) *Acceptable*	00164110 41326802 (TXR 005841 008292)	5000 mg/kg (limit dose) Preliminary test: 200, 1000, 5000 mg/kg	Not mutagenic. Based on scoring 1000 polychromatic erythrocytes per animal for the incidence of micronuclei, TA was comparable to the control. The best 5 slides per sex were scored.
870.5500	Bacterial DNA damage test *Acceptable/guideline*	00132913 00138126 (TXR 004469 004562 004766 Accession #252131)	62.5, 125, 250, 500, 1000 µg/plate (±S9) E. coli p3478 (polA-) & E. coli W3110 (polA+)	Not mutagenic. No measurable inhibition areolae were found for E. coli polA- or polA+ strains (±S9). Under the conditions of this assay, triazole alanine (±S9) did not elicit measurable DNA damage.
870.5550	Bacterial DNA repair test (rat hepatocytes) *Acceptable/guideline*	00164109 (TXR 005841)	0.08, 0.4, 2, 10 mg/ml Induced with Arochlor 1254	Not mutagenic. No evidence that unscheduled DNA synthesis was induced.
Non-guideline	Potential inhibition of protein biosynthesis in microorganisms *Unacceptable*	No MRID TXR 005841 Accession # 265203- 265209	1, 10, 100, 500 ppm for *E. coli*, *S. cerevisiae*, and *A. flavus*	TA inhibited protein synthesis in all three microorganisms in the presence of both radiolabeled phenylalanine and alanine after 1 hr of incubation. Growth curve of E. coli indicated that maximum period of protein synthesis was ~1 hr of incubation. Unacceptable due to lack of individual data, not enough doses of TA tested, no explanation of incubation times used, inconsistent results.

Table 11.3. Subchronic, Chronic, and Other Toxicity Profile for Triazole Alanine

Guideline Number	Study Type/ *Classification*	*MRID Number*	*Doses*	*Results*
870.7485	Metabolism and pharmacokinetics - rat *Acceptable/non-guideline*	45607001	~10.1 mg/day* radiolabeled, 5 days by oral gavage, to 1 rat/sex *Approx. 48-49 mg/kg/day, based on given body weights	Triazole alanine is readily absorbed and excreted within 48 hours following 5 daily doses of ~10 mg/day of either compound. At 168 hours, radioactivity recovery was ~92-98% of the administered dose. Absorption of the administered doses (urine and cage wash) at 168 hours was ~71-81%. Urinary excretion accounted for ~55-63% of the administered radioactivity; fecal excretion accounted for ~11-27% of the administered radioactivity. Minor gender-related quantitative differences were observed, but because only 1 rat/sex/compound was tested, these are likely due to individual variability. Tissue burdens were negligible at 72 hrs post-dosing. Triazole alanine, triazole acetic acid, free triazole, plus three additional unknown metabolites were detected in the urine and feces. The investigators propose that one of these unknown degradates is a pyruvic acid derivative.
870.7485	Metabolism and pharmacokinetics - rat *Acceptable/non-guideline*	00138118 (TXR 004766 Accession # 252132) 00133354	0.5 or 56 mg/kg ^{14}C-triazole alanine, single dose by oral gavage, to 4 rats/sex/dose	For both dose levels, >90% of the administered dose was excreted in urine at 168 hours, ~4-5% in feces, and <1% in volatiles, with most excretion in the first 24 hours. At the low dose, no radioactivity was detected in tissues. At the high dose, 0.002-0.02 ppm of TA equivalents were detected in tissues, mostly in the liver and kidneys. TA made up 72% and 80.3%, and N-acetyl TA made up 19.4% and 12.7% of the radioactivity recovered from the urine of low dose males and females, respectively. TA made up 83.4% and 86.4%, and N-acetyl TA made up 10.6% and 7.7% of the radioactivity recovered from the urine of high dose males and females, respectively.

Table 11.3. Subchronic, Chronic, and Other Toxicity Profile for Triazole Alanine

Guideline Number	Study Type/ *Classification*	*MRID Number*	*Doses*	*Results*
870.7485	Metabolism and pharmacokinetics - rat *Acceptable/non-guideline* Continuation of MRID 00138118	00139575 (TXR 004766 Accession # 252132) 00133355	56 mg/kg ^{14}C-triazole alanine (TA), single dose by oral gavage, to 4 rats/sex/dose Urine and feces samples included the first 24 hours after exposure.	Triazole alanine is completely absorbed and rapidly excreted. The major route of excretion is urine. Most of the radiolabel recovered in the urine sample from the first 24 hours was unchanged TA (72-86%), with 8-19% of the urinary radioactivity as N-acetyl TA. Two or three minor unknown metabolites (<3% each) were also found in the various urine samples. About 50% of the radiolabel recovered in the feces was TA, 16% was recovered as N-acetyl TA, and 30% was not identified but wasn't found in the urine.
870.7485	Metabolism and pharmacokinetics - rat *Acceptable/non-guideline*	00164114 (TXR 005841)	0.56, 54.4 or 993.7 mg/kg ^{14}C triazole alanine, single dose by oral gavage, to 2 rats/sex/dose	Radioactivity recoveries at 168 hours were 101.2%, 90.7%, and 92.1% for the low, mid, and high doses, respectively. There were no major sex differences in excretion patterns. The major route of excretion was urine: 81-82% of the administered dose for males and 84-85% for females. Absorption and excretion was rapid: within 24 hours after dosing, 76-82% of the administered dose in males and 71-91% in females was eliminated in the feces and urine. Tissue residues were low (<1% for both sexes).
870.7485	Metabolism and pharmacokinetics - rat *Acceptable/non-guideline* Continuation of MRID 00164114.	00164115 (TXR 005841)	0.56, 54.4 or 993.7 mg/kg ^{14}C triazole alanine, single dose by oral gavage, to 2 rats/sex/dose Urine samples included the first 24 hours after exposure.	Triazole alanine made up 82-93% of the radioactivity recovered in the first 24 hours urine sample, and N-acetyl triazole alanine made up 13-30%. The significance of an apparent decrease in the percentage of N-acetylation at the high dose is questionable.

Table 11.3. Subchronic, Chronic, and Other Toxicity Profile for Triazole Alanine

Guideline Number	Study Type/ *Classification*	*MRID Number*	*Doses*	*Results*
870.7485	Metabolism and pharmacokinetics - rat *Acceptable/non-guideline*	00138132 (TXR 004766 Accession # 252132)	Metabolism: 5 mg/kg ^{14}C-triazole alanine, by oral gavage or i.v. injection, to 5 males/exposure route Autoradiography: 10 mg/kg ^{14}C-triazole alanine, by i.v. injection, to 6 males	Absorption and excretion was rapid, with most excretion in the urine. At 48 hours after oral exposure, 94.5% and 3.5% of the administered radiolabel was recovered in the urine and feces, respectively. At 48 hours after i.v. exposure, 92.4% and 2.1% of the administered radiolabel was recovered in the urine and feces, respectively. Tissue residues were low, with the highest residues found in the kidney and liver. Following oral administration, radioactivity increased in the plasma and a maximum was attained within 40 minutes. Radioactivity declined in a biphasic manner with half lives of 3 and 8 hours. Following iv administration, radioactivity decreased in triphasic manner with half lives of 15 minutes, 4.4 hours, and 12.4 hours. Whole body autoradiography indicated radioactivity distribution in all tissues and organs except the compacts of the bone.

ND = Study not done

Table 11.4. Subchronic, Chronic, and Other Toxicity Profile for Triazole Acetic Acid

Guideline Number	Study Type/ *Classification*	*MRID Number*	*Doses*	*Results*
Non-guideline	*14-Day oral toxicity in rodents - rat* *Acceptable/non-guideline*	45596801	0, 100, 1000, 8000 ppm M: 0, 10.6, 102.8, 788.3 mg/kg/day F: 0, 10.1, 97.2, 703.5 mg/kg/day	NOAEL = 788.3/703.5 mg/kg/day (M/F) LOAEL = >788.3/>703.5 mg/kg/day (M/F)
870.3050	28-Day oral toxicity in rodents	ND	ND	ND
870.3100	90-Day oral toxicity in rodents	ND	ND	ND
870.3150	90-Day oral toxicity in nonrodents	ND	ND	ND
870.3200	21/28-Day dermal toxicity	ND	ND	ND
870.3250	90-Day dermal toxicity	ND	ND	ND
870.3465	90-Day inhalation toxicity	ND	ND	ND
870.3700	Prenatal developmental toxicity in rodents	ND	ND	ND

Table 11.4. Subchronic, Chronic, and Other Toxicity Profile for Triazole Acetic Acid

Guideline Number	Study Type/ *Classification*	*MRID Number*	*Doses*	*Results*
870.3700	Prenatal developmental toxicity in nonrodents	ND	ND	ND
870.3800	Reproduction and fertility effects	ND	ND	ND
870.4100	Chronic toxicity	ND	ND	ND
870.4200	Carcinogenicity	ND	ND	ND
870.4300	Combined chronic toxicity/ carcinogenicity	ND	ND	ND
870.5100	Bacterial reverse mutation assay *Acceptable/guideline*	45596803	20, 80, 320, 1280 and 5120 ug/plate for *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 (his⁻)	No mutagenic activity in bacteria (*Salmonella typhimurium*) in the presence or absence of S9 activation.
870.5300	*In vitro* mammalian cell gene mutation test	ND	ND	ND
870.5375	*In vitro* mammalian cell chromosome aberration test	ND	ND	ND
870.5395	Mammalian erythrocyte micronucleus test	ND	ND	ND
870.5550	Unscheduled DNA synthesis in mammalian cells in culture	ND	ND	ND

Table 11.4. Subchronic, Chronic, and Other Toxicity Profile for Triazole Acetic Acid

Guideline Number	Study Type/ *Classification*	*MRID Number*	*Doses*	*Results*
870.7485	Metabolism and pharmacokinetics - rat *Acceptable/non-guideline*	45596804 45596805	0.58, 58.63, or 1034.69 mg/kg radiolabeled, single dose by oral gavage.	Triazole acetic acid was readily absorbed and excreted within 48 hours following a single oral dose of 0.58, 58.63, or 1034.69 mg/kg. Average absorption at 168 hours was nearly complete (~93-103%, ~102-104%, and ~92-101% of the administered dose for the males and females in the low-, mid-, and high-dose groups, respectively) and did not appear to be saturated at the highest dose. Urinary excretion accounted for ~90-104% of the administered radioactivity, whereas fecal excretion accounted for only ~1-7% of the administered radioactivity in all treatment groups. Excretory patterns did not exhibit gender-related variability. Because radioactivity in tissues was very low, neither triazole acetic acid nor its metabolites appear to undergo significant sequestration. The urinary metabolite was identified as triazole acetic acid, indicating that the parent compound was excreted intact without being metabolized in the rat.

