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

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

DATE: June 27, 2006

ACTION MEMORANDUM

SUBJECT: Reassessment of the One Exemption from the Requirement of a Tolerance for Copper Naphthenate (CAS Reg. No. 1338-02-9)

FROM: Pauline Wagner, Chief Pauline Wagner 6/30/06
Inert Ingredient Assessment Branch
Registration Division (7505P)

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

I. FQPA REASSESSMENT ACTION

Action: Reassessment of one inert exemption from the requirement of a tolerance. The reassessment decision is to maintain the inert tolerance exemption "as-is."

Chemical: Copper naphthenate

CFR: 40 CFR part 180.920

CAS Registry Number and Name: 1338-02-9; Naphthenic acids, copper salts

Use Summary: Copper naphthenate is approved by the Food and Drug Administration (FDA) as an indirect food additive, and for use in veterinary topical applications to the surface of horse and pony hooves that have Thrush. Commercial uses include use as a preservative in canvas, rope, tents, tarpaulins, gun covers, and varnishes.

List Reclassification Determination: The current List Classification for copper naphthenate is 3. Because EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to copper naphthenate when used as an inert ingredient in pesticide formulations, the List Classification for copper naphthenate will change from List 3 to List 4B.

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the one exemption from the requirement of a tolerance for the inert ingredient copper naphthenate (CAS Reg. No. 1338-02-9), and with the List reclassification determination, as described above. I consider the one exemption established in 40 CFR part 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, Director
Registration Division

7/3/06
Date:

cc: Debbie Edwards, SRRD
Joe Nevola, SRRD

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SUBJECT: Reassessment of One Exemption from the Requirement of a Tolerance for Copper Naphthenate (CAS Reg. No. 1338-02-9)

FROM: Debra Rate, Biologist
Technical Review Branch (TRB)
Registration Division (7505P)

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

BACKGROUND

Attached is the science assessment for copper naphthenate. This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, exposure profile, environmental fate, and ecotoxicity of copper naphthenate. The purpose of this document is to reassess the one existing exemption from the requirement of a tolerance for residues of copper naphthenate under 40 CFR 180.920 as required under the Food Quality Protection Act (FQPA).

EXECUTIVE SUMMARY

This report evaluates the use of copper naphthenate [CAS Reg. No. 1338-02-9] as an inert ingredient in pesticide products. The information presented in this report was derived from published and unpublished studies identified in searches of major bibliographic databases and reliable secondary references.

There is one tolerance exemption for residues of copper naphthenate when used in accordance with good agricultural practice as an inert ingredient in pesticide formulations applied to growing crops only (40 CFR 180.920). This use of copper naphthenate as an inert ingredient is greatly limited by the amount that can be applied and when it can be applied. The tolerance exemption's limitation states that not more than 2.5% copper naphthenate can be present in the pesticide formulation and products containing copper naphthenate can only be applied before the edible portions of plants begin to form. Copper naphthenate is also a pesticide active ingredient that is used as

a wood preservative (non-food use). In addition, non-pesticide commercial uses of copper naphthenate include veterinary topical treatments for hoof thrush and as an indirect food additive approved by the U.S. Food and Drug Administration (FDA).

Copper naphthenate is not sponsored under the Agency's High Production Volume (HPV) Challenge Program. Based on EPA's review of all pertinent Inventory Update Rule (IUR) data from 1998 and 2002, EPA determined that Naphthenic acids, copper salts (AKA Copper naphthenate) no longer meets the criteria for an HPV chemical.

Copper naphthenate appears to have low acute oral toxicity with LD_{50}'s ranging from 450 mg/kg to 6000 mg/kg body weight (bw) in rats. Several studies indicate that the acute inhalation toxicity is low with LC_{50}'s of >5.5 mg/kg bw when tested on rats. In subchronic/chronic dermal toxicity studies on rats, the lowest observable adverse effect level (LOAEL) was determined to be 100 mg/kg bw/day, and the no observable adverse effect level (NOAEL) for systemic toxicity was determined to be 1,000 mg/kg bw/day. No carcinogenicity studies have been reported for copper naphthenate. In a developmental study, the LOAEL for maternal toxicity was 100 mg/kg bw/day based on clinical signs, (reduced food consumption and reduced body weight) and the NOAEL was 30 mg/kg bw/day. The LOAEL for developmental toxicity was 300 mg/kg/day based on post implantation loss, and the NOAEL was 100 mg/kg bw/day.

Copper naphthenate functions in pesticide formulations as a mercaptan scavenger, which likely binds copper naphthenate to the moieties. This function serves to greatly reduce the potential for exposure. Considering the significant limitations on use and the mercaptan scavenger function, dietary and residential exposures of concern are not likely from the use of copper naphthenate as an inert ingredient in pesticide formulations.

Taking into consideration all available information on copper naphthenate, it has been determined that there is reasonable certainty that no harm to any population subgroup will result from aggregate exposure to copper naphthenate when used as an inert ingredient in pesticide formulation 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 one exemption form the requirement of a tolerance established for residues of copper naphthenate under 40 CFR 180.920, and limited to use as a mercaptan scavenger at not more than 2.5% of the formulation and applied before edible portions of plants begin to form, can be considered reassessed as safe under section 408(q) of the FFDCA.

