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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

January 31, 2005

ACTION MEMORANDUM

SUBJECT: Inert Ingredient Tolerance Reassessment – Ammonium Nitrate (CAS Reg. No. 6484-52-2), Magnesium Nitrate (CAS Reg. No. (10377-60-3), Sodium Nitrate (CAS Reg. No. 7631-99-4), and Sodium Nitrite (CAS Reg. No. 7632-00-0)

FROM: Dan Rosenblatt, Chief
Minor Use, Inerts, and Emergency Response Branch

TO: Lois A. Rossi, Director
Registration Division

I. FQPA REASSESSMENT ACTION

Action: Reassessment of three (3) inert ingredient exemptions from the requirement of a tolerance

Chemicals and Use Summary: See table below.

Table 1. Tolerance Exemptions Being Reassessed

Tolerance Exemption Expression	CAS Reg No.	40 CFR §	Use Pattern (Pesticidal)	List Classification
Ammonium nitrate	6484-52-2*	180.920 [1/]	Adjuvant/intensifier for herbicides	4B
Magnesium nitrate	10377-60-3	180.920[2/]	Preservation	4B
	13446-18-9[3/]	--	--	--
Sodium nitrate	7631-99-4	180.920	Solid diluent	4B
Sodium nitrite	7632-00-0	180.920	Stabilizer, inhibitor. Not more than 3% of pesticide formulation	3

1. Residues listed in 40 CFR §180.920 [formerly 40 CFR§ 180.100(d)] are exempted from the requirement of a tolerance when used as inert ingredients in pesticide formulations when applied to growing crops only.
2. The tolerance exemption for magnesium nitrate is listed as being "in combination with 2-methyl-4-isothiazolin-3-one and 5-chloro-2-methyl-4-isothiazolin-3-one." **Reassessment of magnesium nitrate will not be complete until 2-methyl-4-isothiazolin-3-one and 5-chloro-2-methyl-4-isothiazolin-3-one have also been reassessed.**
3. Magnesium nitrate hexahydrate--a common commercial form of magnesium nitrate.

List Reclassification Determination: Ammonium nitrate, magnesium nitrate and sodium nitrate are classified as List 4B inert ingredients. Sodium nitrite is classified as a List 3 inert ingredient. Based on the reasonable certaintly of no harm safety finding, sodium nitrite can be reclassified as a List 4B inert ingredient.

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the three (3) exemptions from the requirement of a tolerance for the inert ingredients ammonium nitrate, sodium nitrate and sodium nitrite, and with the List reclassification determination, as described above as well as with the determination that magnesium nitrate will be eligible for reassessment pending the reassessment of 2-methyl-4-isothiazolin-3-one and 5-chloro-2-methyl-4-isothiazolin-3-one. I consider the three (3) exemptions from the requirement of a tolerance for ammonium nitrate, sodium nitrate and sodium nitrite established in 40 CFR §180.920 [formerly 40 CFR§180.1001(d)] to be reassessed 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

Date: February 7, 2005

cc: Debbie Edwards, SRRD
Joe Nevola, SRRD

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

January 31, 2005

MEMORANDUM

SUBJECT: Reassessment of the Exemptions from the Requirement of a Tolerance for Ammonium Nitrate, Magnesium Nitrate, Sodium Nitrate, and Sodium Nitrite

FROM: Kerry Leifer, Inerts Team Leader
Minor Use, Inerts and Emergency Response Branch
Registration Division (7505C)

TO: Dan Rosenblatt, Chief
Minor Use, Inerts and Emergency Response Branch
Registration Division (7505C)

Background

Attached is the Lower Risk Pesticide Chemical Focus Group's science assessment for ammonium nitrate, magnesium nitrate, sodium nitrate, and sodium nitrite. This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, exposure profile, and environmental fate and ecotoxicity of ammonium nitrate, magnesium nitrate, sodium nitrate, and sodium nitrite. These substances have been the subject of extensive evaluations by a number of organizations; this assessment relies extensively on assessments previously performed by EPA's Office of Drinking Water, the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the National Toxicology Program (NTP), and the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency and others. The purpose of this document is to reassess the existing exemptions from the requirement of a tolerance for residues of ammonium nitrate, magnesium nitrate, sodium nitrate and sodium nitrite as required under the Food Quality Protection Act (FQPA).

Executive Summary

This report evaluates ammonium nitrate (CAS Reg. No. 6484-52-2), magnesium nitrate (CAS Reg. No. (10377-60-3), sodium nitrate (CAS Reg. No. 7631-99-4), and sodium nitrite (CAS Reg. No. 7632-00-0), pesticide inert ingredients for which exemptions from the requirement of a tolerance exists for their residues when used in pesticide formulations applied to growing crops only under 40 CFR §180.920 [formerly 40 CFR §180.1001(d)].