Table 11.4. Subchronic, Chronic, and Other Toxicity Profile for Triazole Acetic Acid				
Guideline Number	Study Type/ *Classification*	*MRID Number*	*Doses*	*Results*
870.7485	Metabolism and pharmacokinetics - rat *Acceptable/non-guideline*	45607001	~10.5 mg/day* radiolabeled, 5 days by oral gavage, to 1 rat/sex *Approx. 50-51 mg/kg/day, based on given body weights	Triazole acetic acid is readily absorbed and excreted within 48 hours following 5 daily doses of ~10.5 mg/day. At 168 hours, radioactivity recovery was ~101-102% of the administered dose. Absorption of the administered doses (urine and cage wash) at 168 hours was ~69-91%. Urinary excretion accounted for ~66-75% of the administered radioactivity. Fecal excretion accounted for ~11-32% of the administered radioactivity. Minor gender-related quantitative differences were observed, but because only 1 rat/sex/compound was tested, these are likely due to individual variability. Tissue burdens were negligible at 72 hrs post-dosing. The sole component identified in extracts of feces and urine from radiolabeled-triazole acetic acid-fed rats was triazole acetic acid, which indicates excretion without metabolic conversion of triazole acetic acid.

ND = Study not done

11.2 FQPA Hazard Considerations

11.2.1 Adequacy of the Toxicity Data Base

The toxicology database for triazole alanine is considered incomplete in terms of endpoint studies and dose-response information to characterize potential pre- and/or post-natal risk for infants and children. Acceptable developmental toxicity and two-generation reproduction studies in the rat were evaluated, but a developmental toxicity study in the rabbit was not available.

No studies on triazole acetic acid, including rat or rabbit developmental toxicity studies or a two-generation reproduction study in the rat, were available to characterize any potential pre- and/or post-natal risk for infants and children.

11.2.2 Evidence of Neurotoxicity

There is no evidence that exposure to triazole alanine results in neurotoxicity. No clinical signs of neurotoxicity, changes in brain weights, changes in brain gross or microscopic pathology, or any other neurotoxic effects were observed in the short-term rat studies, the subchronic rat and

dog feeding studies, the rat developmental toxicity study, or the two-generation reproduction study. Slight salivation and a slightly unsteady gait were seen in the female dog tested in an acute oral dog study; however, the neurotoxicological significance of this effect is questionable, since the effects were seen at an extremely high dose (5000 mg/kg), and similar effects were not seen in the male dog. Spastic gait, piloerection, lethargy, and diarrhea were initially seen in rats tested in an acute intraperitoneal study; however, the significance of these effects is also questionable because the rats were exposed to an extremely high dose (5000 mg/kg), and similar effects were not seen at 5000 mg/kg in three acute oral studies of triazole alanine in rats.

While the available repeated dose studies show no evidence for triazole alanine to adversely affect the nervous system, there is some concern that this is due to an incomplete database, rather than a true inability of the compound to produce neurotoxicity. For instance, no acute or subchronic neurotoxicity tests or an evaluation of perfused brain tissue are available for triazole alanine. Tremors, decreased brain weight, and cerebellar degeneration were seen in the 90-day mouse study on 1,2,4-triazole; however, no mouse studies on triazole alanine are available for comparison. Clinical signs of neurotoxicity were seen in adults in the developmental rabbit study on 1,2,4-triazole, including decreased motor activity, head tilt, lacrimation, drooping eyelids, diarrhea, salivation; however no rabbit studies are available on triazole alanine. Cerebellar lesions and decreased brain weights were seen at the highest dose tested in the two-generation reproduction study on free triazole; however, brains were not microscopically examined in the triazole alanine reproduction study.

11.2.3 Developmental Toxicity Studies

11.2.3.1 Developmental Toxicity Study in Rats

For triazole alanine, increased quantitative and qualitative susceptibility was seen in the developmental toxicity study in rats. (See section A-1.3.1 of the appendix for the executive summary of MRIDs 00138128 and 00147889). In this study, increased incidences of skeletal findings were seen in the offspring at the mid and high doses, while no treatment-related effects were seen in the dams up to the limit dose. The skeletal findings included unossified odontoid processes at 300 and 1000 mg/kg/day, with partially ossified transverse processes of the 7th cervical vertebra (bilateral), unossified 5th sternebra, and partially ossified 13th thoracic centrum observed only at 1000 mg/kg/day.

A developmental toxicity study in rats was not submitted for triazole acetic acid.

11.2.3.2 Developmental Toxicity Study in Rabbits

A developmental toxicity study in rabbits was not submitted for either triazole alanine or triazole acetic acid.

11.2.4 Reproductive Toxicity Study

For triazole alanine, increased quantitative susceptibility was seen in the two-generation reproduction study in rats. (See section A-1.4.1 of the appendix for the executive summary of

MRIDs 164112, 41326803, and 41236804). In this study, mean litter weights were decreased approximately 10-20% for both generations at ~1000 mg/kg/day, compared to controls, but parental body weights were unaffected at all treatment levels tested. The lowest dose associated with decreased body weights and body weight gains in adult rats was 1510 mg/kg/day, from the 90-day toxicity study.

A two-generation reproduction study in rats was not submitted for triazole acetic acid.

11.2.5 Additional Information from Literature Sources

No relevant specific information on the toxicity of triazole alanine or triazole acetic acid was noted in the open scientific literature.

11.2.6 Pre-and/or Postnatal Toxicity

11.2.6.1 Determination of Susceptibility

Increased quantitative and qualitative susceptibility of the offspring was seen in the developmental toxicity rat study, and increased quantitative susceptibility was seen in the two-generation reproduction study. In the developmental toxicity study, increased incidences of skeletal findings were seen in the offspring at the mid and high doses, while no treatment-related effects were seen in the dams up to the limit dose. These skeletal findings include unossified odontoid processes at 300 and 1000 mg/kg/day, with partially ossified transverse processes of the 7th cervical vertebra (bilateral), unossified 5th sternebra, and partially ossified 13th thoracic centrum observed only at 1000 mg/kg/day. In the reproduction study, mean litter weights were decreased approximately 10-20% for both generations at ~1000 mg/kg/day, compared to controls, but parental body weights were unaffected at all treatment levels.

11.2.6.2 Degree of Concern Analysis and Residual Uncertainties for Pre- and/or Postnatal Susceptibility

The toxicology database for triazole alanine is incomplete with respect to pre-and post-natal toxicity because a rabbit developmental toxicity study was not available, and the existing two-generation reproduction study, completed in 1986, did not meet the current guideline protocol. Evidence of increased qualitative and quantitative susceptibility in the offspring was seen in the rat developmental toxicity study in the form of skeletal findings observed in the offspring at dose levels that produced no treatment-related effects in the dams. Evidence of increased quantitative susceptibility was also seen in the two-generation reproduction study as a reduction in mean litter weights for both generations at dose levels that produced no treatment-related effects in the parents. However, the concern is low for the increased susceptibilities seen in these studies, as well as for the residual uncertainties regarding the data gaps, because the doses currently used for dietary, residential, and occupational exposure risk assessments are similar or lower than the doses that caused the effects.

For triazole acetic acid, the toxicology database is incomplete with respect to pre-and post-natal toxicity because no rat or rabbit developmental toxicity studies or a two-generation reproduction

study in the rat are available. Increased qualitative and quantitative susceptibility was seen for both triazole alanine and 1,2,4-triazole. Therefore, there is residual uncertainty for increased pre- and/or postnatal susceptibility following exposure to triazole acetic acid, but this uncertainty is addressed by retaining the 10X database uncertainty factor.

11.3 Recommendation for a Developmental Neurotoxicity Study

At this time, a developmental neurotoxicity study on the triazole conjugates is not required.

11.3.1 Evidence that supports requiring a Developmental Neurotoxicity Study

At present, there is no evidence to support requiring a Developmental Neurotoxicity Study.

11.3.2 Evidence that supports not requiring a Developmental Neurotoxicity Study

There was no evidence of neurotoxicity in any of the studies available in the toxicology database for triazole alanine or triazole acetic acid, including the short-term rat studies, the subchronic rat and dog feeding studies, the rat developmental toxicity study, and the two-generation reproduction study.

11.3.2.1 Rationale for the UF_{DB}

The database uncertainty factor is 10X, based on the lack of a developmental toxicity study in rabbits for both triazole alanine and triazole acetic acid, lack of a chronic study in rats (including additional neuropathological and neurobehavioral measurements) with triazole alanine, and lack of a combined 90-day/subchronic neurotoxicity study in rats for triazole acetic acid.

11.4 Hazard Identification and Toxicity Endpoint Selection

Because no effects were seen in the available acute oral toxicity studies (14-day oral studies in rats and a bacterial reverse mutation assay), a difference in toxicity between triazole alanine and triazole acetic acid could not be evaluated. In the absence of data to suggest otherwise, the endpoint selection discussed in the following sections applies to all triazole conjugates (i.e., triazole alanine, triazole acetic acid, triazole lactic acid, and triazole pyruvate).

11.4.1 Acute Reference Dose (aRfD) - Females (13 to 49 years of age)

Study Selected: Prenatal developmental toxicity in rodents - rat
MRID Number: 00138128 and 00147889
Dose and Endpoint for Establishing aRfD: 100 mg/kg/day (NOAEL), based on increased incidence of skeletal findings (unossified odontoid process) at 300 mg/kg/day (LOAEL).
Uncertainty Factor(s): 1000 (10X for interspecies extrapolation, 10X for intraspecies variations, and 10X for database uncertainty).
Comments about Study/Endpoint/Uncertainty Factor: Adverse effects seen in offspring from an oral developmental study are appropriate for setting an acute dietary endpoint for women of

childbearing age. There is some uncertainty as to whether effects on ossification are due to a single dose. Delays in ossification can indicate an effect on growth, which would be seen with repeated exposure, but no change in fetal body weights was observed in this study. However, in the absence of a developmental rabbit study, which is the most sensitive species for free triazole, this dose and study were selected for this risk assessment. In accordance with current FQPA policy, a 1000X uncertainty factor is applied, which includes a 10X database UF to account for the lack of developmental toxicity studies on triazole alanine and triazole acetic acid in rabbits.

