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

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

DATE: July 31, 2006

ACTION MEMORANDUM

SUBJECT: Inert Reassessment—Diethanolamine (CAS Reg. No. 111-42-2)

FROM: Pauline Wagner, Chief Pauline Wagner 8/1/06
Inert Ingredient Assessment Branch
Registration Division (7505P)

TO: Lois A. Rossi, Director
Registration Division (7505P)

I. FQPA REASSESSMENT ACTION

Action: Reassessment of one exemption from the requirement of a tolerance for diethanolamine (DEA). This chemical is being reassessed and maintained as-is.

Chemicals: Diethanolamine

CFR: 40 CFR 180.920

CAS #: 111-42-2

Use Summary: DEA is a widely-used industrial chemical. It is used in the preparation of diethanolamides and DEA salts of long-chain fatty acids that are formulated into soaps and surfactants used in liquid laundry and dishwashing detergents, cosmetics, shampoos, and hair conditioner. As an inert ingredient, DEA is used as stabilizer or inhibitor in pesticide formulations applied before a crop emerges from the soil.

List Reclassification Determination: The current List Classification for DEA is List 2. Because EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to DEA used as an inert ingredient in pesticide formulations, the List Classification will change from List 2 to List 4B.

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the exemption from the requirement of a tolerance for the inert ingredient DEA (CAS Reg. No. 111-42-2) and with the List reclassification determination, as described above. I consider the exemption established in 40 CFR 180.920 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.

Lois A. Rossi

Lois A. Rossi, Director
Registration Division

August 1, 2006

Date:

pc: Debbie Edwards, SRRD
Joe Nevola, SRRD

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OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

July 31, 2006

MEMORANDUM

SUBJECT: Reassessment of the Exemption from the Requirement of a Tolerance for Diethanolamine (CAS Reg. No. 111-42-2)

FROM: Kathleen Martin, Chemist
Inert Ingredient Assessment Branch
Registration Division (7505P)

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

BACKGROUND

Attached is the science assessment for diethanolamine (DEA). The purpose of this document is to reassess the existing exemption from the requirement of tolerance for residues of DEA as required under the Food Quality Protection Act (FQPA). This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, exposure profile, environmental fate, and ecotoxicity of DEA.

EXECUTIVE SUMMARY

Diethanolamine (DEA) is a widely-used industrial chemical. It is used in the preparation of diethanolamides and DEA salts of long-chain fatty acids that are formulated into soaps and surfactants used in liquid laundry and dishwashing detergents, cosmetics, shampoos, and hair conditioners. As an inert ingredient DEA is exempted from the requirement of a tolerance under 40 CFR 180.920 when used as an inert ingredient (stabilizer or inhibitor) in pesticide formulations applied before the crop emerges from the soil.

In animal studies, DEA has low acute toxicity via the oral and dermal routes with moderate skin irritation and severe eye irritation. In subchronic toxicity testing conducted via the oral route in rats and mice, the main effects observed were increased organ weights and histopathology of the kidney and/or liver, with the majority of other tissue effects noted only at relatively high dosages. In subchronic studies conducted via the dermal route, skin irritation was noted as well as systemic effects similar to those observed in the subchronic oral studies. DEA has not been shown to be mutagenic or carcinogenic in rats; however, there is evidence of its carcinogenicity in mice. IARC (2000) has reviewed the carcinogenicity of DEA and found that: there is *inadequate evidence* in humans for the carcinogenicity of DEA; there is *limited evidence* in experimental animals for the carcinogenicity of DEA; and DEA is *not classifiable as to its carcinogenicity to humans (Group 3)* (See Appendix A for IARC definitions). In a developmental toxicity study conducted via the oral route, effects of concern were observed only in the presence of maternal toxicity. In a developmental toxicity study conducted via the dermal route using two species of mammals, developmental toxicity was observed only in one species and only at doses causing significant maternal toxicity. Metabolically, DEA is excreted largely unchanged in the urine.