Ammonium nitrate, magnesium nitrate, sodium nitrate, and sodium nitrite are all water soluble inorganic salts that readily dissociate into the corresponding cation (i.e., ammonium, magnesium or sodium) and the nitrate/nitrite anion. Nitrate and nitrite are naturally occurring inorganic ions which are part of the nitrogen cycle. Nitrate is a natural constituent of soil and vegetation. Nitrate is also a normal metabolite in mammals. Nitrate in soil, ground and surface water derives mainly from mineralization of soil organic matter as well as from application of mineral fertilizers. The nonpesticidal uses of ammonium nitrate, magnesium nitrate, sodium nitrate, and sodium nitrite are extensive, including the use of ammonium nitrate and sodium nitrate as fertilizers and the use of sodium nitrate and sodium nitrite as direct food additives.

Nitrate and nitrite have been extensively evaluated in conjunction with their use as food additives and as drinking water contaminants. Methemoglobinemia is the primary adverse health effect associated with human exposure to high levels of nitrate or nitrite and is the basis for EPA drinking water standards for nitrate and nitrite. Extensive toxicity data are available on nitrate and nitrite and an oral RfD and ADI have been established for nitrate and nitrite by EPA and FAO/WHO for potential adverse effects.

Nitrate is synthesized endogenously in the body. Humans are primarily exposed to nitrate and nitrite through their diet, as either natural components or intentional additives. These exposures are estimated to be at levels greater than 100 mg/day, far exceeding any dietary exposures to nitrate and nitrite resulting from the use of ammonium nitrate, magnesium nitrate, sodium nitrate, and sodium nitrite as pesticide inert ingredients.

Given the natural occurrence of nitrates and nitrites, their extensive use as fertilizers, the relatively high concentrations of nitrates and nitrites that are found in many vegetables as well as levels found in foods from their use as FDA food additives, and their endogenous formation in the body, it is highly unlikely that dietary exposures resulting from the use of ammonium nitrate, magnesium nitrate, sodium nitrate, and sodium nitrite as pesticide inert ingredients would result in any increase in exposures above these pre-existing levels or would exceed levels currently determined to be safe.

Taking into consideration all available information on ammonium nitrate, magnesium nitrate, sodium nitrate, and sodium nitrite, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to ammonium nitrate, magnesium nitrate, sodium nitrate, and sodium nitrite when considering

dietary exposure and all other nonoccupational sources of pesticide exposure for which there are reliable information. Therefore, it is recommended that the exemptions from the requirement of a tolerance established for residues of ammonium nitrate, magnesium nitrate, sodium nitrate, and sodium nitrite in/on raw agricultural commodities be considered reassessed as safe under section 408(q) of the FFDCA

I. Introduction

This report evaluates ammonium nitrate (CAS Reg. No. 6484-52-2), magnesium nitrate (CAS Reg. No.10377-60-3), sodium nitrate (CAS Reg. No. 7631-99-4), and sodium nitrite (CAS Reg. No. 7632-00-0), pesticide inert ingredients for which exemptions from the requirement of a tolerance exist for their residues when used in pesticide formulations applied to growing crops only under 40 CFR §180.920 [formerly 40 CFR §180.1001(d)].

Ammonium nitrate, magnesium nitrate, sodium nitrate and sodium nitrite are all water soluble inorganic salts that readily dissociate into the corresponding cation (i.e., ammonium, magnesium or sodium) and the nitrate/nitrite anion. Nitrate (NO_3^-) and nitrite (NO_2^-) are naturally occurring inorganic ions, which are part of the nitrogen cycle. Nitrate and nitrite are interconverted in the body as part of normal nitrogen metabolic process, and the evaluation of ammonium nitrate, magnesium nitrate, sodium nitrate, and sodium nitrite as pesticide inert ingredients is largely based on the nitrate and nitrite ions.

Nitrates can be of natural and synthetic origin. Nitrate is an important metabolite in the biological nitrogen cycle, produced during nitrification of reduced nitrogen compounds. It is a natural constituent of soil and vegetation. Nitrate is also a normal metabolite in mammals. Nitrate in soil, ground and surface water is derived mainly from mineralization of soil organic matter as well as from application of mineral fertilizers. Nitrite is also a metabolite in the biological nitrogen cycle; an intermediate in both nitrification and denitrification. It is also a normal metabolite in mammals.

Nitrates and nitrites have been extensively evaluated by a number of organization, including EPA's Office of Drinking Water, The Joint FAO/WHO Expert Committee on Food Additives (JECFA), the National Toxicology Program (NTP), and the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency. This assessment relies extensively on these previously performed evaluations.

II. Use Information

Pesticides

The tolerance exemptions for the inert ingredients ammonium nitrate, magnesium nitrate, sodium nitrate and sodium nitrite being reassessed in this document are given in Table 1 below.