Acute RfD = 100 mg/kg/day (NOAEL) ÷ 1000 (UF) = 0.1 mg/kg/day

11.4.2 Acute Reference Dose (aRfD) - General Population

In 2003, the Triazole Peer Review Committee (PRC) determined that the acute endpoint for the triazole conjugates should be based on the developmental toxicity study in rats discussed previously, with an uncertainty factor of 300X to include a 3X database UF (TXR No. 0052011). However, reevaluation of the triazole alanine database showed that no appropriate endpoints (*i.e.*, effects seen in adult animals following a single, oral dose) were available to set an acute reference dose for the general population.

11.4.3 Chronic Reference Dose (cRfD)

Study Selected: 90-Day oral toxicity in rodents - rat
MRID Number: 00164107
Dose and Endpoint for Establishing cRfD: 90 mg/kg/day (NOAEL), based on decreased leukocyte counts in males at 370 mg/kg/day (LOAEL).
Uncertainty Factor(s): 1000 (10X for interspecies extrapolation, 10X for intraspecies variations, and 10X for database uncertainty).
Comments about Study/Endpoint/Uncertainty Factor: For females, the NOAEL is 160 mg/kg/day, and the LOAEL is 400 mg/kg/day, based on decreased triglycerides. Out of the available toxicology studies on the triazole conjugates, the two-generation reproduction study and the 90-day studies were the longest in duration. Chronic studies in rats, mice, or dogs were not available. Additionally, rabbits, which are more sensitive than rats to free triazole, were not used in any of the available toxicology studies on the triazole conjugates. Although no adverse effects were seen in adults in the reproduction study, fewer endpoints are measured in this study compared to the subchronic feeding studies. Treatment-related effects were seen in both the 90-day dog and rat studies, but the 90-day rat study was chosen because rats were more sensitive to triazole alanine than dogs. The 10X database uncertainty factor used for the chronic endpoint is to account for the lack of a developmental toxicity study in rabbits for both triazole alanine and triazole acetic acid, the lack of a chronic study in rats (including additional neuropathological and neurobehavioral measurements) with triazole alanine, and a lack of a combined 90-day/subchronic neurotoxicity bridging study on triazole acetic acid.

In 2003, the Triazole Peer Review Committee (PRC) determined that the chronic endpoint for the triazole conjugates should be based on the developmental toxicity study in rats discussed above, with an uncertainty factor of 300X to include a 3X database UF (TXR No. 0052011). This decision was made prior to the current FQPA policy; to the receipt of the 90-day/subchronic

neurotoxicity rat study, developmental rabbit toxicity study, and reproduction study on 1,2,4-triazole; and to the reevaluation of the triazole alanine studies. The reanalysis of the triazole alanine studies resulted in a change in chronic dose and endpoint selection. The subchronic rat study is a more appropriate basis for a chronic endpoint than a developmental study. The change in FQPA policy and receipt of additional free triazole studies resulted in an increased database UF.

Chronic RfD = 90 mg/kg/day (NOAEL) ÷ 1000 (UF) = 0.09 mg/kg/day

11.4.4 Incidental Oral Exposure

The endpoint for short- and intermediate-term incidental oral exposure is based on changes in hematology observed in the 90-day oral feeding study in rats (MRID 00164107), which is discussed earlier in section 11.4.3. The oral route of exposure used in this study and the type of effects seen are considered appropriate for short- or intermediate-term incidental oral endpoints. Additionally, the NOAEL from the 90-day study is protective of the offspring toxicity observed in the developmental rat study. The 90-day duration of the study is most appropriate for an intermediate term endpoint. However, due to the lack of studies and of parameters measured in the available studies and because the effects seen in the 90-day rat study could occur with short- to long-term exposure, this study was used as the basis for residential and occupational endpoints for all durations.

11.4.5 Dermal Absorption

No dermal absorption studies on triazole alanine or triazole acetic acid are available in the database. Therefore, there are no data to support a dermal absorption factor other than 100%.

11.4.6 Dermal Exposure (Short-, Intermediate-, and Long-term)

In the absence of dermal studies, the endpoint for short-, intermediate-, and long-term dermal exposure is the same as for short and intermediate term incidental oral exposure. See section 11.4.4 for more details.

11.4.7 Inhalation Exposure (Short-, Intermediate-, and Long-term)

In the absence of inhalation studies, the endpoint for short-, intermediate-, and long-term inhalation exposure is the same as for short- and intermediate-term incidental oral exposure. See section 11.4.4 for more details.

11.4.8 Margins of Exposure and Levels of Concern

The levels of concern (LOCs) for residential and occupational exposure and risk assessment are given below. Each LOC is based on the conventional uncertainty factor of 100X (10X for intraspecies variation and 10X for interspecies extrapolation), as well as a 10X database uncertainty factor for the lack of a developmental toxicity study in rabbits for both triazole alanine and triazole acetic acid, the lack of a chronic study in rats (including additional

neuropathological and neurobehavioral measurements) with triazole alanine, and a lack of a combined 90-day/subchronic neurotoxicity study in rats for triazole acetic acid.

Table 11.5. Summary of Levels of Concern for Residential and Occupational Risk Assessments for Triazole Alanine and Triazole Acetic Acid.

Route of Exposure	Duration of Exposure		
	Short-Term (1-30 Days)	Intermediate-Term (1-6 Months)	Long-Term (>6 Months)
Occupational Exposure			
Dermal	1000	1000	1000
Inhalation	1000	1000	1000
Residential Exposure			
Incidental Oral	1000	1000	1000
Dermal	1000	1000	1000
Inhalation	1000	1000	1000

11.4.9 Recommendation for Aggregate Exposure Risk Assessments

Because the same endpoints are used for all exposure routes, oral, dermal, and inhalation exposures can be aggregated.

11.4.10 Classification of Carcinogenic Potential

There are no available cancer bioassay studies on 1,2,4-triazole. 1,2,4-triazole and its conjugate (triazole alanine), however, are not mutagenic. For a further discussion of carcinogenicity and triazole metabolites, see Section 4.4.11.

11.5 Special FQPA Safety Factor

The special FQPA safety factor has been removed (i.e., reduced to 1X) for the current risk assessment on the triazole conjugates because the currently selected endpoints, together with a 10X database uncertainty factor, are protective of increased susceptibility of infants and children seen in the available studies. Although increased qualitative and quantitative susceptibility of the offspring was seen in the developmental toxicity and two-generation reproduction studies in rats (see section 11.2.6), the currently selected dietary, residential, and occupational endpoints are all based on NOAELs that are protective of these adverse effects. Additionally, no evidence of neurotoxicity was seen in the available toxicology database, so a developmental neurotoxicity study is not recommended at this time. Finally, while the current recommendation is to reduce the special FQPA safety factor to 1X, residual uncertainty is accounted for by a 10X database uncertainty factor. This 10X database uncertainty factor is retained for the lack of developmental toxicity (rabbit) studies with triazole alanine and triazole acetic acid, lack of a chronic rat study (with additional neuropathological and neurobehavioral endpoints) with triazole alanine, and lack of a combined 90-day/subchronic neurotoxicity rat study for triazole acetic acid.

Future receipt of additional, required toxicology studies on triazole alanine (or the other triazole conjugates) may warrant removal of the database uncertainty factor (i.e., reduction to 1X). At

that time, the need for a 10X special FQPA safety factor based on the newly available toxicity data will be re-evaluated.

Table 11.6. Summary of Toxicological Doses and Endpoints for Triazole Conjugates to be Used in Human Health Risk Assessments.

Exposure Scenario	Dose Used in Risk Assessment and UF	Special FQPA SF * and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (females 13-49)	NOAEL = 100 mg/kg/day UF = 1000 Acute RfD = 0.1 mg/kg/day	FQPA SF =1 aPAD = acute RfD / FQPA SF = 0.1 mg/kg/day	Prenatal developmental toxicity in rodents - rat LOAEL = 300 mg/kg/day based on increased incidence of skeletal findings (unossified odontoid process).
Acute Dietary (general population, including infants and children)	None	None	No appropriate dose and endpoint could be identified for these population groups.
Chronic Dietary (all populations)	NOAEL = 90 mg/kg/day UF = 1000 Chronic RfD = 0.09 mg/kg/day	FQPA SF =1 cPAD = chronic RfD / FQPA SF = 0.09 mg/kg/day	90-Day oral toxicity in rodents - rat LOAEL = 370/400 mg/kg/day (M/F) based on decreased leukocyte counts in males and decreased triglycerides in females.
Incidental Oral (all durations)	NOAEL = 90 mg/kg/day	Residential LOC for MOE = 1000[a] Occupational = NA	90-Day oral toxicity in rodents - rat LOAEL = 370/400 mg/kg/day (M/F) based on decreased leukocyte counts in males and decreased triglycerides in females.
Dermal (all durations)	NOAEL = 90 mg/kg/day (dermal absorption rate = 100%)	Residential LOC for MOE = 1000[a] Occupational LOC for MOE = 1000[a]	90-Day oral toxicity in rodents - rat LOAEL = 370/400 mg/kg/day (M/F) based on decreased leukocyte counts in males and decreased triglycerides in females.
Inhalation (all durations)	NOAEL = 90 mg/kg/day (inhalation absorption rate = 100%)	Residential LOC for MOE = 1000[a] Occupational LOC for MOE = 1000[a]	90-Day oral toxicity in rodents - rat LOAEL = 370/400 mg/kg/day (M/F) based on decreased leukocyte counts in males and decreased triglycerides in females.
Cancer (oral, dermal, inhalation)	**Classification:** Not determined. Evaluate by RfD approach.		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

* Refer to Section 11.5

[a] Additional 10x database uncertainty factor for lack of developmental toxicity (rabbit) studies with triazole alanine and triazole acetic acid, a chronic rat study (with additional neuropathological and neurobehavioral endpoints) with triazole alanine, and a combined 90-day/subchronic neurotoxicity rat study for triazole acetic acid.