The use restriction of DEA (application before a crop emerges from the soil) effectively limits the timing and number of applications, therefore, significantly reducing the likelihood of residues on food, the potential for residential exposures (dermal and inhalation), and the contribution to drinking water. Thus, the overall exposure from the use of DEA as an inert ingredient in pesticide products applied before crops emerge from the soil is expected to result in human exposure below any dose level that would produce any adverse effect.

Based on its physical/chemical properties, biodegradation, and use restriction, DEA is not expected to pose a high risk to drinking water, and its potential for bioconcentration in aquatic organisms is low. According to the Agency's ECOTOX database, DEA is categorized as "practically nontoxic" on an acute basis to freshwater invertebrates, estuarine/marine invertebrates, and freshwater plants.

Taking into consideration all available information on DEA, EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to DEA when used as an inert ingredient in pesticide products applied before the crop emerges from the soil when considering dietary (i.e., food and drinking water) exposure and all other nonoccupational sources of pesticide exposure for which there is reliable information. Therefore, it is recommended that the exemption from the requirement of a tolerance established for residues of DEA 40 CFR 180.920 be considered reassessed as safe under section 408(q) of FFDCA.

I. INTRODUCTION

This report provides a qualitative assessment for diethanolamine (DEA), an inert ingredient used as a stabilizer or inhibitor in pesticide formulations applied before a crop emerges from the soil (40 CFR 180.920).

DEA is a widely-used industrial chemical. It is used in the preparation of diethanolamides and DEA salts of long-chain fatty acids that are formulated into soaps and surfactants used in liquid laundry and dishwashing detergents, cosmetics, shampoos, and hair conditioners. However, DEA is not a common food additive. There are no U.S. Food and Drug Administration (FDA) direct food additive uses and it has not been evaluated as a food additive under JEFCA, the Joint World Health Organization (WHO)/Food and Agriculture Organization (FAO) Expert Committee on Food Additives.

The use restriction of pesticide formulations containing DEA as an inert ingredient (application before a crop emerges from the soil) effectively limits the timing and number of applications, therefore, significantly reducing the likelihood of residues on food, the potential for residential exposures (dermal and inhalation), and the contribution to drinking water (from runoff).

DEA is not being sponsored by EPA's High Production Volume (HPV) Challenge Program. However, it is being sponsored by the Organization for Economic Cooperation and Development's (OECD) Screening Information Data Set (SIDS) Program[1]; the United Kingdom is the sponsoring country. In 1995, participants at the SIDS Initial Assessment Meeting (SIAM) for DEA concluded that this "chemical is a candidate for further [SIDS] work" because of concerns regarding "subchronic inhalation, neurotoxicity, reproductive and mouse developmental effects. (OECD SIDS 1995) According to the OECD SIDS website[1], DEA is to be rediscussed at a future SIAM.

II. USE INFORMATION

A. PESTICIDE USES

DEA is used as an inert ingredient in pesticide formulations applied before crops emerge from the soil. The exemption from the requirement of a tolerance for DEA is provided in Table 1 below.

[1]The SIDS Program is a voluntary cooperative international testing program that began in 1989. It is focused on developing base level test information on approximately 600 poorly characterized international HPV chemicals. The SIDS data are used to "screen" the chemicals and set priorities for further testing or risk assessment/management activities. The priorities are set at the SIAM. http://cs3-hq.oecd.org/scripts/hpv/

Table 1. Tolerance Exemption Being Reassessed in this Document

CFR Citation				CAS Reg. No. and 9CI Name
40 CFR 180	Inert Ingredient	Limits	Uses	
.920[a]	Diethanolamine	(none)	Stabilizer, inhibitor for formulations used before crop emerges from soil	111-42-2 Ethanol, 2,2'-iminobis-

[a]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.

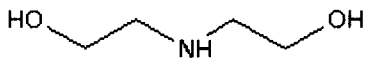
B. OTHER USES

DEA is widely used in the preparation of diethanolamides and DEA salts of long-chain fatty acids that are formulated into soaps and surfactants used in liquid laundry and dishwashing detergents, cosmetics, shampoos, and hair conditioners. DEA is also used in textile processing, in industrial gas purification to remove acid gases, as an intermediate in the manufacture of rubber, and as an anticorrosion agent in metalworking fluids. Aqueous DEA solutions are used as solvents for numerous drugs that are administered intravenously. (NTP 1999a, Cavender 2001)

III. PHYSICAL AND CHEMICAL PROPERTIES

Some of the physical and chemical characteristics of DEA, along with its structure and nomenclature, are found in Table 2.

