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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: **May 9, 2006**

ACTION MEMORANDUM

SUBJECT: Inert Reassessments: Hexamethylenetetramine (HMTA; CAS Reg. No. 100-97-0)

FROM: Pauline Wagner, Chief Pauline Wagner 5/9/06
Inert Ingredient Assessment Branch

TO: Lois A. Rossi, Director
Registration Division

I. FQPA REASSESSMENT ACTION

Action: Reassessment of two inert ingredient exemptions from the requirement of a tolerance. Current exemptions are to be maintained.

Chemical: Hexamethylenetetramine
CFR: 40 CFR 180.910 (formerly 40 CFR 180.1001(c)) and 40 CFR 180.920 (formerly 40 CFR 180.1001(d))
CAS #: 100-97-0

CFR Citation

40 CFR	Exemption Expression	Limits	Uses (Pesticidal)	CAS Reg. No. and 9CI Name
180.910	Hexamethylenetramine	For use in citrus washing solutions only at not more than 1%.	Preservative	100-97-0 1,3,5,7-Tetraazatricyclo [3.3.1.13,7]decane
180.920	Hexamethylenetramine	None	Stabilizer for carriers in solid pesticide formulations	

Use Summary: HMTA is used as a preservative in citrus washing solutions at not more than 1% of the formulation, and as a stabilizer for carriers in solid pesticide formulations for pre-

harvest use only, with typical concentrations of ≤1 to 5%. HMTA is also used in the in the manufacture of rubber and resins, adhesives and coatings, firelogs and briquettes and flame retardant materials, as well as in pharmaceuticals and cosmetics. It is also approved by the US FDA for indirect food uses.

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the two exemptions from the requirement of a tolerance for the inert ingredient hexamethylenetetramine (CAS Reg. No. 100-97-0). I consider the one exemption established in 40 CFR 180.910 [formerly 40 CFR 180.1001(c)] and the one exemption established in 40 CFR 180.920 [formerly 40 CFR 180.1001(d)] to be reassessed for purposes of FFDCA's section 408(q) as of the date of my signature, below. A Federal Register Notice regarding this tolerance exemption reassessment decision will be published in the near future.

/ Donald R Stubbs

Lois A. Rossi, Director
Registration Division

5/10/06

Date:

cc: Debbie Edwards, SRRD
Joe Nevola, SRRD

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

May 9, 2006

MEMORANDUM

SUBJECT: Reassessment of Two Exemptions from the Requirement of a Tolerance for Hexamethylenetetramine (HMTA; CAS Reg. No. 100-97-0)

FROM: R. Tracy Ward, Biologist R. Tracy Ward
Inert Ingredient Assessment Branch
Registration Division (7505C)

TO: Pauline Wagner, Chief
Inert Ingredient Assessment Branch
Registration Division (7505C)

Background

Attached is the science assessment for hexamethylenetetramine (HMTA; CAS Reg. No. 100-97-0). This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, exposure profile, environmental fate, and ecotoxicity of HMTA. The purpose of this document is to reassess the existing exemptions from the requirement of a tolerance for residues of HMTA as required under the Food Quality Protection Act (FQPA).

Executive Summary

This document evaluates the existing tolerance exemptions for HMTA when it is used as an inert ingredient in pesticide formulations. An inert ingredient is defined by the U.S. Environmental Protection Agency as any ingredient in a pesticide product that is not intended to affect a target pest. HMTA has two exemptions from the requirement of a tolerance. One exemption, under 40 CFR 180.910 when applied to growing crops or raw agricultural products after harvest, limits the use of HMTA to a post-harvest use as a preservative in citrus washing solutions at not more than 1% of the solution. The other exemption, under 40 CFR 180.920 when applied to growing crops only, is for use

of HMTA as a stabilizer for carriers in solid pesticide formulations.

HMTA has moderate acute oral toxicity, is slightly irritating to the skin and mildly irritating to the eyes. HMTA may be a strong sensitizer at high concentrations. In subchronic oral and inhalation toxicity studies, weight loss or decreased weight gain was observed at moderate dose levels. In chronic oral toxicity studies, reduced growth rate was observed at high dose levels. In reproductive and developmental studies, there were no effects observed at high dose levels. HMTA was non-carcinogenic in studies, but had conflicting results in genotoxicity studies.