11.6 Endocrine Disruption

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

In the available toxicity studies on triazole alanine and triazole acetic acid, no estrogen-, androgen-, and/or thyroid-mediated toxicity was observed.

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

12.0 Public Health Data

None.

13.0 Exposure Characterization/Assessment

13.1 Dietary Exposure/Risk Pathway

(M. Doherty, D322239, 12/20/05)

13.1.1 Residue Profile

13.1.1.1 Residues in Food

Through a joint effort by the U.S. Triazole Task Force (USTTF) and USDA's Pesticide Data Program (PDP), monitoring data depicting residues of TA and TAA are available for apples, peaches, wheat flour, bananas, eggs, peanut butter, soybeans, finished water, strawberry, milk, grapes, and tomato. For all foods addressed by these assessments, including those with monitoring data, an anticipated residue was derived by converting the tolerance value for each parent triazole-derivative fungicides to its TA equivalent using molecular weight conversion factors. For the acute assessment, the highest anticipated residue was used for a given food; for the chronic assessment, the average anticipated residue was used. For foods with monitoring data, the greater of the maximum monitoring data (maximum TA plus maximum TAA) or the anticipated residue was used in the assessment. For all commodities except those of peanut and cereal grain, the anticipated residues were used. For peanut commodities the maximum monitored residue value from peanut butter was used. For cereal grain commodities, the

maximum monitored residue value from wheat flour was used. The assessments include default processing factors from DEEM Version 7.81. The Agency was recently made aware of an issue with the analytical method for TA in soybeans in which the method underestimates residues by 4 to 12 fold. That issue is still being resolved. In order to ensure that this assessment does not underestimate exposure to TA/TAA via soybean, all inputs for soybean were multiplied by 10 in both the acute and chronic analyses. This is a very conservative, higher-end deterministic assessment.

Table 13.1. Summary of Input Residue Values for the Acute and Chronic Dietary Analyses of Triazole Alanine and Triazole Acetic Acid.

Food	DEEM Input Value, ppm		Anticipated Residue, ppm		Max. Monitored Residue, ppm[1]	Remarks
	Acute	Chronic	Acute	Chronic		
Pome Fruit (Apple)	0.53	0.23	0.53	0.21	0.23	–
Artichoke	0.54	0.43	0.54	0.43	–	–
Asparagus	0.80	0.03	0.80	0.03	–	–
Banana	2.16	0.57	2.16	0.32	0.57	–
Dry Bean/Pea	0.23	0.12	0.23	0.12	–	–
Succulent Bean/Pea	0.54	0.22	0.54	0.22	–	–
Blueberry	0.46	0.30	0.46	0.30	–	–
Caneberry	1.08	0.87	1.08	0.87	–	–
Canola	0.05	0.02	0.05	0.02	–	–
Carrot	0.09	0.09	0.09	0.09	–	–
Leafy Petioles	2.28	2.28	2.28	2.28	–	–
Barley	0.55	0.55	0.046	0.31	–	From wheat flour
Oats	0.55	0.55	0.05	0.03	–	From wheat flour
Rice	3.19	1.11	3.19	1.11	–	–
Rye	0.55	0.55	0.05	0.04	–	From wheat flour
Wheat	0.55	0.55	0.05	0.03	–	From wheat flour
Wheat Flour	0.55	0.55	0.05	0.03	0.55	–
Wild Rice	3.19	1.11	0.23	0.23	–	From rice
Citrus Group	0.46	0.23	0.46	0.23	–	–
Coffee	0.005	0.005	0.005	0.005	–	–
Field Corn	0.55	0.55	0.05	0.03	–	From wheat flour
Sweet Corn	0.55	0.55	0.05	0.03	–	From wheat flour
Cotton	1.01	0.26	1.01	0.26	–	–
Cranberry	0.46	0.24	0.46	0.24	–	–
Cucurbits	0.11	0.08	0.11	0.08	–	–
Currant	1.62	1.04	1.62	1.04	–	–
Elderberry	0.46	0.46	0.46	0.46	–	–
Grape	2.53	0.82	2.53	0.82	0.29	–
Raisin	2.53	0.82	2.53	0.82	–	–
Hops	15.20	7.60	15.20	7.60	–	–
Lychee	0.76	0.76	0.76	0.76	–	–
Mango	0.10	0.10	0.10	0.10	–	–
Mayhaw	0.38	0.19	0.38	0.19	–	–
Bulb Vegetables	0.14	0.09	0.14	0.09	–	–
Okra	0.51	0.51	0.51	0.51	–	–
Peanut	2.32	2.32	0.09	0.04	–	From peanut butter
Peanut Butter	2.32	2.32	0.09	0.04	2.32	–
Peppers	0.54	0.54	0.54	0.54	–	–
Peppermint	1.62	1.62	1.62	1.62	–	–

Table 13.1. Summary of Input Residue Values for the Acute and Chronic Dietary Analyses of Triazole Alanine and Triazole Acetic Acid.

Food	DEEM Input Value, ppm		Anticipated Residue, ppm		Max. Monitored Residue, ppm[1]	Remarks
	Acute	Chronic	Acute	Chronic		
Pineapple	1.59	0.82	1.59	0.82	–	–
Sorghum	0.55	0.55	0.09	0.05	–	From wheat flour
Soybean	9.1	3.3	0.91	0.33	0.12	10X the anticipated residue to account for method issue.
Spearmint	1.62	1.62	1.62	1.62	–	–
Stone Fruit-no cherry	1.08	0.95	1.08	0.74	0.95	–
Cherry	2.70	1.53	2.70	1.53	–	–
Strawberry	0.68	0.48	0.68	0.48	0.13	–
Sugar Beet	0.14	0.07	0.14	0.07	–	–
Sugar Beet Molasses	0.14	0.07	0.14	0.07	–	–
Sunflower	0.03	0.03	0.03	0.03	–	–
Tomato	0.16	0.16	0.16	0.16	0.09	–
Turnip	0.20	0.20	0.20	0.20	–	–
Turnip Greens	2.28	2.28	2.28	0.04	–	From Leafy petiole
Tree Nuts	0.19	0.11	0.19	0.11	–	–
Almond	0.19	0.11	0.19	0.11	–	–
Pecan	0.05	0.05	0.05	0.05	–	–
Pistachio	0.05	0.04	0.05	0.04	–	–
Poultry Meat	0.03	0.02	0.03	0.02	–	–
Poultry Fat	0.03	0.02	0.03	0.02	–	–
Poultry Meat Byprod.	0.03	0.02	0.03	0.02	–	–
Poultry Liver	0.03	0.02	0.03	0.02	–	–
Egg	0.03	0.02	0.03	0.02	0.016	–
Cattle Meat	0.53	0.13	0.53	0.13	–	–
Cattle Fat	0.53	0.15	0.53	0.15	–	–
Cattle Meat Byprod.	0.53	0.14	0.53	0.14	–	–
Cattle Liver	1.68	0.63	1.68	0.63	–	–
Cattle Kidney	0.91	0.29	0.91	0.29	–	–
Milk	0.11	0.04	0.11	0.04	0.01	–

[1] Residue data for TA/TAA from USDA Pesticide Data Program or U.S. Triazole Task Force monitoring data. Values are the combined maxima for TA and TAA for monitored foods and do not reflect the maximum combined residue of TA and TAA for a particular sample.

13.1.1.2 Residues in Drinking Water

As noted in Section 6, there is not sufficient information available to model potential residues of the triazole conjugates in drinking water. As a surrogate for modeled concentrations of TA and TAA, HED has used the modeled estimates for 1,2,4-T (Table 6.2) in the TA/TAA dietary exposure assessment, multiplying the values by 2.26 to correct for differences in molecular weight. Given the infrequent and very low residue levels reported in the monitoring data (Table 13.1), the use of 1,2,4-T residue estimates in drinking water is highly conservative.

13.1.2 Acute and Chronic Dietary Exposure and Risk

Table 13.2. Dietary (Food + Water) Exposure and Risk Estimates for Triazole Alanine and Triazole Acetic Acid.

Population Subgroup	aPAD, mg/kg/day	Exposure Estimate, mg/kg/day			Risk Estimate, %aPAD[a]		
		95th %ile	99th %ile	99.9th %ile	95th %ile	99th %ile	99.9th %ile
Acute							
Females 13-49 yrs	0.1	0.0274	27	0.0412	41	0.0827	83

Chronic			
Population Subgroup	cPAD, mg/kg/day	Exposure Estimate, mg/kg/day	Risk Estimate, % cPAD[a]
U.S. Population (total)	0.09	0.0080	9
All infants (< 1 year)	0.09	0.0160	18
Children 1-2 yrs	0.09	0.0239	27
Children 3-5 yrs	0.09	0.0196	22
Children 6-12 yrs	0.09	0.0121	13
Youth 13-19 yrs	0.09	0.0073	8
Adults 20-49 yrs	0.09	0.0062	7
Adults 50+ yrs	0.09	0.0054	6
Females 13-49 yrs	0.09	0.0060	7

The values for the population with the highest risk for each type of risk assessment are bolded.
[a] Reported to 2 significant figures.

Due to the conservatism of the assessment inputs, HED believes that it is most appropriate to base regulatory recommendations on results at the 95th percentile of exposure for the acute assessment. The results indicate that for both acute and chronic exposure durations and for all population subgroups, risk estimates are well below HED's level of concern.

13.2 Residential (Non-Occupational) Exposure/Risk Pathway

Triazole alanine is formed in plants by the conjugation of 1,2,4-T to serine. The TA may then be further oxidized to form TAA. Because of the nature of this process, HED has assumed that it occurs within the plant itself on not on leaf surfaces. Therefore, the residues are not available for dermal, hand-to-mouth, or object-to-mouth exposures and HED has not conducted a residential exposure assessment for the triazole conjugates. Residues of TA and TAA may occur in soil. 1,2,4-Triazole is more toxic than TA/TAA and exposures to TA/TAA via soil ingestion are unlikely to exceed those of 1,2,4-T. The assessment for soil ingestion of 1,2,4-T shows that risk estimates are below HED's level of concern; therefore, risk estimates for soil ingestion of TA/TAA will also be below HED's level of concern.

