



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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: July 27, 2005

ACTION MEMORANDUM

SUBJECT: Inert Reassessment – Nicotinamide (CAS Reg. No. 98-92-0)

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 one inert ingredient exemption from the requirement of a tolerance. Current exemption is to be maintained.

Chemical: Nicotinamide

CFR: 40 CFR § 180.920 formerly 40 CFR § 180.1001 (d)

CAS #: 98-92-0

Table 1

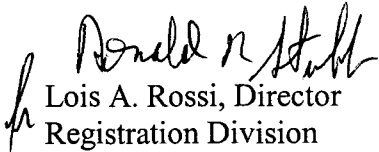
Tolerance Exemption Expression			
40 CFR §**	Inert Ingredient	Limits	Uses
180.920	Nicotinamide (CAS Reg. No. 98-92-0)	Maximum of 0.5% of formulation.	Synergist

Use Summary: Nicotinamide is a water-soluble B complex vitamin which is naturally present in animal products, whole cereals and legumes. Together with nicotinic acid (niacin), it belongs to vitamin B₃ or vitamin PP, and is required as a nutrient to prevent the niacin deficiency disorder pellagra. It functions as a coenzyme or cosubstrate in

many biological reduction and oxidation reactions required for energy metabolism in mammalian systems. It is used as a nutritional supplement, therapeutic agent, skin and hair conditioning agent in cosmetics, and a constituent of consumer household solvent and cleaning products and paints. Nicotinamide is approved for use by the FDA as a food additive to enrich corn meal, farina, rice, and macaroni and noodle products. It is also affirmed as GRAS (Generally Recognized as Safe) by the FDA as a direct human food ingredient which includes its use in infant formula. It is approved for use in pesticide products applied to growing crops only as a synergist with a maximum limitation of 0.5% of formulation.

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the one exemption from the requirement of a tolerance for the inert ingredient nicotinamide (CAS Reg. No. 98-92-0). I consider 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.


Lois A. Rossi, Director
Registration Division

Date: 7/27/05

CC: Debbie Edwards, SRRD
Joe Nevola, SRRD



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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

July 27, 2005

MEMORANDUM

SUBJECT: Reassessment of the One Exemption from the Requirement of a Tolerance for Nicotinamide (CAS Reg. No. 98-92-0)

FROM: Keri Grinstead, Inerts Team *Keri Grinstead*
Minor Use, Inerts, and Emergency Response Branch
Registration Division (7505C)

THROUGH: Pauline Wagner, Inerts Coordinator *Pauline Wagner 7/27/05*
Registration Division (7505C)

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

Background

Attached is the science assessment for nicotinamide. This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, exposure profile, and environmental fate and ecotoxicity of nicotinamide. The purpose of this document is to reassess the one existing exemption from the requirement of a tolerance for residues of nicotinamide when used as an inert ingredient in pesticide formulations on growing crops only with a maximum of 0.5% in the formulation, as required under the Food Quality Protection Act (FQPA).

Executive Summary

This report evaluates the chemical nicotinamide, which has one exemption from the requirement of a tolerance for its residues under 40 CFR § 180.920 when used as a synergist in pesticide formulations applied to growing crops only with a maximum of 0.5% in the formulation. It is sponsored as a High Production Volume (HPV) chemical under the OECD (Organisation for Economic Co-operation and Development). The

corresponding OECD SIAR (SIDS (Screening Information Data Set)¹ Initial Assessment Report) was used as the primary reference for this assessment, unless otherwise noted.

The most common synonyms for nicotinamide are 3-pyridine carboxamide, vitamin B₃, and niacinamide. In open literature, the term niacin often refers to both nicotinamide and nicotinic acid. Nicotinamide is a water-soluble B complex vitamin which is naturally present in animal products, whole cereals and legumes. Together with nicotinic acid (niacin), it belongs to vitamin B₃ or vitamin PP. It can be synthesized directly in the body from the amino acid tryptophan, or synthesized industrially using nicotinic acid or 3-cyanopyridine as starting material. It functions as a coenzyme or cosubstrate in many biological reduction and oxidation reactions required for energy metabolism in mammalian systems. Exogenous nicotinamide is easily absorbed from the gastrointestinal tract and may be deamidated to nicotinic acid by intestinal microorganisms before entering the systemic circulation. This chemical can be either incorporated into NADP (nicotinamide adenine dinucleotide phosphate) directly or after deamidation, or metabolized and excreted in the urine.