Dietary and drinking water exposures of concern are not anticipated from the inert ingredient use of HMTA considering its physical/chemical properties, including high volatility. Dermal and inhalation exposures are possible from the use of HMTA in residential-use pesticide products, including their use in home gardens. However, exposures to the chemical will be limited by the outdoor use of the product and the volatile nature of HMTA.

Based on available toxicity data, HMTA is practically nontoxic to aquatic species and moderately toxic to terrestrial species. HMTA is expected to quickly leach from soils to groundwater, degrade abiotically under certain conditions, and biodegrade in the environment, so it is not expected to be available to terrestrial species at concentrations exceeding Agency levels of concern unless applications rates exceed 10 pounds per acre. Risks to aquatic organisms is likely to be low unless applications exceed 100's of pounds per acre. It is also not expected to bioaccumulate in animals. For these reasons ecological concerns for non-target terrestrial and aquatic species are not likely from the use of HMTA as an inert ingredient in pesticide formulations.

Taking into consideration all available information on HMTA, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to HMTA when used as an inert ingredient in pesticide formulations when considering dietary exposure and all other non-occupational sources of pesticide exposure for which there is reliable information. Therefore, it is recommended that the two exemptions from the requirement of a tolerance established for residues of HMTA, as listed in Table 1, can be considered reassessed as safe under section 408(q) of the FFDCA.

I. Introduction

This report provides a qualitative assessment for HMTA, an inert ingredient used as a preservative in citrus washing solutions only at not more than 1% under 40 CFR 180.910, or as a stabilizer for carriers in solid pesticide formulations for pre-harvest use only under 40 CFR 180.920.

Other names for hexamethylenetetramine include: HMTA; Methamine; hexamethyleneamine; hexilmethylenamine; hexamine; ammonioformaldehyde;

formamine; formin; aminoformaldehyde; Aminoform; Antihydral; Aceto HMT; cystamin; Cystogen; Duirexol; Ekagom H; hexaform; Herax UTS; Heterin; Hexa-Flo-Pulver; Mandelamine; metramine; Preparation AF; Resotropin; Uramin; Uratrine; Urisol; Uritone; Urodeine; Urotropin; Xametrin; 1,3,5,7-tetraazaadamantane; 1,3,5,7-tetraazatricyclo (3.3.1.1(3,7))decane (ChemIDPlus 2004).

HMTA hydrolyzes to form formaldehyde and ammonia under acidic conditions (Restani and Corrado 1991), and in toxicology studies with HMTA, the formaldehyde excreted in the urine reacts with kynurenine in the rat hair causing a yellow discoloration of fur. HMTA is manufactured by the reaction of ammonia with formaldehyde in the liquid phase according to the following chemical reaction:

$$6CH_2O + 4NH_3 \longrightarrow C_6H_{12}N_4 + 6H_2O$$

According to Dreyfors et al (1989), HMTA is an organic amine which has become increasingly important in a large number of industries in the United States and around the world since its discovery over one hundred years ago. The U.S. production exceeded ninety million pounds in 1986 and was projected to remain stable.

HMTA has diverse industrial and chemical applications. HMTA is used in the rubber industry to prevent vulcanized rubber from blocking; as an accelerator; as a curing agent for thermosetting resins; in foundry mold castings as part of binder resins; in the production of nitrilotriacetic acid; in the manufacture of adhesives and coatings; in firelogs and briquettes for camping and in flame retardant materials (Trochimowics et al 2001). It is also used as a urinary tract anti-infective drug (Oslo 1980, as cited in Cosmetic Ingredient Review (CIR) 1992). HMTA is also used as a cosmetic biocide in eye make-up preparations at concentrations of less than 1% (CIR 1992) and is also used as a preservative in lotions and creams (Kabara 1984, as cited in CIR 1992). It has also been approved by the U.S. Food and Drug Administration (FDA) for indirect food uses.

II. Use Information

A. Pesticide Uses

HMTA is used as a preservative in citrus washing solutions at not more than 1% of the formulation, and as a stabilizer for carriers in solid pesticide formulations for pre-harvest use only. Typical concentrations of HMTA when used as a stabilizer range from ≤1 to 5%.

Table 1. Tolerance Exemptions Being Reassessed in this Document

40 CFR	Exemption Expression	Limits	Uses (Pesticidal)	CAS Reg. No. and 9CI Name
180.910[1]	Hexamethylene tetramine	For use in citrus washing solutions only at not more than 1%.	Preservative	100-97-0 1,3,5,7-Tetraazatricyclo [3.3.1.13,7]decane
180.920[2]	Hexamethylene tetramine	None	Stabilizer for carriers in solid pesticide formulations	

1. Residues listed in 40 CFR 180.910 are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops or to RACs after harvest.
2. Residues listed in 40 CFR 180.920 are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops only.