14.0 Aggregate Risk Assessments and Risk Characterization

Dietary exposure is the only pathway of concern for TA/TAA; therefore, aggregate risk estimates are equivalent to those discussed for dietary risk (Section 13.1.2). All aggregate risk estimates are below HED's level of concern.

15.0 Cumulative Risk Characterization/Assessment

See Section 8.0.

16.0 Occupational Exposure/Risk Pathway

Triazole alanine and triazole acetic acid are not present in pesticide formulations; therefore, there is no risk from exposure to these chemicals that results from mixing, loading, or application activities. Although TA and TAA are significant plant metabolites, the residues occur inside the plant structures and are not available for dermal contact (see Section 13.2). Therefore, there is no significant exposure as a result of post-application activities and quantitative occupational exposure and risk assessments are not needed for TA and TAA.

17.0 Data Needs and Label Requirements

17.1 Toxicology

A 10X database uncertainty factor is retained for the lack of the following studies:

Triazole alanine

- Developmental toxicity study in rabbits
- Chronic toxicity study in rats, conducted according to current guidelines that include neurobehavioral assessments, with additional neuropathology evaluations conducted according to the neurotoxicity guidelines

Triazole acetic acid

- Developmental toxicity study in rabbits
- Combined 90-day feeding/ neurotoxicity study in rats

17.2 Residue Chemistry

- Resolution of concerns regarding the prevalence of conjugated residues of TA and the ability of the analytical method to quantify them.

17.3 Occupational and Residential Exposure

- None.

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Attachments:

1. TXR 0052011. Report of the *Ad Hoc* Triazole HED Peer Review Committee

2. TXR 0052012. Second Report of the *Ad Hoc* Triazole HED Peer Review Committee

3. Triazole Summaries - Additional Data Summaries/Literature Articles

Attachment 1: Report of the *Ad Hoc* Triazole HED Peer Review Committee

TXR NO. 0052011

DATE: August 5, 2003

MEMORANDUM

SUBJECT: ***TRIAZOLES*** - Report of the *Ad Hoc* HED Peer Review Committee.

FROM: Kathleen Raffaele, Toxicologist
Registration Action Branch 3
Health Effects Division (7509C)

THROUGH: Stephen Dapson
Senior Scientist, Registration Action Branch 3
Health Effects Division (7509C)

TO: Bob Tomerlin
Registration Division (7505C)

cc: Margaret Stasikowski, HED
Elizabeth Doyle, OW

PC Codes (include but are not limited to): 004401; 120503; 128993; 128847; 123909; 129011; 128835; 128925; 128857; 125601; 122101; 120603; 128997; 109901; 127201; 128976

On 11/4/02, an *ad hoc* HED committee conducted an internal Peer Review of the OPP Triazole Team's 7/8/02 analysis of the Triazolylalanine Group's (TAG) 1/9/02 document entitled "Profile of the Triazole-derivative Fungicide Compounds and their Common Metabolites"(MRID# 45575501). The committee, led by Elizabeth Doyle, addressed toxicology and dietary exposure issues associated with this class of fungicides and its metabolites/degradates of concern. The conclusions of the committee with respect to these issues are presented in this report.

Ad Hoc HED Peer Review Committee Members in Attendance

Elizabeth Doyle (Chair), Karl Baetcke, William Burnam, Vicki Dellarco, Steve Knizner, Nancy McCarroll, Alberto Protzel, Jess Rowland, and Brenda Tarplee (Executive Secretary).

OPP Triazole Team Members in Attendance

Steve Dapson, William Hazel, Rick Loranger, Kathleen Raffaele, Clark Swentzel, and Jean Holmes (EFED).

Also in attendance were: Rick Keigwin (RD), Timothy McMahon (AD)

Chemistry Data Evaluation / Report Presentation:

Rick Loranger,
Chemist

William Hazel,
Chemist

Toxicology Data Evaluation / Report Presentation:

Kathleen Raffaele,
Toxicologist

INTRODUCTION

On 11/4/02, an *ad hoc* HED committee conducted an internal Peer Review of the OPP Triazole Team's 7/8/02 analysis of the Triazolylalanine Group's (TAG) 1/9/02 document entitled "Profile of the Triazole-derivative Fungicide Compounds and their Common Metabolites" (MRID# 45575501). The committee, led by Elizabeth Doyle, addressed toxicology and dietary exposure issues associated with this class of fungicides and its metabolites/degradates of concern.

I. DIETARY EXPOSURE CONCLUSIONS

The conclusions/recommendations of the Peer Review Committee (PRC) related to dietary exposure are as follows:

1. The PRC agreed with the OPP Triazole Team that there will be dietary exposure to 1,2,4-triazole and its conjugates, that such exposure could be significant, and that reliable estimates of dietary exposure cannot be made based upon available data.

2. The PRC had no issues with the dietary exposure components of the 7/8/02 OPP Triazole Team's evaluation of the TAG's 1/9/02 risk assessment including responses to TAG conclusions 3 and 4. The OPP Triazole Team's responses were as follows (the last four bullets are responses to TAG conclusions 3 and 4):

    3. The TAG continues to exclude 1,2,4-triazole conjugates from dietary exposure which the Agency currently considers to be residues of concern for the triazole fungicides.

    4. Exclusion of the triazole conjugates results in a great underestimate of dietary exposure.

    5. Even if found to be less toxic than free 1,2,4-triazole, the much higher exposure to the conjugates is expected to result in significant risk.

    6. Calculation of free triazole residues based on the amount of parent fungicide at harvest also is expected to greatly underestimate dietary exposure (the soil serves as a reservoir).

    7. Exposure to free and conjugated residues in rotational crops, often with some of the highest residues, is expected to result in significant dietary exposure underestimation.

    8. Use of 100% crop treated and 95th percentile of exposure are appropriate assumptions for a Tier 1 assessment but they may not be that conservative due to crop rotation and the soil serving as a reservoir of triazole degradates/metabolites.

9. With all of these exposure uncertainties, hazard uncertainties, and sources of potentially great exposure underestimation, risk due to exposure to free plus conjugated triazole residues is likely to be much higher than the TAG's estimates for free triazole alone.

10. The TAG states that free triazole formation in livestock commodities and water is compound-specific and should be considered only in the context of each individual triazole fungicide's risk. The first statement is likely correct, but the law requires all sources of exposure be considered in aggregate risk assessment.

11. The TAG states that residues of free triazole in plant commodities are very low and occur in ≤15% of samples. We agree there are low, infrequent residues in raw crops, but effects of processing on triazole formation are unknown.

12. The TAG further states that plant residues have a low contribution to total dietary load. We believe that insufficient data exist to determine relative exposure contributions of plant, livestock and water residues.

13. The TAG also believes that there is no need to include free triazole in crop residue definitions. We agree that free triazole should not be part of the residue definition for tolerance enforcement purposes due to its numerous sources. However, from a risk assessment perspective, both free triazole and its conjugates need to be included based on toxicological properties.

3. The PRC agreed that monitoring of 1,2,4-triazole and its conjugates in the U.S. food supply would provide representative and rapid data to permit assessment of human dietary risk associated with this class of fungicides needed for risk management decisions on numerous registration actions and several reregistration eligibility decisions. Based on their significance as major food consumption items (particularly for children), based on properties of free triazole and its conjugates, and based on the need to represent livestock commodities and extensive crop rotation practices, it was highly recommended that survey/monitoring data be generated on **milk, eggs, and soybean protein isolate**.

4. The PRC agreed that the TAG be requested to perform cooking and processing studies (including baking studies to assess flour residues) to determine the potential for, and extent of, conversion of parent fungicides and triazole conjugates to free 1,2,4-triazole at elevated pressure, temperature, and at the pHs of various processed products as well as the fractionation of the various residues in different processed products. In addition, the PRC recommended that the TAG be requested to perform studies in which livestock are fed triazole conjugates to determine distribution of the various residues in tissues and milk and to determine

the likelihood and extent of conversion of triazole conjugates to free 1,2,4-triazole in livestock (metabolism may be more rapid in the rumen).

II. TOXICOLOGY CONCLUSIONS

The conclusions/recommendations of the Peer Review Committee (PRC) related to toxicology are as follows:

1. The PRC concluded that, based on LD_{50} values, the acute toxicity of free triazole and triazole alanine are comparable to the parent compounds.

2. The PRC concluded that the subchronic toxicity data indicate that triazole alanine is less toxic than free triazole; however, there is no data available to evaluate neurotoxic potential.

3. The PRC concluded that there is no need for additional mutagenicity data; available data indicate that free triazole and triazole alanine are not mutagenic.

4. The PRC agreed with the OPP Triazole Team that there is concern for toxicity of free triazole, triazole alanine, and other triazole conjugates

5. The PRC concurred with the OPP Triazole Team that free triazole has not been adequately tested in toxicity studies with the parent triazole fungicides.

6. The PRC determined that no analogies could be made between toxicity of parents and expected toxicity of free triazole and triazole conjugates, based on the following considerations:

   - Target tissues and toxicological effects vary across parent compounds, with some overlap but no consistent pattern.

   - Carcinogenicity also varies across parent compounds, as does tumor site for carcinogenic parents.

   - The relationship between toxicity of free triazole, triazole conjugates, and parent compounds (based on available limited data), is not consistent; e.g. some parent compounds exhibit toxicity at lower doses than free triazole, others at higher doses.

7. The PRC determined that separate risk assessments should be conducted for free triazole and for triazole conjugates, and selected endpoints and Uncertainty Factors:

- For free triazole, the developmental toxicity study, with a NOAEL of 30 mg/kg should be used for both acute and chronic risk assessments; UF=1000 (10x intraspecies, 10x interspecies, 10x database).

- For triazole alanine and other triazole conjugates, the developmental toxicity study, with a NOAEL of 100 mg/kg, should be used for both acute and chronic risk assessments; UF=300 (10x intraspecies, 10x interspecies, 3x database).

- The developmental endpoints from the rat developmental toxicity studies for free triazole and triazole alanine were selected for use based on the available limited database, and are considered to be protective for all risk assessment scenarios, in the absence of reliable alternative endpoints.