Sodium nitrate is also used as an active ingredient in explosive cartridges used for in burrow rodent control.

Table 1. Tolerance Exemptions Being Reassessed in this Document				
Tolerance Exemption Expression	**CAS Reg No.**	**40 CFR §**	**Use Pattern (Pesticidal)**	**List Classification**
Ammonium nitrate	6484-52-2	180.920 [1/]	Adjuvant/intensifier for herbicides	4B
Magnesium nitrate	10377-60-3	180.920[2/]	Preservation	4B
	13446-18-9[3/]	--	--	--
Sodium nitrate	7631-99-4	180.920	Solid diluent	4B
Sodium nitrite	7632-00-0	180.920	Stabilizer, inhibitor. Not more than 3% of pesticide formulation	3

1. Residues listed in 40 CFR §180.920 [formerly 40 CFR§ 180.100(d)] are exempted from the requirement of a tolerance when used as inert ingredients in pesticide formulations when applied to growing crops only.
2. The tolerance exemption for magnesium nitrate is listed as being "in combination with 2-methyl-4-isothiazolin-3-one and 5-chloro-2-methyl-4-isothiazolin-3-one." Reassessment of magnesium nitrate will not be complete until 2-methyl-4-isothiazolin-3-one and 5-chloro-2-methyl-4-isothiazolin-3-one have also been reassessed.
3. Magnesium nitrate hexahydrate--a common commercial form of magnesium nitrate.

Other Uses

Ammonium nitrate

By far the most predominant use of ammonium nitrate is as a source of nitrogen in fertilizer. Some two million tons/yr of ammonium nitrate are used as fertilizer in the U.S.

Magnesium nitrate

The major uses of magnesium nitrate are as a catalyst in the manufacture of petrochemicals, as a desensitizer for lithographic plates and in pyrotechnics.

Sodium nitrate

Sodium nitrate is used as a source of nitrogen in some fertilizers and as an oxidizing component of explosives and blasting agents. Sodium nitrate is a food additive that is approved for use by the U.S. Food and Drug Administration (FDA) for both direct and indirect food use applications (Table 2).

Sodium nitrite

Sodium nitrite serves as an anticorrosion inhibitor for multipurpose greases and is also used in photographic processing applications. Sodium nitrite is a food additive that is approved for use by FDA for both direct and indirect food use applications (Table 2). Sodium nitrite also has been used in human and veterinary medicine as a vasodilator, a bronchial dilator, an intestinal relaxant, and an antidote for cyanide poisoning.

Table 2. FDA Approved Food Uses for Sodium Nitrate and Sodium Nitrite

Chemical	**21 CFR §**	**Uses**
Sodium Nitrate	172.170	(1) As a preservative and color fixative, with or without sodium nitrite, in smoked, cured sablefish, smoked, cured salmon, and smoked, cured shad, so that the level of sodium nitrate does not exceed 500 parts per million and the level of sodium nitrite does not exceed 200 parts per million in the finished product. (2) As a preservative and color fixative, with or without sodium nitrite, in meat-curing preparations for the home curing of meat and meat products (including poultry and wild game), with directions for use which limit the amount of sodium nitrate to not more than 500 parts per million in the finished meat product and the amount of sodium nitrite to not more than 200 parts per million in the finished meat product.
	173.310	Boiler water additives
	175.105	Components of adhesives
	176.180	Components of paper and paperboard in contact with dry food
	181.33	Specific Prior-Sanctioned Food Ingredients subject to prior sanctions issued by the U.S. Department of Agriculture for use as sources of nitrite, with or without sodium or potassium nitrite, in the production of cured red meat products and cured poultry products.

Table 2. FDA Approved Food Uses for Sodium Nitrate and Sodium Nitrite		
Chemical	**21 CFR §**	**Uses**
Sodium Nitrite	172.175	(1) As a color fixative in smoked cured tunafish products so that the level of sodium nitrite does not exceed 10 parts per million (0.001 percent) in the finished product. (2) As a preservative and color fixative, with or without sodium nitrate, in smoked, cured sablefish, smoked, cured salmon, and smoked, cured shad so that the level of sodium nitrite does not exceed 200 parts per million and the level of sodium nitrate does not exceed 500 parts per million in the finished product. (3) As a preservative and color fixative, with sodium nitrate, in meat-curing preparations for the home curing of meat and meat products (including poultry and wild game), with directions for use which limit the amount of sodium nitrite to not more than 200 parts per million in the finished meat product, and the amount of sodium nitrate to not more than 500 parts per million in the finished meat product.
	172.177	Preservative in processing smoked chub
	175.105	Components of adhesives
	175.300	Components of coatings
	176.170	Components of paper and paperboard in contact with aqueous and fatty foods
	176.180	Components of paper and paperboard in contact with dry food
	177.1210	Substance used in the manufacture of closures with sealing gaskets for food containers
	177.2600	Substance used as component of rubber articles intended for repeated use
	178.3570	Rust preventive in mineral oil lubricants with incidential food contact
	178.3910	Rust inhibitor in surface lubricants used in the manufacture of metallic articles
	181.34	Specific Prior-Sanctioned Food Ingredients- subject to prior sanctions issued by the U.S. Department of Agriculture for use as color fixatives and preservative agents, with or without sodium or potassium nitrate, in the curing of red meat and poultry products.