Table 2. Physical and Chemical Properties of Diethanolamine

Parameter	Value	Reference
Structure		
CAS Reg. No. and 9CI Name	111-42-2 Ethanol, 2,2'-iminobis-	
Empirical Formula	$C_4H_{11}NO_2$	
Molecular Weight	105.14	
Common Names	2,2'-Iminodiethanol; 2,2'-iminobisethanol; bis(hydroxyethyl)amine; 2,2'-dihydroxydiethylamine; DEA; diethylolamine; diolamine; N,N-diethanolamine; and iminodiethanol	Cavender 2001
Physical State	Usually a viscous liquid with a ammoniacal odor	Merck 2005
Melting Point	28°C	Merck 2005
Boiling Point	268.8°C	Merck 2005
Water Solubility	infinite	Wypych 2000
Other Solubility	Miscible methanol, acetone	Merck 2005

Parameter	Value	Reference
Relative Density (water=1)	1.0881 @ 30°C	Merck 2005
Relative Vapor Density (air=1)	3.63	Wypych 2000
Vapor Pressure	0.000278 mmHg at 25°C	Verschueren 2001
Log P_{ow}	–2.18 @ pH 7.15 (measured)	Verschueren 2001
Henry's Law Constant	3.87×10^{-11} atm m^3/mol	Wypych 2000

IV. HAZARD ASSESSMENT

A. HAZARD PROFILE

To assess the hazard posed by the use of DEA as an inert ingredient in pesticide formulations, EPA considered a number of publicly-available sources including: published literature, peer-reviewed international documents (e.g., IARC,[2] IUCLID[3]) and other standard available references. A valuable source of information was the U.S. Health and Human Services' National Toxicology Program (NTP) which has conducted several studies on DEA including subchronic toxicity, mutagenicity, carcinogenicity, and developmental toxicity.

B. TOXICOLOGICAL DATA

Acute Toxicity

A summary of the other acute toxicity parameters, along with their corresponding 40 CFR 156.62 Acute Toxicity Categories, is provided in Table 3. Acute oral and dermal LD_{50}'s were >1g/kg with moderate skin irritation and severe eye irritation. Inhalation and sensitization data are not available.

Table 3. Summary of Acute Toxicity Data for Diethanolamine

Parameter	Toxicity Value *Toxicity Category*[a]	Reference
Oral LD_{50} rat	1.82 to 2.83 g/kg *Toxicity Category III*	Cavender 2001, citing work of Smyth and others
Dermal LD_{50} rabbit	1.22 g/kg *Toxicity Category III*	Lewis 2003, citing "Raw Material Data Handbook"
Skin Irritation, rabbit	moderate[b]	Dutertre-Catella 1982
Eye Irritation, rabbit	5,500 mg resulted in severe irritation (time interval not noted)	Lewis 2003, citing "American Journal of Ophthalmology"

[a]40 CFR 156.62
[b]On a scale from 1 to 8, scored 2.6

[2]In 1969, WHO's International Agency for Research on Cancer (IARC) initiated a program to evaluate the carcinogenic risk of chemicals to humans and to produce monographs on individual chemicals. Each volume serves as an authoritative, independent assessment by international experts of the carcinogenic risk posed by a selected chemical, group of chemicals, industrial process, occupational exposure, lifestyle factor, or biological agent.

[3]IUCLID, or the International Uniform Chemical Information Database, is a database of existing chemicals that is being compiled by the European Chemicals Bureau (ECB).

Subchronic Toxicity

According to Knaak et al., (1997), "consistent with other ethanolamines, the skin, kidneys, or liver of test species are observed to be the most sensitive target tissues of DEA. A number of other tissues also appear to be affected by treatment but only at relatively high dosages". "DEA also causes a rat-specific microcytic anemia that does not involve the bone marrow and appears to be unique among this family of compounds."