Nicotinamide is used as a synergist in pesticide products with a maximum limitation of 0.5% in formulation. It is approved for use (see Appendix A) by the FDA (Food and Drug Administration) as a food additive to enrich corn meal, farina, rice, and macaroni and noodle products. It is also affirmed as GRAS (Generally Recognized as Safe) by the FDA as a direct human food ingredient which includes its use in infant formula. The Recommended Dietary Allowance (RDA)² for niacin equivalents (from all sources) is 6.6 mg niacin per 1000 kcal with not less than 13 mg daily for adults. It is also used as a nutritional supplement, therapeutic agent, constituent of consumer household solvent and cleaning products and paints, and hair and skin conditioning agent in cosmetic products.

Nicotinamide is considered to be of very low acute toxicity to mammals, both orally (LD₅₀ of 3-7 g/kg bw in rodents) and dermally (LD₅₀>2000 mg/kg bw in rabbits). Repeated dose oral toxicity testing in rats yielded a NOAEL (No Observed Adverse Effect Level) of 215 mg/kg bw/d based on minor effects on the liver and the spleen (females only). There was no indication of dermal irritation in rabbit studies or dermal sensitization in guinea pig studies; however it was considered to be irritating to the eyes when tested on rabbits. Nicotinamide was not mutagenic in bacterial strains and did not induce clastogenic effects in both *in vitro* and *in vivo* micronucleus testing in mice. Both promoting and antitumorigenic effects were reported when nicotinamide was administered with known carcinogens; however, no increased incidence of tumors was

¹ The Screening Information Data Set (SIDS) Program, which is under the auspices of the (OECD), 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 SIDS Meeting (SIAM).

² Recommended Dietary Allowances represent the amounts of essential nutrients considered adequate to meet the nutritional needs of most healthy persons in the United States (<http://www.fda.gov/bbs/topics/ANSWERS/ANS00112.html>).

observed in a lifetime carcinogenicity study in Swiss mice receiving 1% nicotinamide in the diet. In a rat study using nicotinic acid, developmental toxicity was only seen at levels that were maternally toxic and there was no evidence of teratogenicity. For nicotinamide, a qualitative assessment for all pathways of human exposure (food, drinking water, and residential) is appropriate given that it is an essential nutrient found naturally and as a direct food additive in many foodstuffs, and the lack of human health concerns associated with exposure to nicotinamide when used as an inert ingredient in pesticide formulations.

Based on its physical/chemical properties, rapid biodegradation, and concentration limitation in pesticide formulations, dermal, inhalation, and dietary (food and drinking water) exposures of concern are not expected. The non-volatile nature of nicotinamide, its use outdoors, and its limitation in pesticide formulations (maximum 0.5%) is expected to minimize any inhalation exposures from residential use. Residential dermal exposure to nicotinamide used in pesticide products is of low human health concern because study results indicate it is non-irritating and non-sensitizing. Dietary and dermal exposures from its use in pesticide products are expected to be less than from its natural occurrence in foodstuffs, its use as a direct food additive and dietary supplement, and its use in personal care products and cosmetics.

Nicotinamide is of low hazard to the aquatic environment. Reported aquatic toxicity data indicate nicotinamide is of low acute toxicity to fish, aquatic invertebrates, algae, and microorganisms. There are no available terrestrial data; however, based on available mammalian toxicity studies, including the rodent LD₅₀ values of 3-7 g/kg bw, the potential for adverse effects to non-target terrestrial animals is unlikely.

Taking into consideration all available information on nicotinamide, including the lack of risk concerns and prevalence in the diet, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to nicotinamide 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 exemption from the requirement of a tolerance established for residues of nicotinamide on growing crops only under can be considered reassessed as safe under section 408(q) of the FFDCFA.