Table 2. FDA Approved Food Uses for Sodium Nitrate and Sodium Nitrite		
Chemical	**21 CFR §**	**Uses**
	573.700	Preservative and color fixative in canned pet food containing fish, meat, and fish and meat byproducts

III. Physical and Chemical Properties

The physical and chemical characteristics of ammonium nitrate, magnesium nitrate, sodium nitrate, and sodium nitrite are given in Appendix A.

IV. Hazard Assessment

A. Hazard Profile

Ammonium nitrate, magnesium nitrate, sodium nitrate, and sodium nitrite are all water soluble inorganic salts that readily dissociate into the corresponding cation (i.e., ammonium, magnesium or sodium) and the nitrate/nitrite anion. A previous Focus Group assessment considered the effects of various metal cations including sodium and magnesium, as well as the ammonium cation. That assessment concluded that these cations are integral components of normal human metabolic processes and are metabolized in the human body through well-understood pathways (EPA 2002a).

Methemoglobinemia is the primary adverse health effect associated with human exposure to nitrate or nitrite. To cause methemoglobinemia, nitrate must be converted to nitrite. Methemoglobinemia occurs when nitrite oxidizes the Fe^{2+} in hemoglobin to Fe^{3+}, a form that does not allow oxygen transport. Methemoglobinemia can lead to cyanosis (insufficient oxygenation of the blood characterized by bluish skin and lips) and, ultimately, death. Methemoglobinemia in adults is rare; most methemoglobinemia victims are infants who have been fed formula mixed with nitrate-containing well water or food with a high nitrate content or who have diarrhea.

B. Toxicological Data

The toxic effects of nitrate are closely related to its conversion to nitrite by bacteria in the alimentary tract. These effects depend not only on dose, but also on the concentration and type of bacteria present. Dose-response relationships are highly variable among species. The available toxicological data on nitrates and nitrites includes numerous animal studies, with many of these studies being discussed in the previously performed evaluations of nitrates and nitrites noted in section I.. A table summarizing some of the key studies used in these evaluations to establish dose-response relationships and for toxicity endpoint selection is given in Appendix B.

C. Epidemiological Data

There are a number of studies that have been performed to examine nitrate-induced methemoglobinemia in humans. The most noteworthy study and the basis for the current EPA drinking water standard for nitrate is that of Walton (1951). The American Public Health Association sent questionnaires to all [then] 48 states investigating the morbidity and mortality among infants due to methemoglobinemia induced by nitrate-contaminated water. The survey identified 278 cases and 39 deaths that could be "definitely associated with nitrate-contaminated water." Nitrate exposures were known for 214 cases, and all of them exceeded 50 mg/L; of the 214 cases, 81% occurred above 220 mg/L, 17% at 90-220 mg/L, and only 2% at 50-90 mg/L. The presence of nitrite, of bacteriologic contamination, and of gastrointestinal disease and methemoglobin concentrations were not reported.

A recent WHO investigation of the relationship between high levels of drinking water nitrate concentration and methemoglobinemia could not identify an exposure-response relationship between drinking water nitrate level and methemoglobinemia; nitrate may be only one of a number of cofactors that play a role in expression of the disease. The investigation concluded that "given the apparently low incidence of possible water-related methemoglobinemia, the complex nature of the role of nitrates, and that of individual behavior, it is currently inappropriate to attempt to link illness rates with drinking-water nitrate levels" (Fewtrell, 2004).

D. Metabolism And Pharmacokinetics

The metabolism and pharmacokinetics of nitrate and nitrite are interrelated and cannot be considered separately from one another as nitrate and nitrite are readily interconverted by oxidation-reduction reactions in biological systems. As part of an evaluation of sodium nitrite, the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency (CAL/EPA) discussed the metabolism and pharmacokinetics of nitrate and nitrite:

> "Ingested nitrate is readily absorbed from the proximal small intestine, reaching peak levels within 1-3 hours in human serum, urine, and saliva (Walker, 1996). In humans, about 25% of an ingested and absorbed dose of nitrate is actively secreted in the saliva, due to the functioning of an active transport mechanism common to iodide, thiocyanate, and nitrate (NAS, 1981a; Walker, 1996; WHO, 1996a). Salivary secretion of nitrate also occurs in most laboratory animals, apart from the rat. The apparent lack of this particular transport mechanism in rats complicates extrapolation of experimental toxicology results obtained in that species to humans (NAS, 1981a;Walker, 1996; WHO, 1996a). Additionally, although nitrate reduction in the lower part of the gastrointestinal (GI) tract is relatively greater in rats than in humans, the nitrite formed there is less efficiently absorbed. These metabolic differences may be responsible for the observation that

the no observed adverse effect level (NOAEL) for (sub)acute toxicity in humans is 10-60 times lower than the NOAEL in rats (WHO, 1996a).