Oral

Fischer-344 rats were administered DEA in their drinking water at dosages of 0, 630, 1250, 5000, or 10000 ppm (estimated to be 77-1016 mg/kg/day for males and 79-1041 mg/kg/day for females) for two weeks. The following effects were noted: **males and females**: ≥5000 ppm, mortality; ≥2500 ppm, kidney histopathology; ≥1250 ppm, decreased body weight, altered serum chemistries; most dosages, anemia, altered urine chemistries; **males**: ≥1250 ppm, increased kidney weight; **females**: all dosages, increased kidney weight. (Hejtmancik et al. (1987a); NTP (1992) as cited in Knaak et al., 1997).

B6C3F1 mice were administered DEA in their drinking water at dosages of 0, 630, 1250, 5000, or 10000 ppm (estimated to be 110-1362 mg/kg/day for males and 197-2169 mg/kg/day for females) for two weeks. The following effects were noted: **males and females**: 10000 ppm, severe dehydration; ≥2500 ppm, increased liver weight, decreased thymus weight, lymphoid tissue depletion; **males**: ≥2500 ppm, liver histopathology. "No significant treatment-related effects were observed in mice imbibing a 630-ppm DEA drinking water solution." (Hejtmancik et al. (1987a); NTP (1992) as cited in Knaak et al., 1997)

Rats (strain unspecified) were administered DEA at 4000 ppm in their drinking water for ≤7 weeks. Observed effects included mortality, "liver and kidney damage," normocytic anemia without bone marrow depletion. (Hartung et al. (1970) as cited in Knaak et al. 1997)

Wistar rats were administered DEA at dosages of 0, 5, 20, 90, 170, 350, or 680 mg/kg/day in their feed for ≤13 weeks. The following effects were noted: ≥170 mg/kg/day, mortality, kidney, liver, small intestine, and lung histopathology; ≥90 mg/kg/day, increased liver and kidney weight. (Smyth et al. (1951) as cited in Knaak et al., 1997)

Fischer-344 rats were administered DEA at dosages of 0, 160 (females only), 320, 630, 1250, 2500, or 5000 (males only) ppm (estimated to be 25-436 mg/kg/day for males and 12-242 mg/kg/day for females) in their drinking water for 13 weeks. The following effects were noted: **males**: 5000 ppm, mortality;

≥2500 ppm, kidney and CNS (gonads, hypospermia)[4] histopathology; ≥630 ppm, anemia; all dosages, decreased body weight; **females**: 2500 ppm, severe dehydration; ≥1250 ppm, CNS (adrenal cortex) histopathology; ≥320 ppm, anemia; all dosages, decreased body weight, increased kidney[5] and liver[5] weight, kidney histopathology. (Melnick et al., (1994a); NTP (1992) as cited in Knaak et al. 1997)

B6C3F1 mice were administered DEA at dosages of 0, 630, 1250, 2500, 5000, or 10000 ppm (estimated to be 104-1674 mg/kg/day for males and 142-1154 mg/kg/day for females) in their drinking water for 13 weeks. The following effects were noted: **males and females**: ≥2500 ppm, mortality, severe dehydration, heart and salivary gland histopathology; all dosages, increased liver weight, liver histopathology; **males**: ≥2500 ppm, decreased body weight, ≥1250 ppm, increased kidney weight, kidney histopathology; **females**: ≥2500 ppm, increased heart weight, heart histopathology; ≥1250 ppm, decreased body weight. (Melnick et al., (1994a); NTP (1992) as cited in Knaak et al. 1997)

Dermal

Subchronic dermal (skin painting) toxicity studies were also conducted on rats and mice. Generally, in addition to skin irritation, systemic effects caused by the dermally-administered DEA were similar to those caused by orally administered DEA (Knaak et al. 1997).

Mutagenicity and Genotoxicity

NTP has conducted *in vitro* (salmonella, mouse lymphoma, and CHO—Chinese hamster ovary—cell cytogenetics) and *in vivo* (micronucleus) genetic toxicity studies (NTP no date); the data are summarized in Table 4 below. IARC (2000) has indicated that DEA does not appear to be genotoxic.