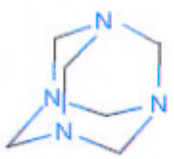
B. Other Uses

HMTA is used in the rubber industry as a rubber blocking preventative; as an accelerator and as a curing agent for thermosetting resins. It also has other industrial applications such as use in foundry mold castings as part of binder resins; in the production of nitrilotriacetic acid; in the manufacture of adhesives and coatings; in firelogs and briquettes for camping, and in flame retardant materials.

HMTA is used as a pharmaceutical for intestinal infections. Doses range from 500 mg to 1.5 g, or 1 g four times a day in adults, to 500 mg four times a day for children 6 to 12 years, to 50 mg/kg/day three times a day for children under 6 years old. It is also used as a cosmetic biocide in eye make-up preparations (up to 1%), and as a preservative in lotions and creams. It has been approved for indirect food uses as listed in Appendix A by the U.S. FDA.

III. Physical and Chemical Properties

Table 3. Physical and Chemical Properties of HMTA

Parameter	Value	Reference
Structure		ChemIDPlus 2004
CAS Reg. No.	100-97-0	ChemIDPlus 2004
Molecular formula	$C_6H_{12}N_4$	HSDB 2003
Molecular Weight	140.19	ChemIDPlus 2004

Parameter	Value	Reference
Physical State	Hygroscopic, white crystalline solid	Trochimowics et al 2001
Melting Point	>250°C (M)	ChemIDPlus 2004
Density	1.331 g/mL @ -5° C	Weast 1982 as cited in CIR 1992
Water Solubility	4.49×10^5 mg/L @ 12°C (M)	ChemIDPlus 2004
Log P (octanol-water)	-4.150 (E)	ChemIDPlus 2004
Henry's Law Constant	1.64×10^{-9} atm-m^3/mole @ 25°C (E)	ChemIDPlus 2004
Vapor Pressure	0.004 mm Hg @ 25°C (M)	ChemIDPlus 2004
Atmospheric OH Rate Constant	5.09×10^{-10} cm^3/molecule-sec @ 25°C (E)	ChemIDPlus 2004

IV. Hazard Assessment

A. Hazard Profile

This assessment of HMTA utilizes data and information available from the National Institute of Health's Hazardous Substance Data Bank (HSDB 2003), the ChemIDPlus database (2004), a 1992 Cosmetic Ingredient Review (CIR), JECFA (Joint WHO/FAO Expert Committee on Food Additives 1974), Trochimowics et al (in Patty's Industrial Hygiene and Toxicology 2001), a genotoxicity study by the National Toxicology Program (NTP 1989), and other selected published literature.

HMTA has moderate acute oral toxicity, is slightly irritating to the skin and mildly irritating to the eyes. HMTA may be a strong sensitizer at high concentrations. In subchronic oral and inhalation toxicity studies, weight loss or decreased weight gain was observed at moderate dose levels. In chronic oral toxicity studies, reduced growth rate was observed at high dose levels. In reproductive and developmental studies, there were no effects observed at high dose levels. HMTA was non-carcinogenic in studies, but had conflicting results in genotoxicity studies.

B. Metabolism and Pharmacokinetics

HMTA is known to slowly hydrolyze into ammonia and formaldehyde in acidic conditions (Staples 1983; Sax 1984, as cited in Dreyfors et al 1989 and Restani and Galli 1991).

However, according to Gollamudi et al (1979, as cited in Trochimowicz 2001), "Most of ingested HMTA was reportedly excreted unchanged within 3h (species unspecified)."

C. Toxicological Data

Acute Toxicity:

Gigiena I Sanitariya (1970, as cited by RTECS 2003) reported the LD_{50} for an

oral exposure of HMTA in mice to be 569 mg/kg of body weight (bw), with the mice showing excitement, muscle contraction or spasticity. Trochimowicz et al (2001) reported that an acute oral exposure of mice to 512 mg/kg of bw resulted in some deaths, suggesting that HMTA is moderately toxic to mice following acute exposure. A 1966 study by Della Porta (as cited in CIR 1992) reported no mortality in rats orally intubated with either 10 or 20 g/kg bw of HMTA as an 80% aqueous solution.