I. Introduction

This report evaluates one exemption from the requirement of a tolerance for residues of the inert ingredient nicotinamide (limited to a maximum of 0.5% of formulation) on growing crops only. Nicotinamide is a water-soluble B complex vitamin that, together with nicotinic acid (niacin), belongs to vitamin B₃ or vitamin PP. In open literature, the term niacin often refers to both nicotinamide and nicotinic acid. The most common synonyms for nicotinamide are 3-pyridine carboxamide, vitamin B₃, and niacinamide. Nicotinamide occurs as a white, odorless or practically odorless, crystalline powder with a bitter taste. Nicotinamide can be synthesized directly in the body from the

amino acid tryptophan or synthesized industrially using nicotinic acid or 3-cyanopyridine as starting material.

Nicotinamide is naturally present in animal products, whole cereals, and legumes. It is a constituent of the enzyme cofactors NAD (nicotinamide adenine dinucleotide) and NADP which function as electron carriers in cell metabolism of amino acids, fatty acids, and carbohydrates. It is also the nutrient required to treat and prevent pellagra, a niacin deficiency disorder. Nicotinamide is approved for use by the FDA (see Appendix A) as a food additive to enrich corn meal, farina, rice, and macaroni and noodle products. It is also affirmed as GRAS (Generally Recognized as Safe) as a direct human food ingredient by the FDA which includes its use in infant formula. The Recommended Dietary Allowance (RDA) for niacin equivalents (from all sources) is 6.6 mg niacin per 1000 kcal with not less than 13 mg daily for adults. Nicotinamide is also used as a nutritional supplement, therapeutic agent, constituent of consumer household solvent and cleaning products and paints, and hair and skin conditioning agent in cosmetic products.

II. Use Information

A. Pesticides

The tolerance exemption for nicotinamide is provided in Table 1 below.

Table 1

Tolerance Exemption Expression			
40 CFR §**	Inert Ingredient	Limits	Uses
180.920	Nicotinamide (CAS Reg. No. 98-92-0)	Maximum of 0.5% of formulation.	Synergist

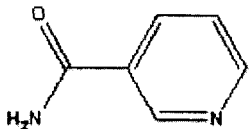
**Residues listed in 40 CFR § 180.920 are exempt from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops only.

B. Other Uses

Nicotinamide is naturally present in animal products, whole cereals and legumes and is used in human and animal nutrition to enrich various foods, drinks, or feed. It is used as a dietary supplement incorporated in tablets and capsules and as a skin and hair conditioning agent in cosmetic products. Nicotinamide is also used as a constituent of consumer household solvent and cleaning products and paints. It is used as a therapeutic agent to prevent and treat the niacin deficiency disorder pellagra, and to treat other disorders such as hypercholesterolemia, chronic alcoholism, schizophrenia, and type I diabetes (AHFS 1997).

III. Physical and Chemical Properties

Table 2. Physical and Chemical Properties of Nicotinamide

Nicotinamide (CAS 98-92-0)		
Parameter	Value	Source
Structure		http://chemfinder.cambridgesoft.com/
Physical Form	Solid, white, odorless crystalline powder	OECD SIDS 2002
Molecular Wt.	122.13 Experimental	OECD SIDS 2002
Melting Point	130 °C Experimental	ChemIDplus Advanced*
Water solubility	5.00E+05 mg/L (25°C) Experimental	ChemIDplus Advanced*
Vapor Pressure	4.20E-04 mmHg (25°C) Estimated	ChemIDplus Advanced*
Henry's Law Constant	2.90E-12 atm·m ³ /mole (25°C) Estimated	ChemIDplus Advanced*
Octanol-water partition coefficient K _{ow}	-0.37 Experimental	ChemIDplus Advanced*

*ChemIDplus Advanced on ToxNet

<http://chem.sis.nlm.nih.gov/chemidplus/jsp/common/PhysicalProperties.jsp> (7/11/2005)

IV. Hazard Assessment

A. Hazard Profile

Nicotinamide has undergone evaluation based upon its significant role in human nutrition and disease prevention. It is sponsored as a High Production Volume (HPV) chemical under the OECD (Organisation for Economic Co-operation and Development) and its corresponding OECD SIAR was used as the primary reference for this assessment, unless otherwise noted. It is considered by OECD as “currently of low priority for further work based on a low hazard potential”.