Table 4. Summary of Mutagenicity Data for Diethanolamine (NTP no date)

Test		Species	Dose or Concentration	Result	Study ID Start Date
in vivo	Micronucleus	Mice, peripheral blood	0 to 1,250 mg/kg	negative	A08796; Jan 1990
in vitro	Ames Test	*Salmonella typhimurium* TA100; TA1535; TA1537; TA98	10%	negative[a]	310797; 1980
	mammalian cell mutagenicity assay	mouse lymphoma	0 to 600 µg/mL	negative[a]	375254
	CHO Cell Cytogenetics: Chromosome Aberrations	CHO cells	up to 3,010 µg/mL	negative[a]	095123; Aug 1990
	CHO Cell Cytogenetics:	CHO cells	up to 1,500	negative[a]	095123;

[4] "Change was attributed to direct effect of treatment, inanition, and dehydration-related weight loss, or a combination of these."

[5] "Change observed was not dose related and may or may not have been treatment related."

Test		Species	Dose or Concentration	Result	Study ID Start Date
	Sister Chromatid Exchange (SCE)		µg/mL		Aug 1984

[a]With and without activation.

Carcinogenicity

Because of the large scale production of DEA and the potential for widespread human exposure (NTP 1999a), NTP decided to evaluate the carcinogenic potential by conducting a two-year dermal study using two species of rodents—rats and mice.

Male rats were dermally-dosed with DEA in ethanol for a period of two-years at concentrations of: 0; 16; 32; or 64 mg/kg bw and female rats: 0; 8; 16; or 32 mg/kg bw. The only clinical finding attributed to DEA administration was irritation of the skin at the site of application. Minimal to mild nonneoplastic lesions occurred at the site of application in the epidermis.

Male and female mice were dermally-dosed with DEA in ethanol for a period of two-years at concentrations of: 0; 40; 80; or 160 mg/kg bw. In male mice, the incidences of hepatocellular adenoma and of hepatocellular adenoma or carcinoma (combined) in all dosed groups and of hepatocellular carcinoma and hepatoblastoma in 80 and 160 mg/kg males were significantly increased compared to the vehicle controls. The incidences of hepatocellular neoplasms were significantly greater in dosed groups of female mice than in the vehicle control group. The incidences of hepatocellular neoplasms in all dosed groups of males and females exceeded the historical control ranges.

In conclusion, NTP found that under the conditions of these two-year dermal studies, there was no evidence of carcinogenic activity of DEA in male or female rats. However, there was clear evidence of carcinogenic activity of DEA in male and female mice based on increased incidences of liver neoplasms in males and females and increased incidences of renal tubule neoplasms in males.

IARC (2000) has reviewed the carcinogenicity of DEA and found that: there is *inadequate evidence* in humans for the carcinogenicity of DEA; there is *limited evidence* in experimental animals for the carcinogenicity of DEA; and DEA is *not classifiable as to its carcinogenicity to humans (Group 3)* (See Appendix A for IARC definitions).

Developmental and Reproductive Toxicity

Oral. In a developmental toxicity study (NTP 1999b), investigators gavaged female rats with DEA (50; 125; 200; 250; or 300 mg/kg bw/day) throughout the embryonic and fetal period, which is gestation day (GD) 6 through 19. On postnatal day (PND) 21 the animals were sacrificed and the maternal

clinical condition; body, liver, and paired kidney weights; and number of uterine implantation sites were recorded. Maternal effects included reduced body weight or weight gain (greater than or equal to 200 mg/kg/day), increased absolute kidney weight (greater than or equal to 125 mg/kg/day), altered feed intake (greater than or equal to 200 mg/kg/day) and water intake (greater than or equal to 125 mg/kg/day). Postimplantation mortality (PND 0) was elevated at greater than or equal to 200 mg/kg/day, and early postnatal mortality (PND 0 to 4) was increased at greater than or equal to 125 mg/kg/day. Pup body weight was reduced at greater than or equal to 200 mg/kg/day. Thus, maternal and developmental toxicity NOAELs were 50 mg/kg/day and the LOAELs were 125 mg/kg/day.