Reduction of nitrate to nitrite occurs in vivo as a result of mammalian nitrate reductase activity, as well as due to the nitrate reductase activity of microorganisms resident in the oral cavity and upper GI tract (NAS, 1981a; Walker, 1996; WHO, 1996a). In particular, the typically stable population of nitrate-reducing bacteria colonizing the base of the tongue is thought to be responsible for the significant level of nitrate reduction which takes place in the mouth. Salivary nitrite concentrations are considered to be directly related to the orally ingested dose of nitrate, although the reduction process may be saturable at high intakes. Allowing for considerable inter-individual variation, it has been estimated that 25% of total nitrate ingested by humans is secreted in the saliva. Of this 25%, 20% (or about 5% of the ingested dose) is reduced to nitrite. Hence, oral reduction of nitrate is considered to be the most important source of nitrite in humans, as well as in other species possessing an active salivary secretion mechanism."

E. Dose-Response Assessment

The Environmental Protection Agency's Integrated Risk Information System (IRIS) lists an oral reference dose (RfD) for chronic noncarcinogenic health effects for nitrate (as nitrate nitrogen) of 1.6 mg/kg/day. This reference dose is derived from human epidemiological surveys (Bosch et al., 1950; Walton, 1951) using a NOAEL of 10 mg nitrate-nitrogen/L (equivalent to 1.6 mg/kg/day) and a LOAEL of 11-20 mg nitrate-nitrogen/L (equivalent to 1.8-3.2 mg/kg/day) based on early clinical signs of methemoglobinemia in excess of 10% (0-3 months old infants' formula).

A conversion factor of 1 mg nitrate-nitrogen = 4.4 mg nitrate and a dose conversion based on ingestion of drinking water used to prepare infants' formula: 0.64 L/day by a 4 kg infant (0.16 L/kg/day) (Davidson et al., 1975) 10 mg/L x 0.64 L/day divided by 4 kg = 1.6 mg/kg/day is also given.

The most recent evaluation by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) states that " In the light of the overall information on the toxicity of nitrate, the NOEL of 370 mg nitrate ion/kg bw/day was considered to be the most appropriate for safety evaluation" based on effects on the heart and lung in a 2-year rat study. On the basis of that NOEL from a 2-yr rat study of 370 mg/kg bw per day, expressed as nitrate ion, and a safety factor of 100, an Acceptable Daily Intake (ADI) of 0-5 mg/kg bw expressed as sodium nitrate or 0-3.7 mg/kg bw expressed as nitrate ion was allocated. The ADI for nitrite ion is 0-0.07 mg/kg bw/day. (JECFA 2002).

These results are summarized in Table 5.

Table 5. RfD and ADI for Nitrate and Nitrite		
	Source	Dose in mg/kg-bw/day
Oral RfD	IRIS	1.6 (nitrate nitrogen)= 7 (nitrate ion)
ADI	JECFA	0 - 3.7 (nitrate ion) 0 - 0.07 (nitrite ion)

F. Special Considerations for Infants and Children

The toxicological endpoint used to establish a reference dose for nitrate/nitrite is based upon epidemiological data and effects seen in human infants, the most sensitive subpopulation. A safety factor analysis has not been used to assess the risks resulting from the use of ammonium nitrate, magnesium nitrate, sodium nitrate and sodium nitrite. Since the toxicological endpoint utilized in establishing the oral RfD, as well as the Maximum Contaminant Level (MCL) for nitrate in drinking water of 10 mg/L established by EPA's Office of Water is based upon effects seen in human infants, and a safety factor analysis was not utilized in this qualitative assessment, the use of an additional tenfold safety factor is unnecessary.

G. Endocrine Disruption

The Food Quality Protection Act requires that EPA develop a screening program to determine whether certain substances (including all pesticide chemicals) ". . .may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect . . ." Following the recommendations of its Endocrine Disruptor Screening 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).

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

V. <u>Exposure Assessment</u>

Most nitrate and nitrite to which humans are exposed is in their diet, as either natural components or intentional additives. In addition, nitrate is synthesized endogenously in the body.