- The use of a smaller database factor (3x) for triazole alanine and other triazole conjugates is based on the following considerations:
  - Available studies for triazole alanine showed minimal toxicity in adults at doses approaching the limit dose;
  - There is no indication of neurotoxicity in the available triazole alanine studies;
  - If additional studies were requested for triazole alanine, they would likely also be conducted at doses approaching the limit dose, leading to endpoints higher than that selected above from the developmental toxicity study;
  - The absence of a developmental toxicity study in rabbits, given the findings in the developmental toxicity study in rats, supports the use of an additional 3x database factor.

8. The PRC determined toxicology data needs for free triazole and triazole alanine (following evaluation of requested studies, it is possible that additional data may be needed):

   - For free triazole, the following studies should be required:
     Acute neurotoxicity study in rat
     Combined 90-day/subchronic neurotoxicity study in rat
     Developmental toxicity study in rabbit
     Reproductive toxicity study in rat (2-generation)
     Two-year chronic toxicity/oncogenicity study in female mice and male rats

   - For triazole alanine, requirements for additional studies should be reserved pending re-review of previously submitted studies or results of monitoring studies.

III. REFERENCES

Triazolylalanine Group (TAG). January 9, 2002. Profile of the Triazole-derivative Fungicide Compounds and their Common Metabolites. MRID# 45575501.

Review of "Profile of the Triazole-derivative Fungicide Compounds and their Common Metabolites". *Memorandum* from C. Swentzel to R. Keigwin dated July 8, 2002.

Attachment 2: Second Report of the *Ad Hoc* Triazole HED Peer Review Committee

TXR NO. 0052012

DATE: August 5, 2003

MEMORANDUM

SUBJECT: ***TRIAZOLES*** - 2nd Report of the *Ad Hoc* HED Peer Review Committee.

FROM: Kathleen Raffaele, Toxicologist
Registration Action Branch 3
Health Effects Division (7509C)

THROUGH: Stephen Dapson
Senior Scientist, Registration Action Branch 3
Health Effects Division (7509C)

TO: Bob Tomerlin
Registration Division (7505C)

PC Codes (include but are not limited to): 004401; 120503; 128993; 128847; 123909; 129011; 128835; 128925; 128857; 125601; 122101; 120603; 128997; 109901; 127201; 128976

On 11/4/02, an *ad hoc* HED committee conducted an internal Peer Review of the OPP Triazole Team's 7/8/02 analysis of the Triazolylalanine Group's (TAG) 1/9/02 document entitled "Profile of the Triazole-derivative Fungicide Compounds and their Common Metabolites"(MRID# 45575501). The committee, led by Elizabeth Doyle, addressed toxicology and dietary exposure issues associated with this class of fungicides and its metabolites/degradates of concern, including toxicology data needs (see Memo dated July 10, 2003, TXR# 0052011, K. Raffaele to Bob Tomerlin). On June 16, 2003, the Committee reconvened, to address a data waiver request submitted by the US Triazole Task Force (USTTF, DP Barcode 289197), requesting that data requirements for the acute neurotoxicity study, the rabbit developmental study, and the chronic/oncogenicity studies on male rats and female mice be waived.

Ad Hoc HED Peer Review Committee Members in Attendance

Elizabeth Doyle, Karl Baetcke, William Burnam, Vicki Dellarco, George Herndon (substituting for Steve Knizner), Alberto Protzel, Jess Rowland, and Brenda Tarplee (Executive Secretary).

OPP Triazole Team Members in Attendance

Kathleen Raffaele, Paula Deschamp, and Mike Metzger.

Also in attendance were: Timothy McMahon (AD)

Toxicology Data Evaluation / Report Presentation: _____

Kathleen Raffaele,
Toxicologist

INTRODUCTION

On 11/4/02, an *ad hoc* HED committee conducted an internal Peer Review of the OPP Triazole Team's 7/8/02 analysis of the Triazolylalanine Group's (TAG) 1/9/02 document entitled "Profile of the Triazole-derivative Fungicide Compounds and their Common Metabolites" (MRID# 45575501). The committee, led by Elizabeth Doyle, addressed toxicology and dietary exposure issues associated with this class of fungicides and its metabolites/degradates of concern, including toxicology data needs (for conclusions from this meeting, see TXR#0052011). On June 16, 2003, the Committee reconvened, to address a data waiver request submitted by the US Triazole Task Force (USTTF, DP Barcode 289197), proposing that data requirements for the acute neurotoxicity study, the rabbit developmental toxicity study, and the chronic/oncogenicity studies on male rats and female mice be waived.

BACKGROUND

In their meeting on 11/4/02, the *ad hoc* Triazole Peer Review Committee (PRC) determined toxicology data needs for free triazole. These data needs were transmitted to the US Triazole Task Force (USTTF) in November, 2002. The OPP Triazole Team met with the USTTF to discuss toxicology data needs on February 20, 2003, and a detailed proposal for generation of toxicology data, including a rationale for waiver of several studies, was submitted by the USTTF on March 28, 2003. This proposal was reviewed by the OPP Triazole Team, and the PRC was reconvened on June 16, 2003 to evaluate the proposed waiver.

CONCLUSIONS

The conclusions/recommendations of the Peer Review Committee (PRC) regarding the toxicology study waiver requests are as follows:

1. Acute Neurotoxicity Study

The PRC determined that the data requirement for the acute neurotoxicity study should be placed in reserve, pending the outcome of the combined subchronic/neurotoxicity study in rats. Upon receipt of the combined subchronic/neurotoxicity study, the need for the acute neurotoxicity study will be reassessed. In the absence of data from an acute neurotoxicity study, the PRC concluded that the use of the developmental endpoint from the developmental toxicity study in rats, when used for acute risk assessments in all populations, would be protective for effects that might have been seen in the acute neurotoxicity study.

2. Developmental Toxicity Study in Rabbits

The PRC reaffirmed their previous decision that the developmental toxicity study in rabbits should be required. Given the developmental effects seen in the rat study, the potential for developmental toxicity cannot be fully evaluated in the absence of a study in rabbits (to assess the possibility that the rabbit may be more sensitive than the rat). Although the USTTF argued,

based on results from parent compounds, that the rat is more sensitive to developmental toxicity from triazole-derivative compounds, the PRC reaffirmed its previous decision that the toxicity of free triazole cannot be predicted based on results from parent compounds. The PRC also noted that the results from studies in parent compounds were mixed with respect to most sensitive species for developmental effects (for some compounds, lower NOAELs were seen in rabbit studies).

3. Chronic toxicity/oncogenicity studies in male rats and female mice

The previous recommendation for chronic toxicity/oncogenicity studies in male rats and female mice was based on the widespread presence and persistance of free triazole in the environment and concerns regarding possible carcinogenicity of free triazole. To perform an adequate assessment of carcinogenicity, the PRC determined that both rat and mouse studies were needed.

The USTTF argued that chronic toxicity studies for free triazole are not needed; they suggested that chronic endpoints could be extrapolated based on subchronic data, since subchronic and chronic endpoints are within an order of magnitude for parent compounds. As mentioned above, the PRC previously concluded that toxicity of free triazole could not be predicted based on results of studies conducted in parent compounds. In addition, the PRC noted that the relationship between subchronic and chronic NOAELs/LOAELs has much to do with dose selection, so comparisons of NOAELs/LOAELS between subchronic and chronic studies provides limited information. The PRC also noted that subchronic studies do not evaluate the potential for carcinogenicity, which is seen with many triazole-derivative compounds.

The USTTF stated that the parent triazole compounds are not mutagenic or genotoxic, and that available mutagenicity data for free triazole are also negative, mitigating the need for carcinogenicity data. The PRC agreed that available mutagenicity data are negative, but also noted that many triazole-derivative compounds are carcinogenic, in the absence of mutagenicity or genotoxicity, limiting the reliance that can be placed on these negative data.

The USTTF stated that there was no indication of increased toxicity over time in the available 30- and 90-day studies with free triazole, and no accumulation of free triazole was seen in available metabolism studies. The PRC concluded that differences in the route of administration (gavage vs. dietary) and dose selection, and limitations on the endpoints evaluated, preclude direct comparison of results across the 30- and 90-day studies (both of which were unacceptable, with multiple deficiencies). The PRC also noted that the length of the cited studies was not substantially different, when compared to the duration of chronic studies. Regarding the metabolism data, the PRC noted that cumulative toxicity can occur due to repeated insult, without need for bioaccumulation, therefore the presence or absence of bioaccumulation is not definitive. In addition, the estimated half-life of 10-12 h from these available metabolism studies does not preclude the possibility of bioaccumulation. The PRC also noted that the available metabolism studies for free triazole are limited (single exposure only), and have been classified as Unacceptable, based on multiple deficiencies (including inadequate methodological information, inadequate characterization of test substance, etc.); the reliability of these data is therefore questionable.

The USTTF indicated that additional endpoints would be included in subchronic rat and mouse studies to address possible cancer issues. Based on review of submitted protocols by the Triazole team, the added endpoints were limited (retention of liver tissue for possible enzyme analyses [criteria for performance of analyses was not provided] and analysis of thyroid hormone levels in the subchronic rat study). No mechanistic data were proposed or provided, nor was there any discussion of how proposed enzyme analyses (if performed) or thyroid hormone analyses would be predictive of carcinogenicity.

In conclusion, the PRC determined that the subchronic studies do not assess carcinogenicity, increased severity of effects, or changes in dose/response curve, which may occur with long term continuous exposure. In the absence of chronic toxicity/oncogenicity studies, long term risk from exposure to free triazole, including possible carcinogenic effects, cannot be evaluated. The requirement for chronic toxicity/oncogenicity studies in male rats and female mice was reaffirmed.

Attachment 3: Triazole Summaries - Additional Data Summaries/Literature Articles

1. O. Hockwin and A. Wegener. (1989). Final Expert Opinion on the In-Vivo examination of the lens using slit-lamp microscope and Schiempflug photography and post-mortem biochemistry of the lenses from Bayer Study T 3 027 392 in Beagle Dogs. Department of Exp. Ophthalmology of the Rheinische Friedrich-Wilhelm University Bonn, Sigmund-Freud Street 25, 5300 Bonn 1, Germany. Laboratory Project ID AC Report No. 109988. MRID 45284013. Unpublished.