B. Metabolism and Pharmacokinetics

In humans, nicotinamide is required for lipid metabolism, tissue respiration, and glycogenolysis. It is readily absorbed in the GI tract. *In vivo*, nicotinamide is formed from conversion of nicotinic acid (niacin), while some dietary nicotinamide is oxidized to nicotinic acid and then to nicotinamide *in vivo*. Nicotinamide is incorporated into two coenzymes: NAD and NADP which act as hydrogen-carrier molecules in glycogenolysis, tissue respiration, and lipid metabolism (AHFS 1997). It can be incorporated into NADP either directly or after deamidation, or metabolized in the liver and excreted in the urine. The primary metabolites are N-methylniacinamide, other N-methylated derivatives, and nicotinuric acid.

C. Toxicological Data

Nicotinamide is considered to be of very low acute toxicity to mammals, both orally (LD₅₀ 3-7 g/kg bw in rodents) and dermally (LD₅₀>2000 mg/kg bw in rabbits). Repeated dose oral toxicity testing in rats yielded a NOAEL of 215 mg/kg bw/d based on minor effects on the liver and the spleen (females only). There was no indication of dermal irritation in rabbit studies or dermal sensitization in guinea pig studies; however it was considered to be irritating to the eyes when tested on rabbits. Nicotinamide was not mutagenic in bacterial strains and did not induce clastogenic effects in both *in vitro* and *in vivo* micronucleus testing in mice. Both promoting and antitumorigenic effects were reported when nicotinamide was administered with known carcinogens; however no increased incidence of tumors was observed in a lifetime carcinogenicity study in Swiss mice receiving 1% nicotinamide in the diet. In a rat study using nicotinic acid, developmental toxicity was only seen at levels that were maternally toxic and there was no evidence of teratogenicity. (For study details, please refer to the SIDS SIAR for 3-pyridinecarboxamide (nicotinamide).)

Oral - The acute toxicity of nicotinamide after oral exposure was very low: oral LD₅₀ 3-7 g/kg bw in rodents. In a 4-week oral toxicity study, male rats dosed with 215 and 1000 mg/kg bw showed a significant decrease in body weight gain and food consumption during part of the treatment period. Liver weight was increased, accompanied histopathologically by mild liver centrilobular hypertrophy in all treated animals. These effects were considered to be an adaptive response to nicotinamide treatment. Extramedullary hematopoiesis was reported in females in the high dose group. It was also noted that no effects on male and female gonads were found. The NOAEL derived from this study is 215 mg/kg bw.

Dermal – The acute toxicity of nicotinamide after dermal application was very low with a dermal LD₅₀ >2000 mg/kg bw in rabbits. Skin irritation studies indicated that nicotinamide showed no potential to irritate the skin and was negative for sensitization in guinea pig maximization and Beuhler tests.

Ocular – Nicotinamide was considered to be irritating to the eyes. Application of 0.1 g of nicotinamide to the eyes of 3 rabbits induced irritation in two animals, which was

reversible within 7 days. In a second, similar study, irritant effects were reversible within one week, except for hyperaemia of the conjunctivae in one animal.

Mutagenicity – Nicotinamide was negative in an Ames test both with and without metabolic activation. No chromosomal aberrations were observed in another study. Positive results were seen in sister chromatid exchange (SCE) induction investigations; however, it is noted that activity was only seen at excessively high concentrations. Two independent micronucleus tests with male and female mice concluded nicotinamide was not clastogenic. It was concluded that “Nicotinamide is considered not mutagenic in bacterial strains. No chromosomal effects in mammalian cells were reported. In an *in vivo* micronucleus test no clastogenic effects were seen. Thus nicotinamide is not mutagenic.”

Carcinogenicity - Both promoting and antitumorigenic effects were reported when nicotinamide was administered with known carcinogens; however, no increased incidence of tumors was observed in a lifetime carcinogenicity study in Swiss mice receiving 1% nicotinamide in the diet.