The National Academy of Science's (NAS) 1995 report "Nitrate and Nitrite in Drinking Water" (NAS, 1995) states:

> "Vegetables are the primary source of nitrate and nitrite in food, and cured meat and dairy products can also contribute. The highest nitrate concentrations are found in celery, spinach, lettuce, beets, radishes, melon, turnip greens, and rhubarb (over 1000 mg/kg of vegetable) (Walker 1990). Low concentrations of nitrite (less than 10 mg/kg) can also be present in those vegetables. Concentrations of nitrate in vegetables depend on agricultural practices, storage conditions, the temperature and light in which they are grown, and the concentrations of nitrate in the soil, fertilizers, and water used to grow the vegetables (NRC 1981; Hwang et al. 1994). The concentrations of nitrate and nitrite in cured-meat products depend on the curing process and on the amounts added as preservatives. Concentrations of nitrite in bacon, for example, can be up to 120 ppm, which is the maximum allowed by law (9CFR 318.7B). Nitrate and nitrite are used as preservatives because of their ability to inhibit the growth of *Clostridium botulinum* (NRC 1981). Improved manufacturing processes have led to a steady decline in the concentrations of nitrate and nitrite in preserved meats (nitrate is now used only rarely)."

The EPA IRIS Nitrate health assessment states that "Nitrate is a normal component of the human diet. A typical daily intake by an adult in the United States is about 75 mg/day (about 0.2-0.3 mg nitrate- nitrogen/kg/day) (NAS, 1981). Of this, over 85% comes from the natural nitrate content of vegetables such as beets, celery, lettuce and spinach. Daily intakes of nitrate by vegetarians may exceed 250 mg/day (0.8 mg nitrate- nitrogen/kg/day) (NAS, 1981). The contribution from drinking water is usually quite small (about 2-3% of the total) (NAS, 1981), but could reach 85 mg/day (0.29 mg nitrate-nitrogen/kg/day) if water containing 10 mg nitrate-nitrogen/L was consumed."

Nitrate and nitrite can occur in drinking water as a result of human and other activities. The microbial oxidation of ammonia to nitrate and nitrite is the primary nonhuman source. Inorganic fertilizers and human and animal wastes (from livestock operations and septic tanks) are the primary human sources. Nitrate released to soil can enter groundwater or surface water as a result of leaching or runoff. Nitrate concentrations in groundwater are typically less than 10 mg/L but can exceed that in areas of concentrated human sources. Concentrations of nitrate in surface water seldom exceed 1 mg/L except in areas of severe contamination. The nitrite in groundwater and surface water is negligible compared with the nitrate; in oxygenated waters, nitrite is rapidly converted to nitrate.

The NAS Nitrate and Nitrite in Drinking Water Report discusses the endogenous formation of nitrates by stating "Some nitrate and nitrite exposure also originates in the endogenous production of nitric oxide, which can be converted to nitrate, by many types of cells, including macrophages (Iyengar et al. 1987), neutrophils (McCall et al. 1989), endothelial cells (Palmer et al. 1988), neurons (Knowles et al. 1989), and hepatocytes (Billiar et al. 1990). As a result, nitrate excretion in urine exceeds nitrate intake from food and water. In the absence of infection, endogenous nitrate synthesis approximates 62 mg/day (Tannenbaum et al. 1978; Green et al. 1981; Wagner et al. 1983; Lee et al. 1986). Infections and inflammatory reactions can increase endogenous nitrate synthesis in both infants and adults (Hegesh and Shiloah 1982; Wagner and Tannenbaum 1982)."

Based upon the various estimates of exposures to natural and synthetic sources of nitrates in the diet and drinking water, combined with endogenous nitrate synthesis, typical nitrate exposures would be greater than 100 mg/day, far exceeding exposures to nitrates and nitrites resulting from their use as pesticide inert ingredients.

VI. Aggregate Exposures

In examining aggregate exposure, 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 ammonium nitrate, magnesium nitrate, sodium nitrate and sodium nitrite, a qualitative assessment for all pathways of human exposure (food, drinking water, and residential) is appropriate given the extensive natural occurrence of nitrate and nitrite in the environment.

VII. 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 ammonium nitrate, magnesium nitrate, sodium nitrate, and sodium nitrite and any other substances and these materials do not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that ammonium nitrate, magnesium nitrate, sodium nitrate and sodium nitrite have 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/.

VIII. Environmental Fate/Ecotoxicity/Drinking Water Considerations

A. Environmental Fate Characterization

Due to their high water solubility and weak retention by soil, nitrates are very mobile in soil, moving at approximately the same rate as water, and have a high potential to migrate to ground water. Because it does not volatilize, nitrate/nitrite is likely to remain in water until consumed by plants or other organisms. Ammonium nitrate will be taken up by bacteria. Nitrate is more persistent in water than the ammonium ion. Nitrate degradation is fastest in anaerobic conditions (EPA 2002b).