This document contains information regarding a study evaluating ocular effects in Beagle dogs during exposure to several Bayer compounds, including tebuconazole (referred to in the document as HWG 1608) and triazole (1,2,4-Triazole). The document contains no information regarding the study protocol, exposure levels, or clinical signs in the exposed animals. Administered doses are not described in the document, although a listing on one page seems to indicate doses of 100 mg/kg for both triazole and tebuconazole. The report does contain detailed information regarding the ocular findings, including in vivo examinations and in vitro studies of changes in lens biochemistry. Statistically significant changes were found on some parameters for both tebuconazole and triazole. Given the lack of procedural information, the results are difficult to interpret.

Unless additional information can be provided for this study (for example, clinical signs or necropsy data, and a more adequate explanation of the procedures), the data available do not provide information usable in assessing risk from triazole exposure.

2. J. Thyssen and G. Kimmerle. (1976). 1,2,4-Triazole Occupational Toxicology Study. Bayer AG, Department of Toxicology, Friedrich-Ebert-Strasse 217-333, D-42096 Wuppertal, Germany. Bayer AG Report No. 5926. MRID 45284004. Unpublished.

This document contains short summaries of several acute toxicity studies on 1,2,4-triazole (studies are described separately below). Very little information was provided on the specific procedures used, nor was there analytical data on the test substance.

Acute oral toxicity: 1,2,4-triazole was administered by gavage to Wister rats (size of most dose groups was 15/sex, but there was some variation among doses). Doses ranged from 250-2500 mg/kg for males, 100-2500 mg/kg for females; there were 9 dose levels/sex, with dose intervals usually varying by 250 mg/kg. Results were presented as the number of animals/group who died or showed clinical signs, as well as a range of days on which death occurred for each group. An LD50 was also calculated separately for each sex.

For males, clinical signs were not seen at 250 mg/kg, but were seen in all animals for all other dose groups (starting at 500 mg/kg). For females, clinical signs were not seen at 100 mg/kg, but were seen in all animals for all dose groups starting at 250 mg/kg. Clinical signs were not listed for individual animals, but the summary listed the following clinical signs: reduction in general well-being, sedation, and breathing disorders; at higher doses, lying in the abdominal or side position (doses at which these occurred was not stated, time of occurrence was given as "within

an hour of administration and ... for a maximum of up to 13 days after administration" [study report, p. 6]). The lowest dose at which death occurred was 1250 mg/kg for both sexes, with the death occurring on the day of dosing. The oral LD50 was similar for both sexes (1650 mg/kg for males, 1648 mg/kg for females).

Dermal toxicity: 1,2,4-triazole (moistened with Cremophor EL) was applied to the shaven dorsal skin of male and female Wistar rats. After 24 h, substance was washed off (with soap and water). Animals were observed for 14 days. The summary stated that studies were carried out using the occlusive dressing method (not further described, although a citation was provided). Group size varied from 5 to 20, with most groups including 10 animals/sex. The dose range was 1000-5000 mg/kg for males (4 dose groups) and for females (6 dose groups). Clinical signs were seen in all animals from all treatment groups. Again, individual data were not provided but the summary stated that the symptoms were similar to those seen in the oral studies. Death was seen at the 2500 mg/kg dose in both sexes; time of death varied from 1-9 days after treatment, with earlier deaths occurring after exposure to higher dose levels. The calculated dermal LD50 was somewhat lower for females (3129 mg/kg) than for males (4200 mg/kg).

Inhalation: No effects were observed in the inhalation studies (using 5 male rats and 5 male mice), but the summary also states that "no substance vaporized or atomized in the 4 and 6-hr. experiments", so it is not clear that any exposure actually occurred.

Dermal irritation: 1,2,4-triazole was applied to cellulose patches (1.5 cm2, 500 mg/patch). The patches were applied for 24 h to the hairless skin of the ears of 2 rabbits. Treated skin was observed for 7 days following removal of patches. The summary stated that the 'skin revealed no changes'.

A similar study was also performed using similar treatment on the human forearm (specific procedure and dose not provided), with exposure from 2-8 h and 7 day observation periods (a total of six subjects, 1 female and 5 male). The summary stated that treated skin was 'physiologically normal' after removal of the dressing and for the remainder of the observation period.

Ocular irritation: 1,2,4-triazole was applied to the conjuctival sac of the left eye (50 mg/animal) of 2 rabbits. Intense reddening and very intense swelling of the eye and conjuctivae were observed immediately after application and at 24 h. After 5 days, one animal had returned to normal but the other still had some redness and swelling of the conjuctivae. Effects on the cornea and iris were also observed during the first 2 days after application. The test substance was classified as a severe eye irritant.

Summary: The report concluded that 1,2,4-triazole was moderately acutely toxic by the oral and dermal route, and that the central nervous system was affected at high oral and dermal doses.

3. P.K. Chan, P.M. Fisher, and R.D. Morrison. (1981). 1,2,4-Triazole Acute range-finding studies. Rohm and Haas Toxicology Department, 727 Norristown Rd., Spring House, PA 19477. Rohm and Haas Report No. 81R 0057. MRID No. 45284006. Unpublished.

and

K.R. Procopio and J.D. Hamilton. (1992). 1,2,4-Triazole Acute range-finding studies. Rohm and Haas Company, Toxicology Department, 727 Norristown Rd., Spring House, PA 19477. Rohm and Haas Report No. 81R-057A. MRID No. 45324301 (Supplemental submission to EPA MRID No. 45284006). Unpublished.

Both of the above-cited documents provide information regarding the same series of acute toxicity studies on 1,2,4-triazole, with the second submission including additional information not provided in the first submission.

Acute oral toxicity: 1,2,4-triazole (Sample No. TD 81-112, Lot No. 113296, 92.8% pure), in 0.5% methylcellulose, was administered by gavage to male rats (Crl:CDBR, 3/group) at 0.5 or 5 mg/kg. At 5.0 mg/kg, all rats died within 10 min. of dosing; at 0.5 mg/kg, all rats survived and no clinical signs were noted.

Acute dermal toxicity: 1,2,4-triazole (lot number as above), was moistened with saline and applied to shaven intact skin of rabbits (2 males/dose level) at 0.2, 2.0, and 5.0 g/kg. Application sites were occluded. After 24 hours, covers were removed and site was wiped with paper towels. Animals were observed for 14 days; skin irritation was also recorded.

All animals treated with 2.0 or 5.0 g/kg died; the higher dose animals died on days 1 and 2, the lower dose animals on day 3 and 4. Observed clinical signs at those doses included passiveness, scant droppings, soft feces, tremor, ataxia, salivation, abdominal breathing, gasping, and nasal discharges. No clinical signs were seen in animals treated at 0.2 g/kg. Skin irritation was noted as well defined erythema and very slight edema. It was not clear at which dose(s) these irritant effects were observed.

Skin irritation: 1,2,4-triazole, 0.5 g/patch, was moistened with saline and applied to the skin of 2 male rabbits. Two patches were applied to each rabbit, 1 on intact skin and 1 on abraded skin. Application sites were occluded, under a gauze lined patch and an impervious cuff, for 24 h, after which the patches were removed and the site wiped with paper towels.

No edema was observed for either site on either rabbit. Erythema, scored 1 or 2, was observed on one or both sites for both rabbits. Based on these results, 1,2,4-triazole was rated as 'slightly irritating' to skin.

Eye irritation: 1,2,4-triazole, 0.1 g/eye, was applied to the conjunctival sac of the left eye of two male rabbits. Eye irritation was evaluated according to the method of Draize, for up to 14 days. Effects were seen on the cornea, iris, and conjunctivae starting at 4 h. By day 7, corneal and conjunctival effects had cleared. Iridal effects had cleared by day 14. Based on these results, 1,2,4-triazole was rated as 'substantially irritating' to the eye.

Summary: Findings in this series of studies were similar to those in the previous report. The only notable difference was that there were no clinical signs reported in the current acute oral

study at 0.5 g/kg, while clinical signs were seen in both sexes in the previous acute oral study at 500 mg/kg (the same dose). We also note that only males were tested in the current study, and that females were found to be more sensitive in the previous report.

4. Wickramaratne, G.A. de S. (1987). The Chernoff-Kavlock Assay: Its validation and application in rats. Teratogenesis, Carcinogenesis, and Mutagenesis 7:73-83. MRID No. 45284010.

This document consists of a copy of a literature article reporting on a study intended to validate the use of an abbreviated Chernoff-Kavlock assay in rats to predict chemicals likely to cause teratogenic effects (testing was conducted at Central Toxicology Laboratory, Imperial Chemical Industries PLC, Cheshire, UK). Test substance was administered to pregnant rats (Wistar-derived) from gestation days 7-17. Maternal observations consisted of maternal bodyweights on days 1, 7-17, and 22 of gestation; offspring observations included only litter weights of live pups on PNDs 1 and 5, and number of live and dead pups on PNDs 1 and 5.

Triazole, at dose of 25 and 100 mg/kg, was included as one of the many substances tested in this assay. Authors reported no differences between triazole-treated animals and control animals.

The parameters evaluated and reported in this study were very limited; data collected in the rat developmental studies conducted by Bayer are much more complete and would supercede those reported in this study.

5. Wickings, E.J., M.C. Middleton,. and S.G. Hillier. (1987). Non-Steroidal Inhibition of Granulosa Cell Aromatase Activity in vitro. J. Steroid Biochem. 26 (6):641-646. MRID No. 45284014.

In this published article, a substituted triazole (R151885 [1,1-di(4-fluorophenyl)-2-1,2,4-triazol-1-yl)-ethanol) was evaluated in several in vitro assays for effects on steroid metabolism/synthesis (including granulosa cell estradiol production, progesterone production, and testosterone aromatization). A series of structurally related compounds were then evaluated, to determine which structual components of the compound were responsible for aromatase inhibition. Results indicated that imidazolyl or pyridyl moieties, when replacing the triazolyl substituent, produced more potent and specific inhibition.

These results appear to indicate that the triazole moiety was not the active component of this compound, with respect to inhibition of the aromatase enzyme in the assay used in this study.

6. Flucke, W. (1978). 1,2,4-Triazole. Determination of Acute Toxicity (LD50). Bayer AG, Department of Toxicology, Friedrich-Ebert-Strasse 217-333, D-42096 Wuppertal, Germany. AC Report No. 109972. MRID No. 45284008. Unpublished.