Dermal. Marty et al (1999) administered DEA to the skin of pregnant rats and rabbits during the periods of major organogenesis, which was GD 6 through 15 for rats and 6 through 18 for rabbits. Developmental toxicity was observed only in the rat and only at doses causing significant maternal toxicity, including hematological effects. Due to a dose discrepancy, the study investigator adjusted the NOEL for developmental toxicity in rats to 380 mg/kg/day. In rabbits, the embryonal/fetal NOEL was 350 mg/kg/day. Study details are provided below:

Rats were dosed at: 0; 150; 500; or 1,500 mg/kg/day. Rat dams exhibited reduced body weight at 1,500 mg/kg/day; skin irritation and increased kidney weights at 500 and 1,500 mg/kg/day; and a slight microcytic anemia with abnormal red blood cell morphology at all dose levels. Rat fetuses had increased incidences of six skeletal variations at 1,500 mg/kg/day; lower doses were without effect on the fetuses.

Rabbits were dosed at: 0; 35; 100; or 350 mg/kg/day. Rabbit dams administered 350 mg/kg/day exhibited various skin lesions; reduced food consumption; and color changes in the kidneys but no hematological changes. Body weight gain was reduced at ≥100 mg/kg/day. There was no evidence of maternal toxicity at 35 mg/kg/day and no evidence of developmental toxicity in rabbits at any dose level.

C. METABOLISM AND PHARMACOKINETICS

In the body, DEA is metabolized by biosynthetic routes common to endogenous alkanolamines and incorporated into phospholipids. It is excreted predominantly unchanged with a half-life of approximately one week in urine (IARC 2000). If a source of nitrite is available (for example, from a nitrite-preserved food), it may combine with DEA *in vivo* to form a nitrosoamine; however, the right set of conditions must exist such as the correct acidity in the stomach. (IARC 2000; Bingham et al 2001)

Matthews et al (1997) administered carbon-14 labeled DEA to rats via the oral, intravenous (i.v.), and dermal routes of exposure to determine how this chemical is taken up and excreted; mice were also exposed via the dermal route. Oral administration was by gavage of 7 mg/kg doses of DEA once to examine the metabolic profile after a single dose and then daily for up to eight weeks to look at DEA's potential for bioaccumulation. Oral doses were well absorbed but excreted very slowly. DEA accumulated to high concentrations in certain tissues, particularly liver and kidney. The steady-state of bioaccumulation was approached only after several weeks of repeat oral dosing, and the half-life of elimination was approximately one week. After application to the skin of rats (2 to 28 mg/kg), DEA was slowly absorbed (3 to 16% after 48 hours of exposure). In mice, DEA was more readily absorbed. After application to mouse skin (8 to 80 mg/kg), 25 to 60% was absorbed after 48 hours, with the percent of the applied dose absorbed increasing with dose. Single doses (oral or i.v.) of DEA were excreted slowly in urine (about 22 to 25% in 48 hours) predominantly as the parent compound. There was minimal conversion to carbon dioxide or volatile metabolites in breath. The profile of metabolites appearing in urine changed after several weeks of repeat oral administration, with significant amounts of N-methyl DEA and more cationic metabolites appearing along with unchanged DEA.

D. Special Considerations for Infants and Children

DEA has low acute toxicity. Oral and dermal LD_{50} values are in Toxicity Category III. In a developmental toxicity study conducted via the oral route (NTP 1999b), developmental effects of concern were observed only in the presence of maternal toxicity. In a developmental toxicity study conducted via the dermal route on rats and rabbits, developmental toxicity was observed only in the rat and only at doses causing significant maternal toxicity. (Marty et al 1999). In addition, *in vivo* exposure to DEA is expected to be low. Any ingested DEA is expected to be readily metabolized and excreted in the urine.