Under the Safe Drinking Water Act, EPA's Office of Water has established a Maximum Contaminant Level Goal (MCLG) for nitrates of 10 ppm and for nitrites at 1 ppm. These MCLGs are established by EPA's Office of Water under the Safe Drinking Water Act and represent a determination of safe levels of these chemicals in drinking water, based solely on possible health risks and exposure. Use of ammonium nitrate, magnesium nitrate, sodium nitrate, and sodium nitrite as pesticide inert ingredients would not result in drinking water concentrations that would exceed the MCLG.

B. Ecotoxicity and Ecological Risk Characterization

Ammonium nitrate is considered to be not acutely toxic to slightly toxic in a number of studies on various fish and amphibian species (EPA 2002c). Toxicity to terrestrial organisms resulting from the use of ammonium nitrate, magnesium nitrate, sodium nitrate, and sodium nitrite as pesticide inert ingredients would not be expected to be of concern. Overall, use of ammonium nitrate, magnesium nitrate, sodium nitrate, and sodium nitrite as pesticide inert ingredients would be of negligible ecological concern.

IX. Risk Characterization

Any risk concerns associated with the use of ammonium nitrate, magnesium nitrate, sodium nitrate and sodium nitrite as pesticide inert ingredients would be related to their dissociation to the nitrate and nitrite ion and the potential for resultant oral exposures as there are no identified concerns for dermal and inhalation exposures. Given the natural occurrence of nitrates and nitrites, their extensive use as fertilizers, the relatively high concentrations of nitrates and nitrites that are found in many vegetables and as well as levels found in foods from their use as FDA food additives, and their endogenous formation in the body, it is highly unlikely that dietary exposures resulting from the use of ammonium nitrate, magnesium nitrate, sodium nitrate and sodium nitrite as pesticide inert ingredients would result in any increase in exposures above these pre-existing levels or would exceed levels currently determined to be safe, such as the enforceable Maximum Contaminant Level of 10 ppm for nitrates and 1 ppm for nitrites in drinking water permitted under the Safe Drinking Water Act and established by EPA's Office of Water.

Taking into consideration all available information on ammonium nitrate, magnesium nitrate, sodium nitrate, and sodium nitrite, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to ammonium nitrate, magnesium nitrate, sodium nitrate, and sodium nitrite when considering dietary exposure and all other nonoccupational sources of pesticide exposure for which there are reliable information. Therefore, it is recommended that the exemptions from the requirement of a tolerance established for residues of ammonium nitrate, magnesium nitrate, sodium nitrate, and sodium nitrite in/on raw agricultural commodities be considered reassessed as safe under section 408(q) of the FFDCA.

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APPENDIX A

Physical and Chemical Properties of Ammonium Nitrate, Magnesium Nitrate, Sodium Nitrate, and Sodium Nitrite

Physical Chemical Properties		
Parameter	**Value**	**Source**
Ammonium Nitrate (CAS Reg. No. 6484-52-2)		
Molecular Weight	80.1	ICPS http://www.inchem.org/documents/icsc/icsc/eics0216.htm
Water Solubility	192 g/100 mL at 20°°C	
Boiling Point	210° C@ 11 mm HG	
Melting Point:	169.6° C	CRC Handbook of Chemistry and Physics 72nd ed. as cited in HSDB
Specific Gravity	1.73 @ 23° C	UNEP http://www.unepie.org/pc/apell/disasters/toulouse/nh4no3.html#characteristicsH
pH	5.4	
Magnesium Nitrate (CAS Reg. No. 10377-60-3)		
Molecular Weight	148.33	ICPS http://www.inchem.org/documents/icsc/icsc/eics1041.htm
Water Solubility	very good	
Boiling Point	Decomposes below boiling point at 330°C	
Melting Point:	-5° C	
Specific Gravity	1.73 @ 23 °C	UNEP http://www.unepie.org/pc/apell/disasters/toulouse/nh4no3.html#characteristicsH
pH	5.4	
Sodium Nitrate (CAS Reg. No. 7631-99-4)		

Physical Chemical Properties		
Parameter	**Value**	**Source**
Molecular Weight	84.99	ICPS http://www.inchem.org/documents/icsc/icsc/eics0185.htm
Solubility in water	92.1 g/100 mL at 25°C	
Boiling point	380°C (decomposes	
Melting point	308°C	
Density	2.3 g/cm³	
pH	Aqueous solution is neutral	J.T. Baker 2004 http://www.jtbaker.com/msds/englishhtml/s4442.htm
Octanol/water partition coefficient	log P = -0.790	ChemIDplus http://chem.sis.nlm.nih.gov/chemidplus/jsp/chemidheavy/ChemFull.jsp?MW=84.994
Sodium Nitrite (CAS Reg. No. 7632-00-0)		
Molecular Weight	69.00	ICPS http://www.inchem.org/documents/icsc/icsc/eics1120.htm
Solubility in water	82 g/100 mL at 20°C	
Boiling point	Decomposes below boiling point at 320 °°C	
Melting point	(decomposes): 280°C	
Density	2.2 g/cm³	
pH	8-9 (100 g/L, 20 °C)	J.T. Baker http://www.jtbaker.com/msds/englishhtml/s4466.htm
Octanol/water partition coefficient	log P = -3.7	ICPS http://www.inchem.org/documents/icsc/icsc/eics1120.htm