This document consists of a one page report, with no procedural information or explanation of the data. It appears to report on an acute oral LD50 study; doses were administered to male rats only, 10/dose. Doses ranged from 850-2500 mg/kg (8 dose levels tested). It appears that clinical signs (not described) were seen in all animals at all doses. The lowest dose at which death

occurred was 1200 mg/kg, all animals died at 2000 and 2500. The LD50 was calculated to be 1375 mg/kg (range 1273-1485 mg/kg).

The findings from this study appear to be similar to those described above.

7. Rakhmatov, R.M., V.B. Danilov, U.A. Madzhidov, and S.A. Gamiyants. (1991). Basis data for setting the limiting allowed concentration (LAC) of 1,2,4-triazole in workplace air. Gigiena i Sanitariya 2:30-1. [Abstract only]. MRID No. 45284011.

This submission consists of a translated Russian abstract that describes very briefly a series of studies conducted for use in setting safe exposure levels (in air) for 1,2,4-triazole. Little or no procedural information was provided for the various studies. The results reported are described below.

-Oral LD50s for mice (3650 mg/kg), rats (3080 mg/kg) and rabbits (666 mg/kg). Signs reported were lethargy and ataxia, with death on the 'first day of observation.'

-Inhalation LC50 (4 hour) for mice (2200 mg/m3) and rats (2050 mg/m3).

-Skin irritation was not seen upon dermal exposure to rats.

-Eye irritation (slight) was seen in rabbits.

-Subacute exposure (dose, route, and duration not specified) to rats demonstrated some potential for cumulative toxicity. Effects seen after repeated oral exposure were described as 'macrovesicular fatty dystrophy of the liver, plethora and acirculatory expansion of vessels in the kidneys with filling of canal loops of glomerulus capillaries by blood, and shallow hemorrhaging.'

-Threshold concentration following single inhalation exposure (duration not specified) was stated as 226.6±10.5 mg/m3, with findings of 'increased methemoglobin concentration and decreased cholinesterase activity in the blood.'

-Effects of aerosol exposure were evaluated in rats and rabbits at doses of 19.8 ±0.33 mg/m3 and 4.9±0.08 mg/m3. Following 3 months exposure (apparently at the higher dose), decreased levels of urea in urine were seen; following 4 months, decreased cholinesterase and increased methemoglobin were seen in blood. No effects were noted at the lower dose.

-Mutagenic (as represented by chromosome aberrations in rat marrow cells) or 'embryotropic' activity (not further described) were not found (studies not described but conducted using inhalation exposure at the above doses).

The abstract concluded that toxic effects of the compound included 'primarily effects on the liver, kidneys, and CNS.' A LAC of 5 mg/m3 in workplace air was proposed.

8. Saratikov, A.S., E.M. Trofimovich, T.P. Novozheeva, T.A. Zimina, M.R. Ozhegina, and E.L. Morokova. (1986). Toxicological and Health Evaluation of 1,2,4-triazole for health standards in aquifers. Gigiena i Sanitariya 51 (11):65. [Abstract only]. MRID 45284012.

This submission also consists of a translated abstract, describing briefly a series of studies conducted for use in evaluating safe levels of 1,2,4-triazole in aquifers. It was stated that the triazole used for studies was 98% pure. In addition to toxicity, several properties of triazole in aqueous solutions were evaluated.

Acute toxicity in mice and rats was evaluated following intraperitoneal administration of an aqueous solution. Average toxic dose was stated to be 1350 mg/kg for mice and 1750 mg/kg for rats, with clinical signs listed as decreased motor activity, excitability, muscle cramp, and (in some cases) tremors and difficulty breathing.

Irritancy to skin was evaluated using a 25% solution, eye irritation using a 12.5% solution; no irritant effects were noted.

Cumulative properties were also evaluated, and it was stated that the compound has moderatively cumulative properties, but insufficient information was provided to interpret the stated results.

A six-month study was performed in male white rats (strain not specified), using i.p. doses of 0.02, 0.20, 2.0 mg/kg. Evaluated parameters included body weights, blood cell counts, and a variety of clinical chemistry parameters; apparently no histopathology or necropsy data were collected. Stated results included an increase in urine protein content, changes in leukocytes, and changes in alkaline phosphatase activity at the high dose (no other description provided). No changes were noted at the two lower doses. An LAC for aquifers was recommended at 4 mg/dm3.

9. Holzum, B. (2000). Developmental toxicity of triazole-fungicides, Characterization and risk assessment. Bayer AG, Department of Toxicology, Friedrich-Ebert-Strasse 217-333, D-42096 Wuppertal, Germany. AC Report No. 109973. MRID No. 45284009. Unpublished.

This submission consists of a copy of a presentation by a Bayer scientist, regarding common developmental toxicity of triazole fungicides, and discussion of classification of developmental effects under the European classification and labelling requirements (used within the European Community). Several of the slide copies include tables listing the specific types of developmental toxicity seen following exposure to triazole fungicides (including the doses at which effects were seen maternally and in offspring), with the rat and rabbit studies compared separately.

In rats, the summary notes that common effects generally seen include embryolethality, retarded development, and supernumerary ribs, with urinary tract variations and malformations seen in a subgroup of compounds. In rabbits, the only general effect noted was embryolethality, with a variety of malformations again seen in a subgroup of compounds.

Included in the summary is a reference to developmental toxicity studies using triazole; these studies have been reviewed separately and the results will not be discussed here.

With respect to common toxicity across triazoles, the report authors concluded "we may conclude that, to a certain extent, a typical pattern exists for triazole developmental toxicity in animals." (p. 9), although they did point out some differences in the patterns of abnormalities across studies. The report author, however, attributes developmental effects to maternal toxicity for this group of compounds (perhaps acting via maternal hypoxia or adrenal effects); this attribution of causation appears to be relevant in the European system of classification.

10. Menegola, E., M.L. Broccia, F. DiRenzo, and E. Giavini. (date not provided). Poster Presentation: In Vitro Comparative Study of the Teratogenic Activity of Some Triazoles. University of Milan, Dept. of Biology, Milan-Italy. [Copy of a poster, presentation meeting not specified.] MRID No. 45344602. Unpublished.

This submission consists of a one page copy of a poster. Two substituted triazoles (Flusilazole and fluconazole) and triazole were evaluated for teratogenic potential in vitro in 48 h whole embryo cultures of 9.5 day old rat embryos. Methodological details regarding the culture conditions (including the number of embryos evaluated in each condition) and analytical procedures were not provided. The results stated that flusilazole (6.25-250 μM) and fluconazole (125-500 μM) "showed abnormalities at the branchial apparatus level and increased cell death at the branchial mesenchymes" (hypoplasia of I and II branchial arches and fusion of I-II branchial arches) without indication of developmental delays. Exposure to triazole (2500-5000 μM) caused slight developmental delays and severe anemia of the visceral yolk sac. Authors concluded that both mono-triazole derivatives showed teratogenic potential, in particular for cranio-facial abnormalities, but that triazole was not teratogenic.

We note that insufficient information was provided for us to evaluate the conclusions stated in this document, and that the conditions of exposure for this in vitro study may not represent those that would occur in vivo. We also note that the results from the available developmental toxicity study in rats would supercede findings from this study with respect to evaluating teratogenic effects of triazole.

Old metabolism studies

In a series of metabolism/disposition studies (MRID 45284018, 45284019, and 45297202), groups of male and female Sprague-Dawley rats were given a single intraduodenal (1 mg/kg), intravenous (0.1-100 mg/kg), or oral dose (0.4-866 mg/kg) of ^{14}C-labeled triazole (MRID 45284018 – Lot No. not reported, sp. act. 470 μCi/mg, purity ≈97%; MRID 45284019 – Lot No. CL-V-70, sp. act. >67 μCi/mg, purity >98%; MRID 45297202, Lot No. CFQ 2458, sp. act. 103 μCi/mg, purity ≥99%). The test material is a common moiety found in several compounds under development by Ciba-Geigy at the time these studies were conducted. Urine and feces were collected up to 7 days postdose and expired air was monitored for residual activity. Bile samples were collected up to 24 hours after treatment with the radiolabel. Tissue/carcass burdens were investigated at selected time intervals up to 7 days postdose.

No treatment-related signs of toxicity among any of the test animals were reported. Overall recovery of administered radioactivity ranged from 97-105%. Based upon urinary and biliary excretion and tissue/carcass burden data, 80% - 95% of the administered dose was absorbed. Elimination of administered radioactivity was primarily via the urine, accounting for 80-95% of the dose, and was ~95% complete within 48 hours after treatment. Elimination via expired air was negligible (<0.1%). Fecal excretion typically accounted for <15% of the administered radioactivity and was essentially complete within 48 hours. Biliary excretion accounted for approximately 10% of the dose during the 24 hr study period, and the results were suggestive of enterohepatic circulation and diffusion/secretion by the stomach mucosa.

The only compound identified in the urine was the unchanged parent which constituted ~95% of the radioactivity. There were possibly three other potential polar metabolites in the urine, each constituted <3% of the administered dose. Their structures were not elucidated, but all three seem to be more polar than triazole as judged by their delayed migration relative to triazole under normal-phase TLC separation conditions. Based on the study results, triazole was nearly completely absorbed and rapidly excreted mostly unchanged in the urine.

These metabolism/disposition studies in rats are Unacceptable/Guideline and do not satisfy the requirements for a Metabolism and Pharmacokinetics Study [OPPTS 870.7485 (§85-1)]. None of the studies were described in detail and gave the impression they were more laboratory notes than metabolic study reports. Neither the care and treatment of the animals nor the test material were adequately described. Details concerning dose preparation, such as stability and homogeneity were also lacking. Finally, the potential metabolites in the feces were not identified, particularly in those instances when the feces contributed >5% of the total isotope recovery (MRID 45284019). The study can be upgraded to acceptable if it can be shown that the feces also contained unchanged parent compound and if more information were provided for the test material (description, purity, stability, homogeneity, etc.).

13544

R124628

Chemical:	1H-1,2,4-Triazole (A metabolite of tebuconazole & metabolite of acaricidal & fungicidal compounds) 1H-1,2,4-Triazole-1-propanoic acid, .alpha.-amino- Triazolyl acetic acid (A metabolite)
	PC Code: 600074 600011 600082
HED File Code:	14000 Risk Reviews
Memo Date:	2/7/2006
File ID:	DPD322215
Accession #:	412-06-0013

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