HMTA was found to be slightly irritating to the skin of rabbits when 0.5 mL of a 0.20% concentration in distilled water was applied under an occlusive patch for 24 hours (COLIPA (the European Cosmetic, Toiletry and Perfumery Association) 1989, as cited in CIR 1992). In an unpublished study by the DuPont Company (1976, as cited in Trochimowicz et al 2001), a 5% solution of a compound with 40% HMTA was found to be mildly irritating to the skin of guinea pigs.

In an eye irritation test, a mascara containing 0.1% HMTA was applied to the rabbit eye. HMTA was found to be mildly irritating in both rinsed and unrinsed eyes (Stillmeadow, Inc. 1980, unpublished study, as cited in CIR 1992).

In the guinea pig maximization test, HMTA was not dermally sensitizing at a concentration of 0.20% (COLIPA 1989, as cited in CIR 1992). However, AH26, a compound with 25% HMTA (and 10% silver powder, 60% bismuth oxide and 5% titanium dioxide) was rated a strong or potent sensitizer (Kallus et al 1983, as cited in CIR 1992).

There were no acute dermal or inhalation animal studies available for use in this assessment.

Subchronic Toxicity:

No toxic effects were observed in mice fed up to 5.0 g/kg bw/day HMTA for 10 days (Krasovskii and Fridlyand 1967 as cited in CIR 1992). No adverse effects were noted in rats given a daily dose of 400 mg/kg bw/day HMTA for 90 or 333 days (Brendel 1964, as cited by Restani and Galli 1991). Rabbits fed 525 mg/kg HMTA intermittently for 15 weeks had decreased weight gain or weight loss at this dose (Bandman et al 1994, as cited in RTECS 2003).

HMTA was found to be non-irritating to rabbit skin when 2 mL of 0.20% HMTA in distilled water was applied five days a week for six weeks (COLIPA 1989, as cited in CIR 1992).

In an inhalation toxicity study, rats were exposed to 350 mg/m^3 HMTA for two hours at a time, intermittently for three weeks. At this dose, weight loss or decreased weight gain were observed (Bandman et al 1994).

Chronic Toxicity:

Natvig et al (1971) fed rats a lifelong diet with 0.16% HMTA. There were no observed differences in voluntary muscular activity, body-weight, lifespan, causes of death and relative weights for the major organs in treated rats when compared to controls.

In a study by Della Porta et al (1968), mice received drinking water with 0.5 or 1% concentration of HMTA (equivalent to 1,250 and 2,500 mg/kg bw/day, respectively) over a 60 week period. Another group received drinking water with 5% HMTA (or 12,500 mg/kg bw/day) for 30 weeks. The 5% HMTA dosed group showed slightly but statistically insignificant reduced growth rate and survival, but no histopathological effects or increased incidence of tumors compared to control animals. This study was conducted prior to the establishment of currently acceptable research guidelines, nonetheless, a NOAEL of 12,500 mg/kg bw/day HMTA was determined, with no LOAEL established.

In a concurrent study, Della Porta et al (1968) also dosed the drinking water of rats. Rats were given drinking water with 1% concentration of HMTA (1,500-2,000 mg/kg bw/day in males, and 2,000-2,500 mg/kg bw/day in females) for 104 weeks, or 5% HMTA (calculated to be 7,250 mg/kg bw/day for both males and females) for two weeks. The rats were observed for up to three years in the 1% treated group, and for up to two years in the 5% treated group. There was 50% mortality in rats in the 5% treatment group after two weeks, but no other pathology attributable to HMTA was observed and the surviving animals recovered rapidly with no lasting ill-effects at the end of the treatment period. The NOAELs were determined to be 1,500-2,000 mg/kg bw/day in males, and 2,000-2,500 mg/kg bw/day in females. The LOAEL was determined to be 7,250 mg/kg bw/day.

Genetic Toxicity:

Only a limited number of genetic toxicology assays have bee conducted with HMTA and the overall results provided contradictory information. In the Ames assay, conflicting results were found at excessive concentrations in *Salmonella* typhimurium strain TA100. HMTA did not induce dominant lethal mutations in male mice and was cytotoxic to mouse lymphoma cells. There was, however, limited information of chromosome aberrations in HeLa cells. Summaries of the genetic toxicology studies on HMTA are listed below:

As part of the NTP (1989) interlaboratory evaluation of the Ames test, the mutagenicity of HMTA was tested on six tester strains of *S. typhimurium*, both with and without activation and over a wide range of HMTA concentrations (from 10 to 10,000 µg/plate). Some of the experiments conducted with TA97 and TA100 were rated as equivocal both with and without activation using either rat or hamster liver microsomes.