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

V. ENVIRONMENTAL FATE CHARACTERIZATION AND DRINKING WATER CONSIDERATIONS (NIH 1991, US EPA 2006c, US EPA 2006d)

In soil and water, DEA is expected to biodegrade fairly rapidly following acclimation (half-life on the order of days to weeks). In soil, DEA should leach. In the atmosphere, DEA is expected to exist almost entirely in the vapor phase. Reaction with photochemically generated hydroxyl radicals is expected to be the dominant removal mechanism (half-life, four hours). This compound may also be removed from the

atmosphere in precipitation. The Henry's Law constant for DEA is 3.87×10^{-11} atm m^3/mol (Wypych 2000) which suggests that DEA is essentially nonvolatile from water. The half-life for DEA vapor reacting with photochemically generated hydroxyl radicals in the atmosphere has been estimated to be four hours based on an estimated reaction rate constant of $8.9 \times 10^{-11} cm^3$/molecules/sec at 25°C and an average ambient hydroxyl concentration of 5×10^5 molecules/cm^3.

DEA, in the presence of nitrites, can form N-nitrosodiethanolamine (NDELA)[6]. In air, NDELA is expected to exist solely as a vapor based on a vapor pressure of 2.78×10^{-4} mmHg at 25°C (Verschueren 2001). Vapor-phase NDELA will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals with an estimated half-life of 13 hours. NDELA is stable to direct photolysis. In soil, an estimated K_{oc} of 4.8 suggests that this compound is expected to have very high mobility; it is expected to biodegrade slowly in soil.

In summary, it appears that DEA is relatively short lived and that it does not present a high risk to contaminate drinking waters. NDELA, a potential formation product, is persistent to biotic and abiotic processes, and mobile. The amounts formed are uncertain (it is only indicated that the half-life is in the order of days to weeks). The water quality criteria (WQC) for nitrosamines is 0.0008 µg/L (Clean Water Act).

VI. EXPOSURE ASSESSMENT

DEA is used as a stabilizer or inhibitor in pesticide formulations applied to agricultural crops before they emerge from the soil. Individuals may be exposed to DEA through the oral, dermal, and inhalation routes of exposure. The use restriction of DEA (application before a crop emerges from the soil) effectively limits the timing and number of applications (typically one). In soil, DEA is expected to biodegrade fairly rapidly (half-life on the order of days to weeks); therefore, concentrations of concern in drinking water are not expected. Thus, dietary (food and drinking water) exposures of concern are not anticipated.

Additional exposure may occur through the dermal and inhalation routes from residential use of pesticide products (e.g., home gardens). The use restriction of DEA effectively limits the number of pesticide applications; therefore, residential exposures of concern are not expected from DEA's use as an inert ingredient in pesticide formulations applied before the crop emerges from the soil.

VII. AGGREGATE EXPOSURES

In examining aggregate exposure, the Federal Food, Drug, And Cosmetic Act (FFDCA) section 408 directs EPA to consider available information concerning exposures from the pesticide residue in food and all other nonoccupational exposures,

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[6]While NDELA is not acutely toxic (oral LD_{50} >7,500 mg/kg in rats), "it is a reasonably potent carcinogen" (Bingham 2001)

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 DEA, 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 DEA 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 DEA and any other substances and, DEA 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 DEA 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

Taking into consideration all available information on DEA, EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to DEA when used as an inert ingredient in pesticide products applied before the crop emerges from the soil when considering dietary (i.e., food and drinking water) exposure and all other nonoccupational sources of pesticide exposure for which there is reliable information. Therefore, it is recommended that the exemption from the requirement of a tolerance established for residues of DEA 40 CFR 180.920 be considered reassessed as safe under section 408(q) of FFDCA.

In animal studies, DEA has low acute toxicity via the oral and dermal routes with moderate skin irritation and severe eye irritation. In subchronic toxicity testing conducted via the oral route in rats and mice, the main effects observed were increased organ weights and histopathology of the kidney and/or liver, with the majority of other tissue effects noted only at relatively high dosages. In subchronic studies conducted via the dermal route, skin irritation was noted as well as systemic effects similar to those observed in the oral studies. DEA has not been shown to be mutagenic or carcinogenic in rats; however, there is evidence of its carcinogenicity in mice. IARC (2000) has reviewed the carcinogenicity of DEA and found that: there is *inadequate evidence* in humans for the carcinogenicity of DEA; there is *limited evidence* in experimental

animals for the carcinogenicity of DEA; and DEA is *not classifiable as to its carcinogenicity to humans (Group 3)* (See Appendix A for IARC definitions). In a developmental toxicity study conducted via the oral route, effects of concern were observed only in the presence of maternal toxicity. In a developmental toxicity study conducted via the dermal route using two species of mammals, developmental toxicity was observed only in one species and only at doses causing significant maternal toxicity. Metabolically, DEA is excreted largely unchanged in the urine.