Reproductive/Developmental - The kinetics of nicotinamide and nicotinic acid are considered to be similar in the rat, as nicotinamide is deamidated to nicotinic acid to a large extent by microorganisms in the gut. Therefore, nicotinamide is expected to be absorbed mainly as nicotinic acid. For these reasons, the study results with nicotinic acid for the assessment of potential developmental effects after nicotinamide administration is assumed to be relevant. Pregnant rats were exposed orally to 0, 4, 200, and 1000 mg/kg nicotinic acid during days 6-15 of gestation. Body weight gain of the dams of the highest dose group was slightly decreased and the placental weight was significantly decreased. Fetuses did not show any adverse effects, except for a significantly lower body weight in male offspring at the highest dose. There was no teratogenic effect up to the maximum dose of 1000 mg/kg bw/d. The study results concluded “effects of nicotinic acid on reproductive parameters were only present at maternally toxic doses. There was no evidence of teratogenicity. The NOAEL for developmental toxicity is 200 mg/kg bw/d (198 mg/kg bw/d for nicotinamide).”

D. Special Consideration for Infants and Children

As a naturally occurring substance and normal component of the diet, this nutrient plays an important role in metabolic processes and disease prevention. A relevant developmental toxicity study with nicotinic acid indicated reproductive effects only at doses that were maternally toxic with a developmental NOAEL of 200 mg/kg bw/d (equivalent to 198 mg/kg bw/d nicotinamide), with no teratogenic effects observed. Based on this information there is no concern, at this time, for increased sensitivity to infants and children to nicotinamide 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

According to the 2002 OECD SIAR, nicotinamide is considered to be readily biodegradable (100% within one week), has a calculated half-life for photo-oxidation of 2.23 days in the atmosphere, and is not expected to bioaccumulate based on its low log Kow value of -0.38 (BCF of 3.162). The predicted log Koc value of 0.97 classifies it as negligible for soil sorption. Based on these physical/chemical properties as well as its limitation of a maximum 0.5% in formulation, nicotinamide is unlikely to be present at any appreciable levels in the environment, including drinking water, when used as an inert ingredient in pesticide formulations.

VI. Exposure Assessment

Nicotinamide is an essential nutrient required for metabolic processes in the body and disease prevention. Nicotinamide is naturally present in animal products, whole cereals and legumes and is used in human and animal nutrition to enrich various foods, drinks, or feed. It is used as a dietary supplement incorporated in tablets and capsules and as a skin and hair conditioning agent in cosmetic products. Studies demonstrate that the minimum requirement for the prevention of the niacin deficiency disease pellagra is approximately 8-13 mg per day. The RDA for adults is not less than 13 mg per day. Deficiencies can be treated with nicotinamide dosages up to 250 mg/day.

For the general population, the majority of exposure to nicotinamide occurs from its natural presence in animal products, whole cereals, and legumes, and its use as a direct food additive and dietary supplement. It is currently approved for use in pesticide products with a maximum of 0.5% in formulation applied to growing crops, including home gardens. The nonvolatile nature of nicotinamide, its use outdoors, and its limitation in formulation is expected to minimize any residential inhalation exposures. Dietary and dermal exposures from its use in pesticide products is expected to be less than from its natural occurrence in foodstuffs, its use as a direct food additive and dietary supplement, and its use in personal care products and cosmetics; therefore, dietary and dermal exposures of concern are not likely from its use in pesticide products.

Based on the 2002 OECD SIAR, nicotinamide is expected to partition primarily to water, undergoes a substantial degree of degradation in the sewage treatment plant, is readily biodegradable, and does not bioaccumulate. Therefore, nicotinamide is not expected to be present in drinking water at levels of concern from its use as an inert ingredient in pesticide formulations.

VII. Aggregate Exposure

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 nicotinamide, a qualitative assessment for all pathways of human exposure (food, drinking water, and residential) is appropriate given that it is an essential nutrient found naturally and as a direct food additive in many foodstuffs, and the lack of human health concerns associated with exposure to nicotinamide when used 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 safety finding as to nicotinamide and any other substances, and nicotinamide does not appear to produce toxic metabolites produced by other substances. For the purpose of these tolerance actions, therefore, EPA has not assumed that nicotinamide 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

Nicotinamide has low toxicity by the oral and dermal routes in animal studies, and is not considered mutagenic. It did show both promoting and antitumorigenic effects when administered with known carcinogens; however, no increase in tumors was seen in a lifetime carcinogenicity study of mice administered 1% nicotinamide in the diet. In a rat study using nicotinic acid, reproductive effects were only seen at maternally toxic doses. Nicotinamide is an essential nutrient required by the body for metabolic processes and disease prevention. It is found both naturally and as a direct food additive in many foodstuffs. Nicotinamide is metabolized and excreted by the body.