In one experiment, TA97 with 10% rat liver microsomes tested weakly positive. Tester strains TA98, TA1535, TA1537 and TA1538 were uniformly negative with or without activation.

In an Ames test performed by Crebelli et al (1985, as cited in CIR 1992), *S. typhimurium* strains TA1535, TA98, TA1537 and TA100 were negative for mutagenicity up to the dose limit (5000 µg/plate). The tests were conducted in triplicate, and the assay was repeated.

Crebelli (1984, as cited in CIR 1992) also conducted a reversion test with *S. typhimurium* strains TA98 and TA100 both with and without activation. Results were negative before nitrosation, but positive after nitrosation in TA98 and TA100 both with and without activation. Andrews et al (1980, as cited in CIR 1992) had similar results. HMTA was negative for mutagenicity before nitrosation, but mutagenic with nitrosation in TA98 both with and without metabolic activation.

Orstavik and Honglso (1984, as cited in CIR 1992) tested the compound AH26, which contains 25% HMTA, on TA98 and TA100. The compound had mutagenic activity with TA100 that was dose-dependent, both with and without S9 activation. However, HMTA was negative for mutagenicity when tested individually.

In a mutagenicity study by Shimizu et al (1985), HMTA was mutagenic both with and without activation to *S. typhimurium* TA98, and without activation to TA100. It was reported that there was a weak dose-response correlation between the number of histidine revertant colonies of TA100 and the concentration of the HMTA in the absence of the S9 mix. No mutagenic activity of HMTA, either with or without activation, was noted in strains TA1535, TA1537 and TA1538. Assays were not repeated in this study and increases were found at concentrations in excess (10,000 µg/plate with or without S9) of the limit concentration for this test system (5,000 µg/plate).

A dominant lethal assay was negative in male mice receiving doses of HMTA as high as 25,000 mg/kg (Baldermann et al 1967). Baldermann found induction of chromosomal aberrations in HeLa cells only at 1×10^{-3} M concentrations. No additional information could be determined from the abstract (the full article is in German).

Reitz and Jaeger (1989) found that HMTA inhibited growth and decreased cell volume and the nuclear size of treated L5178Y mouse lymphoma cells.

Reproductive/Developmental Toxicity:

In an unpublished reproduction and developmental toxicity study submitted to JECFA (1974) by Berglund (1966), rats were fed 400, 800, or 1,600 mg/kg bw/day of HMTA in a normal basic diet for two years. There were no observed effects on rat body growth, survival, reproduction or viability of offspring, and there were no pathological changes at any dose level. Based on these results, a NOAEL of 1600 mg/kg bw/day

was determined by the Agency for rats, with no LOAEL established.

In a follow-up study to their chronic toxicity studies described above, Della Porta et al (1970, as cited in CIR 1992) reported no effects on fertility in rats given 1% HMTA in drinking water two weeks prior to mating through gestation and lactation. There were no malformations in offspring. Offspring were also given 1% HMTA in drinking water from birth to 20 weeks of age. There were significantly lower body weights in treated pups relative to the controls during the treatment period, but there were no weight differences at the end of 20 weeks. The weight loss can be attributed to the pups adjusting to the decreased palatability of the drinking water. Based on the temporary weight loss, the Agency assessed an adult rat NOAEL of 1% HMTA, or about 1,500-2,000 mg/kg bw/day in males, and 2,000-2,500 mg/kg bw/day in females. These values were LOAELs in HMTA-treated pups.

Available rat developmental and reproductive studies indicate no observed effects to HMTA up to 1,500 mg/kg/day. However, dog studies suggest a greater sensitivity in dogs to HMTA than rats. Kewitz (1966) submitted an unpublished reproduction and developmental study to JECFA (1974) in which mongrel dogs were treated with 1,250 to 1,875 mg/kg bw/day of HMTA in feed. Offspring were also fed a diet with 1,250 mg/kg bw/day of HMTA for 22 months. No effect was observed on food consumption, growth, weights, litter size, monthly blood chemistry and cell total and differential counts, or periodic urine examinations. However, in treated dogs, 67% of litters were unusual in having stillborn pups and cannibalism, as well as 5 pups born with malformations. These results were significantly higher than for the untreated control dogs, which had 8% of their litters with stillborn pups and no malformations. This study used concentrations of HMTA similar to the rat studies. The information in the JECFA report provided no insight into possible lab conditions that may have caused stress to the dogs and developmental effects (stillborns, cannibalism and malformations).