The use restriction of DEA (application before a crop emerges from the soil) effectively limits the timing and number of applications, therefore, significantly reducing the likelihood of residues on food, the potential for residential exposures (dermal and inhalation), and the contribution to drinking water. And, based on its physical/chemical properties, biodegradation, and use restriction, DEA is not expected to pose a high risk to drinking water. Therefore, the overall exposure from the use of DEA as an inert ingredient in pesticide products applied before crops emerge from the soil is expected to result in human exposure below any dose level that would produce any adverse effect.

X. ECOTOXICITY AND ECOLOGICAL RISK CHARACTERIZATION

DEA's potential for bioconcentration in aquatic organisms is low. Provided below are summaries of its acute toxicity to freshwater invertebrates, estuarine/marine invertebrates, and freshwater plants.

Freshwater Invertebrates, Acute

According to the Agency's ECOTOX database (US EPA 2006b), DEA is categorized as ranging from moderately toxic to practically nontoxic to freshwater invertebrates based on EC_{50} values ranging from 2,150 to 306,000 µg/L. Table 5 below provides the acute toxicity values that DEA may pose to freshwater invertebrates. (US EPA 2006a)

Table 5. Diethanolamine Acute Toxicity Values to Freshwater Invertebrates

Species	Acute Toxicity Value, EC_{50} (ppb)	Toxicity Category	Ecotox Database Reference Number
Water flea (*Daphnia magna*)	2,150	moderately toxic	17445
Water flea (*Daphnia magna*)	2,640	moderately toxic	15998
Water flea (*Ceriodaphnia dubia*)	19,000	slightly toxic	15998
Water flea (*Daphnia magna*)	77,500	moderately toxic	15998
Water flea (*Daphnia magna*)	109,000	practically nontoxic	12771
Water flea (*Daphnia magna*)	110,000	practically nontoxic	15998
Water flea (*Daphnia magna*)	123,800	practically nontoxic	17344
Water flea (*Daphnia magna*)	131,000	practically nontoxic	17344
Water flea (*Daphnia magna*)	158,000	practically nontoxic	17344
Water flea (*Daphnia magna*)	173,000	practically nontoxic	17344
Water flea (*Daphnia magna*)	235,000	practically nontoxic	17344
Water flea (*Daphnia magna*)	306,000	practically nontoxic	12771

Estuarine/Marine Invertebrates, Acute

According to the Agency's ECOTOX database (US EPA 2006b), DEA is categorized as "practically nontoxic" to estuarine/marine invertebrates. EC_{50} values for estuarine/marine invertebrates (shrimps and mollusks) exposed to DEA ranged from >100,000 to 2,800,000 µg/L. Table 6 below provides the acute toxicity values DEA may pose to estuarine/marine invertebrates.

Table 6. Diethanolamine Acute Toxicity to Estuarine/Marine Invertebrates

Species	Acute Toxicity Value, EC_{50} (ppb)	Toxicity Category	Ecotox Database Reference Number
Scud (*Gammarus fasciatus*)	>100,000	practically nontoxic	12111
Scud (*Gammarus fasciatus*)	100,000	practically nontoxic	12111
Opossum shrimp (*Americamysis bahia*)	207,000	practically nontoxic	12111
Brine Shrimp (*Artema salina*)	2,800,000	practically nontoxic	12111

Freshwater Plants, Acute

Based on the data in the Agency's ECOTOX database, DEA is categorized as practically nontoxic to freshwater plants on an acute basis based on EC_{50} values ranging from 103,000 to 522,800 µg/L.

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Appendix A

IARC defines *inadequate evidence* to mean the "available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

Limited evidence means a "positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence."

Not classifiable as to its carcinogenicity to humans (Group 3) means an agent "for which the evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals.... An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations." (IARC 2006)