APPENDIX B

Summary of Toxicity Data for Nitrates and Nitrites				
Test	**Species**	**Method/ Duration**	**Result**	**Source**
Nitrates				
Oral LD_{50} (mg/kg)	Rat	single dose	4500 (ammonium nitrate)	Environment Canada; Tech Info for Problem Spills: Ammonium Nitrate p.59 (1981) as cited in HSDB
Oral LD_{50} (mg/kg)	Mouse	single dose	2480-6250 (sodium nitrate)	Mammalian Toxicity Array 1982; Corréé & Breimer 1979 as cited in JECFA 1995
Oral LD_{50} (mg/kg)	Rat	single dose	4860-9000 (sodium nitrate)	
Oral LD_{50} (mg/kg)	Rabbit	single dose	1600 (sodium nitrate)	
Bacterial Reverse Mutation Test	*S. Typhimurium*, *E. Coli*	*in vitro* with and without activation	Nitrate did not induce mutagenic effects in bacterial tests with *S. typhimurium.* When tested under aerobic and anerobic conditions in *E. coli,* mutagenicity was only found under anaerobic conditions. [The mutations, however, were probably due to the reduction of nitrate to nitrite under the test conditions]	Konetzka 1974 as cited in JECFA 1995
Chromosome Aberration Assay	Mammalian polychromatic erythrocytes		Unconfirmed positive response (Sodium nitrate)	EMICBACK 1990 as cited in GENE-TOX

Summary of Toxicity Data for Nitrates and Nitrites				
Test	**Species**	**Method/ Duration**	**Result**	**Source**
2-Year Oral	Rats	20/sex/group were fed a diet containing 0, 0.1, 1, 5 or 10% sodium nitrate	NOEL=1% (equivalent to 500 mg sodium nitrate/kg bw/day, or 370 mg/kg bw/day expressed as nitrate ion). LOEL= 5% (2000 mg sodium nitrate/kg-bw/day or 1850 mg/kg bw/day expressed as nitrate ion) based on slight growth inhibition	Lehman 1958 as cited in JECFA 1995
Nitrites				
Bacterial Reverse Mutation Test	*S. Typhimurium* TA 98 and TA100	*in vitro* with and without activation	Positive in strain TA100 with and without S9; negative in strain TA98 (Sodium nitrite)	Zeiger 1992 as cited in NTP 2001
Chromosomal Aberration Assay	Male F344/N Rats Bone Marrow Micronucleus	*in vivo*	No increase in mononucleated polychromatic erythrocytes (PCE) at levels to 50 mg/kg of sodium nitrite	Shelby et al. 1993 as cited in NTP 2001
Chromosomal Aberration Assay	Male B6C3F1 Mice Bone Marrow Micronucleus	*in vivo*	No increase in mononucleated polychromatic erythrocytes (PCE) at levels to 250 mg/kg of sodium nitrite	Shelby et al. 1993 as cited in NTP 2001
Chromosomal Aberration Assay	Mouse Peripheral Blood Micronucleus	*in vivo*	No significant increase in the frequency of micronucleated NCEs at levels up to 5000 ppm of sodium nitrite	MacGregor et al. 1990 as cited in NTP 2001
14-week Oral	F344/N Rat	0, 375, 750, 1,500, 3,000, or 5,000 ppm sodium nitrite in drinking water	NOEL not achieved	NTP 2001

Summary of Toxicity Data for Nitrates and Nitrites				
Test	**Species**	**Method/ Duration**	**Result**	**Source**
14-Week Oral	B6C3F1 Mouse	0, 375, 750, 1,500, 3,000, or 5,000 ppm sodium nitrite in drinking water	NOEL not achieved	NTP 2001
2-Year Oral	F344/N Rat	0, 750, 1,500, or 3,000 ppm sodium nitrite in drinking water	No evidence of carcinogenic activity of sodium nitrite in male or female rats exposed to 750, 1,500, or 3,000 ppm.	NTP 2001
2-Yr Oral	B6C3F1 Mouse	0, 750, 1,500, or 3,000 ppm sodium nitrite in drinking water	No evidence of carcinogenic activity of sodium nitrite in male B6C3F1 mice exposed to 750, 1,500, or 3,000 ppm. There was equivocal evidence of carcinogenic activity of sodium nitrite in female B6C3F1 mice based on the positive trend in the incidences of squamous cell papilloma or carcinoma (combined) of the forestomach	NTP 2001