Hurni and Ohder (1973) studied the effects of HMTA on reproduction in beagle dogs. Mated females were treated with 15 or 31 mg/kg bw/day of HMTA in feed from the 4th to the 56th day after mating. Treatment did not affect implantation, maintenance and duration of pregnancy, or litter size. At 31 mg/kg bw/day of HMTA, the number of stillbirths was slightly increased (10 stillbirths out of 56 pups compared to four stillbirths out of 60 control pups), mainly because of one litter in which there were only two pups born live out of nine. Also at the high dose level, post-natal survival to weaning was decreased (33 of 46 pups survived compared to 49 out of 56 control pups). At both dose levels of HMTA, birth weight (equal to 90-92% of control pup birth weights) and post-natal growth (equal to 91-94% of control pup weights in the 8th week) were slightly decreased. No gross abnormalities were observed in any offspring either at birth or weaning, and no skeletal or tissue malformations were observed in the stillborn pups of treated dogs.

Although there are two dog studies, the results are not consistent. Two different breeds of dog were used in the studies, and although the dosing in the studies differed

by two orders of magnitude, the effects were not consistent among the dose levels. The details of the studies that would allow an understanding of the inconsistencies were not provided in either study. However, the results of the two rat studies are consistent, and therefore, only the rat studies are being considered for this assessment.

Carcinogenicity:

In the chronic toxicity studies by Della Porta et al (1968) described above, mice given HMTA at 0.5, 1, or 5% dose levels in drinking water for 30 to 60 weeks displayed no increase in the incidence and severity of tumors compared to controls. There was also no carcinogenic activity demonstrated in rats given drinking water with 1 or 5% HMTA.

Lijinsky and Taylor (1977, as cited in CIR 1992) gave rats 0.1% HMTA in drinking water, or 0.1% HMTA with 0.2% sodium nitrite in drinking water five days/wk for 50 wks. There was no significant difference in survival between treated rats and controls, and no neoplasms were induced by HMTA alone or in combination with sodium nitrite.

D. Special Considerations for Infants and Children

In oral reproductive and developmental studies in rats, except for a temporary decrease in pup body weights, there were no other maternal or developmental toxicity effects observed at dose levels of 1,500-2,000 mg/kg bw/day in males, and 2,000-2,500 mg/kg bw/day in females. The temporary weight loss in pups is attributable to an adjustment period due to the decreased palatability of the HMTA-treated drinking water.

Although there are two dog studies, the results are not consistent. Two different breeds of dog were used in the studies, and although the dosing in the studies differed by two orders of magnitude, the effects were not consistent among the dose levels. The details of the studies that would allow an understanding of the inconsistencies were not provided in either study. However, the results of the two rat studies are consistent, and therefore, only the rat studies are being considered for this assessment.

Based on this information there is no concern, at this time, for increased sensitivity to infants and children to HMTA when used as an inert ingredient in pesticide formulations. For the same reason, a safety factor analysis has not been used to assess risk and, therefore, the additional tenfold safety factor for the protection of infants and children is also unnecessary.

V. Environmental Fate Characterization/Drinking Water Considerations

From the HSDB (2004):

"Methenamine's production and use as an ammonia or formaldehyde donor may result in its release to the environment through various waste streams. If released to air,

methenamine's vapor pressure of $4.0X10^{-3}$ mm Hg at 25°C indicates methenamine will exist solely as a vapor in the ambient atmosphere, but, residuals will be readily removed during rain events due to its high water solubility. Vapor-phase methenamine will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 15 minutes. If released to soil, methenamine is expected to have high mobility based upon an estimated K_{OC} of 55. Volatilization from moist soil surfaces and from water is not expected to be an important fate process based upon an estimated Henry's Law constant of $1.6X10^{-9}$ atm-cu m/mole. Hydrolysis may be important in some soils. Methenamine hydrolyzes in water at pH 3 or 7, the half-life in each case is slightly over 1 day. If released into water, methenamine is not expected to adsorb to suspended solids and sediment in water based upon the estimated K_{OC}. An estimated BCF of 0.40 suggests the potential for bioconcentration in aquatic organisms is low. In a semi-continuous activated sludge system, methenamine removal ranged from 1.1% after 5 days to 52.5% after 50 days; removal was attributed to acid hydrolysis of methenamine to formaldehyde and ammonia followed by biodegradation of these two compounds. 70 to 87% removal was observed after 28 days using an activated sludge inoculum. In a 5-day BOD test using a sewage seed, methenamine reached 2.02% of its theoretical BOD."