Based on its physical/chemical properties, biodegradation, and concentration limitation in pesticide formulations; dermal, inhalation, and dietary (food and drinking water) exposures of concern are not expected. Residential dermal exposure to nicotinamide used in pesticide products is of low human health concern as exposure is further limited by the maximum 0.5% in formulation and study results indicating it is non-irritating and non-sensitizing. Dietary and dermal exposures from its use in pesticide products are expected to be less than from its natural occurrence in foodstuffs, its use as a direct food additive and dietary supplement, and its use in personal care products and cosmetics.

Taking into consideration all available information on nicotinamide, including its lack of risk concerns, prevalence in the diet, and requirement by the body as an essential nutrient, EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to nicotinamide used as an inert ingredient in pesticide formulations when considering the dietary exposure and all other non-occupational 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 nicotinamide (limited to a maximum of 0.5% of formulation) on growing crops only can be considered reassessed as safe under section 408(q) of the FFDCFA.

X. Ecotoxicity and Ecological Risk Characterization

Nicotinamide is of low hazard to the aquatic environment and is currently of low priority for further work according to the 2002 OECD SIDS. It is of low acute toxicity to fish and aquatic invertebrates with LC₅₀/EC₅₀ values all in excess of 1000 mg/L. It is also of low acute toxicity to algae with EC₅₀ values in excess of 1000 mg/L and to microorganisms with an EC₁₀ value of 4235 mg/L. There are no available terrestrial data; however, based on available mammalian toxicity studies, including the rodent LD₅₀ values of 3-7 g/kg bw, the potential for adverse effects to non-target terrestrial animals is unlikely.

References:

EAFUS (Everything Added to Food in the United States) Database,
<http://vm.cfsan.fda.gov/~dms/eafus.html>, 7/20/2005.

McEvoy, Gerald, Pharm. D, Editor, AHFS (American Hospital Formulary Service)1997 Drug Information, pp. 2811-2813, 1997.

National Archives and Records Administration, Code of Federal Regulations,
<http://www.cfsan.fda.gov/~dms/reg-2.html>, 7/20/2005.

NTIS (National Technical Information Service), Evaluation of the Health Aspects of Niacin and Niacinamide as Food Ingredients, 1979.

OECD SIDS. Organisation for Economic Co-operation and Development – Screening Information Data Set. OECD Integrated High Production Volume (HPV) Chemical Database. October 2002. <http://cs3-hq.oecd.org/scripts/hpv/>

ORNL (Oak Ridge National Laboratory), Literature Summary Report (3-Pyridine carboxamide [98-92-0] (nicotinamide)), April 2005.