VI. Exposure Assessment

HMTA is used in consumer products such as cosmetics (less than 1% HMTA), pharmaceuticals, firelogs and briquettes used in campfires and grills. In addition, HMTA has a safe history of use as indirect food additives in adhesives and in paperboard for food packaging.

Dietary and drinking water exposures of concern are not anticipated from the inert ingredient use of HMTA considering its physical/chemical properties, including volatility. Dermal and inhalation exposures are possible from the use of HMTA in residential-use pesticide products, including their use in home gardens. However, exposures to the chemical will be limited by the outdoor use of the product and the volatile nature of HMTA.

VII. Aggregate Exposure

In examining aggregate exposure, the FFDCA section 408 directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures, including drinking water from ground water or surface water and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

For HMTA, a qualitative assessment for all pathways of human exposure (food, drinking water, and residential) is appropriate given the lack of human health concerns associated with exposure to HMTA as an inert ingredient in pesticide formulations.

VIII. Cumulative Exposure

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

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

IX. Human Health Risk Characterization

HMTA is used in consumer products such as cosmetics (less than 1% HMTA), pharmaceuticals, firelogs and briquettes used in campfires and grills. In addition, HMTA has several indirect food additive uses, including its use in adhesives and in paperboard for food packaging.

HMTA has moderate acute oral toxicity, is slightly irritating to the skin and mildly irritating to the eyes. HMTA may be a strong sensitizer at high concentrations. In subchronic oral and inhalation toxicity studies, weight loss or decreased weight gain was observed at moderate dose levels. In chronic oral toxicity studies, reduced growth rate was observed at high dose levels. In reproductive and developmental studies, there were no effects observed at high dose levels. HMTA was non-carcinogenic in studies, but had conflicting results in genotoxicity studies.

Dietary and drinking water exposures of concern are not anticipated from the inert ingredient use of HMTA considering its physical/chemical properties, including volatility. Dermal and inhalation exposures are possible from the use of HMTA in residential-use pesticide products, including their use in home gardens. However, exposures to the chemical will be limited by the outdoor use of the product and the volatile nature of HMTA.

Taking into consideration all available information on HMTA, there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure when considering dietary exposure (including crops, meats, and fish) and all

other non-occupational sources of pesticide exposure for which there is reliable information. Therefore, it is recommended that the two exemptions from the requirement of a tolerance established for residues of HMTA, one under 40 CFR 180.910 when applied to growing crops or RACs after harvest (when used as a preservative in citrus washing solutions at not more than 1% of the solution), and one under 40 CFR 180.920 when applied as a stabilizer for carriers in solid pesticide formulations used on growing crops only can be considered reassessed as safe under section 408(q) of the FFDCA.

X. Ecotoxicity and Ecological Risk Characterization

For HMTA, the Agency's Ecotox Database (http://www.epa.gov/ecotox) consists of a variety of studies on aquatic organisms. The experimental acute toxicity values for fish ranged from 10,000 mg/L (or ppm) to 66,900 mg/L in 96h LC_{50} studies. Water fleas (*Daphnia magna*) had 24h EC_{50} of approximately 44,000 mg/L, and a 48h EC50 of approximately 36,000 mg/L, while the harpacticoid copepod (*Nitocra spinipes*) had a 96h EC_{50} of about 92,500 mg/L.

Based on these acute toxicity values HMTA is practically nontoxic to aquatic species, and based on laboratory toxicity studies on rats and mice (representative of terrestrial animals), moderately toxic to terrestrial species. HMTA is expected to quickly leach from soils to groundwater, degrade abiotically, and biodegrade in the environment, so it is not expected to be available to terrestrial species at concentrations exceeding Agency Levels of Concern unless applications rates exceed 10 pounds per acre. Risks to aquatic organisms is likely to be low unless applications exceed 100's of pounds per acre. It is also not expected to bioaccumulate in animals. For these reasons ecological concerns for non-target terrestrial and aquatic species are not likely from the use of HMTA as an inert ingredient in pesticide formulations.

References:

Baldermann, K.H., Röhrborn, G. and T.M. Schroeder. 1967. Mutagenitätsuntersuchungen mit Trypaflavin und Hexamethylentetramin am Säuger in vivo und in vitro. Humangenetik 4, 112-126.

ChemIDPlus. 2004. ChemIDPlus. National Library of Medicine. National Institute of Health. Last Updated: September 9, 2004. < http://chem.sis.nlm.nih.gov/chemidplus/>

CIR. 1992. Cosmetic Ingredient Review. Final report on the safety assessment of methenamine. J. Am. Coll. Toxicol. 11(4), 531-558.

Della Porta, G., M.I. Colnaghi, and G. Parmiani. 1968. Non-carcinogenicity of hexamethylenetetramine in mice and rats. Fd. Cosmet. Toxicol. 6, 707-715.

Dreyfors, J.M., S.B. Jones, and Y. Sayed. 1989. Hexamethylenetetramine: A review. Am. Ind. Hyg. Assoc. J. 50(11), 579-585.

HSDB. 2003. Hazardous Substance Data Bank. National Library of Medicine, National Institute of Health. Updated: 1/24/2003. <http://www.toxnet.nlm.nih.gov>.

Hurni, H. and H. Ohder. 1973. Reproduction Study with Formaldehyde and Hexamethylenetetramine in Beagle Dogs. Fd. Cosmet. Toxicol. 11, 459-462.

JECFA. 1974. Toxicological evaluation of some food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers and thickening agents . Seventeenth Report of the Joint FAO/WHO Expert Committee on Food Additives. Technical Report Series 1974, No. 539; FAO Nutrition Meetings Report Series, 1974, No. 53. <http://www.inchem.org/documents/jecfa/jecmono/v05je10.htm>.

Natvig, H., Andersen, J., and E.W. Rasmussen. 1971. A contribution to the toxicological evaluation of hexamethylenetetramine. Fd. Cosmet. Toxicol. 9, 491-500.

NTP. 1989. National Toxicology Program studies on urotropine. *Salmonella* study details. Study ID: 334557. <http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm? fuseaction= ntpsearch.ntpstudiesforchemical&cas_no=100-97-0>.

Reitz, M. and K.H. Jaeger. 1989. Effects of methenamine on mouse lymphoma cells. Arzneim.-Forsch./Drug Res. 39(11), 1411-1412.

Restani, P. and C.L. Galli. 1991. Oral toxicity of formaldehyde and its derivatives. Critical Reviews in Toxicology. 21(5), 315-328.

RTECS. 2005. NIOSH Registry of Toxic Effects of Chemical Substances #MN4725000. Updated November 2003. <http://www.cdc.gov/niosh/ipcsneng/neng1228.html>.

Shimizu, H., Y. Suzuki, N. Takemura, S. Goto, and H. Matsushita. 1985. The results of microbial mutation test for forty-three industrial chemicals. Jpn. J. Ind. Health 27, 400-419.

Trochimowicz, H.J., Kennedy, G.L. and N.D. Krivanek. 2001. Aliphatic and Aromatic Nitrogen Compounds, in Patty's Industrial Hygiene and Toxicology, 5th edition. John Wiley & Sons, Inc.

APPENDIX A

Indirect Food Additive Citations for Hexamethylenetetramene from 21 CFR (http://www.cfsan.fda.gov/~dms/opa-indt.html 3/15/2006)

175.105 Substances for Use Only as Components of Adhesives: Adhesives
176.170 Components of paper and paperboard in contact with aqueous and fatty foods: For use only as polymerization cross-linking agent for protein, including casein.
176.180 Components of paper and paperboard in contact with dry food: Polymerization crosslinking agent for protein, including casein. As neutralizing agent with myristochromic chloride complex and stearato-chromic chloride complex.
177.1210 Closures with sealing gaskets for food containers: 1 percent.
177.1460 Melamine-formaldehyde resins in molded articles: For use only as polymerization reaction control agent.
177.1900 Urea-formaldehyde resins in molded articles: For use only as polymerization-control agent.
177.2410 Phenolic resins in molded articles: For use as curing agent.
177.2600 Rubber articles intended for repeated use.
181.30 Substances used in the manufacture of paper and paperboard products used in food packaging: As a setting agent for protein, including casein.*

*Under the conditions of normal use, these substances would not reaosnably be expected to migrate to food, based on available scientific information and data.