APPENDIX A

FDA Approved Uses of Nicotinamide

21 CFR § *	Applicable Citation **
137.260	<p>Sec. 137.260 Enriched corn meals.</p> <p>... (1) It contains in each pound not less than 2.0 milligrams (mg) and not more than 3.0 mg of thiamin, not less than 1.2 mg and not more than 1.8 mg of riboflavin, not less than 16 mg and not more than 24 mg of niacin or niacinamide, not less than 0.7 mg and not</p>
137.305	<p>Sec. 137.305 Enriched farina.</p> <p>... (1) It contains in each pound not less than 2.0 milligrams (mg) and not more than 2.5 mg of thiamin, not less than 1.2 mg and not more than 1.5 mg of riboflavin, not less than 16.0 mg and not more than 20.0 mg of niacin or niacinamide, not less than 0.7 mg and not more than 0.87 mg of folic acid, and not less than 13.0 mg of iron (Fe).</p>
137.350	<p>Sec. 137.350 Enriched rice.</p> <p>...(1) Not less than 2.0 milligrams (mg) and not more than 4.0 mg of thiamin, not less than 1.2 mg and not more than 2.4 mg of riboflavin, not less than 16 mg and not more than 32 mg of niacin or niacinamide, not less than 0.7 mg and not more than 1.4 mg of folic acid, and not less than 13 mg and not more than 26 mg of iron (Fe).</p>
139.115	<p>Sec. 139.115 Enriched macaroni products.</p> <p>... (1) Each such food contains in each pound not less than 4.0 milligrams (mg) and not more than 5.0 mg of thiamin, not less than 1.7 mg and not more than 2.2 mg of riboflavin, not less than 27 mg and not more than 34 mg of niacin or niacinamide, not less than 0.9 mg and not more than 1.2 mg of folic acid, and not less than 13 mg and not more than 16.5 mg of iron (Fe);</p>
139.117	<p>Sec. 139.117 Enriched macaroni products with fortified protein.</p> <p>(b)(1) Each food covered by this section contains in each pound 5 milligrams of thiamin, 2.2 milligrams of riboflavin, 34 milligrams of niacin or niacinamide, and 16.5 milligrams of iron.</p>
139.122	<p>Sec. 139.122 Enriched nonfat milk macaroni products.</p> <p>... (3) Each such food contains in each pound not less than 4.0 milligrams (mg) and not more than 5.0 mg of thiamin, not less than 1.7 mg and not more than 2.2 mg of riboflavin, not less than 27 mg and not more than 34 mg of niacin or niacinamide, not less than 0.9 mg and not more than 1.2 mg of folic acid, and not less than 13 mg and not more than 16.5 mg of iron (Fe). These substances may be added through direct addition or wholly or in part through the use of dried yeast, dried torula yeast, partly defatted wheat germ (as provided for in paragraph (a)(4) of this section), enriched farina, or enriched flour. They may be added in a harmless carrier, such carrier being used only in the quantity reasonably necessary to effect an intimate and uniform distribution of such substances in the finished food. Iron may be added only in a form that is harmless and assimilable.</p>

21 CFR § *	Applicable Citation **
139.155	<p>Sec. 139.155 Enriched noodle products.</p> <p>... (1) Each such food contains in each pound not less than 4 milligrams (mg) and not more than 5 mg of thiamin, not less than 1.7 mg and not more than 2.2 mg of riboflavin, not less than 27 mg and not more than 34 mg of niacin or niacinamide, not less than 0.9 mg and not more than 1.2 mg of folic acid, and not less than 13 mg and not more than 16.5 mg of iron (Fe)</p>
184.1535	<p>PART 184 DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE--Table of Contents</p> <p>Subpart B Listing of Specific Substances Affirmed as GRAS</p> <p>Sec. 184.1535 Niacinamide.</p> <p>(a) Niacinamide (C₆H₆N₂O, CAS Reg. No. 98-92-0) is the chemical 3-pyridinecarboxylic acid amide (nicotinamide). It is a white crystalline powder that is soluble in water, alcohol, ether, and glycerol. It melts between 128[deg] and 131 [deg]C.</p> <p>(b) The ingredient meets the specifications of the Food Chemicals Codex, 3d Ed. (1981), p. 205, which is incorporated by reference. Copies are available from the National Academy Press, 2101 Constitution Ave. NW., Washington, DC 20418, or available for inspection at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC 20408.</p> <p>(c) In accordance with Sec. 184.1(b)(1), the ingredient is used in food with no limitation other than current good manufacturing practice. The affirmation of this ingredient as generally recognized as safe (GRAS) as a direct human food ingredient is based upon the following current good manufacturing practice conditions of use:</p> <p>(1) The ingredient is used as a nutrient supplement as defined in Sec. 170.3(o)(20) of this chapter.</p> <p>(2) The ingredient is used in foods at levels not to exceed current good manufacturing practice. The ingredient may also be used in infant formula in accordance with section 412(g) of the Federal Food, Drug, and Cosmetic Act (the act) or with regulations promulgated under section 412(a)(2) of the Act.</p> <p>(d) Prior sanctions for this ingredient different from the uses established in this section do not exist or have been waived.</p>

*The FDA approved used of Niacinamide (nicotinamide) were found in the EAFUS (Everything Added to Food in the United States) Database found on the following website:

<http://vm.cfsan.fda.gov/~dms/efus.html>

**The information in the table is taken directly from the applicable parts and subparts of the Code of Federal Regulations found on the following website:

<http://www.access.gpo.gov/cgi-bin/cfrassemble.cgi?title=200421>