I. Introduction

This report provides a qualitative assessment of copper naphthenate, an inert ingredient used as a mercaptan scavenger at a limit of 2.5% in pesticide formulations that is applied before edible portions of plants begin to form. Mercaptans are compounds of carbon, hydrogen and sulfur found in sour crude (crude oil with high sulfur content) and gas. A mercaptan scavenger neutralizes mercaptans by either oxidation or molecular

coupling to reduce their volatility. Copper naphthenate has one exemption from the requirement of a tolerance for its residues when used in accordance with good agricultural practice as an inert ingredient in pesticide formulations applied to growing crops only (40 CFR 180.920).

II. Use Information

A. Pesticides

As an inert ingredient, copper naphthenate is used mainly in insecticide and nematicide formulations when applied to soil and/or growing crops (prior to formation of edible parts). The tolerance exemption for copper naphthenate is provided in Table 1 below. In addition, copper naphthenate is a registered pesticide active ingredient for use as a wood preservative, a mildewcide in textiles, and fouling-inhibitor in boat paints.

Table 1. Tolerance Exemptions Being Reassessed in this Document

Citation as it Appears in the CFR				CAS Registry Number and Name
40 CFR 180	Tolerance Exemption Expression	Limits	Uses	
920[a]	Copper naphthenate	Not more than 2.5% of formulation; application limited to before edible portions of plants begin to form.	Mercaptan scavenger in technical pesticide.	1338-02-9 Naphthenic acids, copper salts

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

Copper naphthenate is approved by the Food and Drug Administration (FDA) as an indirect food additive, and for use in veterinary topical applications to the surface of horse and pony hooves that have Thrush (Tables 2 and 3). Commercial uses include use as a preservative in canvas, rope, tents, tarpaulins, gun covers, and varnishes.

Table 2. FDA Uses for Copper Naphthenate.

Name	21 CFR	Use Pattern
Copper Naphthenate	524.463	Topical use of copper naphthenate solution on horses and ponies as an aid in treating thrush caused by organisms susceptible to copper naphthenate. 37.5% in the formulation.

Table 3. FDA Indirect Food Additive Uses for Copper Naphthenate.

Name	21 CFR	Use Pattern
Copper Naphthenate	177.2430	Adjuvant substance used to facilitate the production of resins. It is used as an accelerator, not to exceed 1.5%.

III. Physical and Chemical Properties

Some of the physical and chemical characteristics of copper naphthenate, along with its structure and nomenclature, are found in Table 4. Copper naphthenate is commonly prepared by the direct reaction of naphthenic acid with copper(II) hydroxide or basic copper(II) carbonate in an organic diluent, or by precipitation from aqueous media when copper(II) sulfate solution is mixed with the sodium salt of the respective fatty acid. It can also be prepared by the addition of a solution of cupric sulfate to an aqueous solution of sodium naphthenate.

Table 4. Physical and Chemical Properties of Copper Naphthenate.

Parameter	Value	Reference
Structure	Unspecified	HSDB
CAS #	1338-02-9	
Empirical Formula	Variable	
Molecular Weight	405.86 (variable)	
Physical State	Solid: Green-blue	
Melting Point	Average ~ 102°C	
Boiling Point	154 - 202°C (310-395°F) @ 1 atm	
Water Solubility	Practically insoluble in water; soluble in most organic solvents.	
Other Solubility	Soluble in most organic solvents Moderately soluble in petroleum oils	
Relative Density (water=1)	1.055	
Vapor Pressure	<133 mPa @ 100 EC	
Heat of Combustion	-9.8 kcal / g	
Surface Tension	20 dynes / cm @ 20°C	
Other	Not compatible with concentrated acids and alkalis.	

IV. Hazard Assessment

This hazard assessment of copper naphthenate was developed using the BIBRA toxicity profile of copper napthenate, a robust study summary by Morning Star Consulting on the Metal Carboxylates Category (published on EPA's HPV Challenge website), and information in the Hazardous Substances Data Bank (HSDB).

A. Toxicological Data

Acute Toxicity

Several studies report oral LD_{50}'s in rats from 450 mg/kg to 6,000 mg/kg.

Lacap and Letizia, as cited in Morning Star Consulting, conducted an oral acute study according to the FIFRA 81-1 Guideline in which Sprague-Dawley rats were treated with

single doses (5/sex/dose) of an 8% solution of copper naphthenate dissolved in corn oil. The doses were 1000, 3000, 5000, 7000, 9000, and 10,000 mg/kg, with the LD_{50} reported to be 5800 mg/kg and a 95% confidence interval of 4580 - 7350 mg/kg. All mortalities, except for one, occurred within the first 4 days after dosing. Gross pathology of dead animals showed hemorrhagic lungs, darkened livers, slightly dark to dark kidneys and spleens, hemorrhagic stomachs and intestines with discolored fluids. The report noted that the test substance purity and composition were unknown (Lacap and Letizia, as cited in Morning Star Consulting).

Collins, as cited in Morning Star Consulting, using a FIFRA 81-3 Guideline procedure, treated Crl:CD(SD)BR rats (5/sex) to inhalation exposure of copper naphthenate in xylene for 4 hours at a measured concentration of 2.966 mg/L. The mean mass aerodynamic diameter of the particles in the chamber was 1.71 µm. Animals were observed for 14 days post-exposure. There were no deaths in the study, although treatment-related clinical signs were seen on the day of exposure. These included piloerection, salivation, nasal secretion, lethargy and respiratory distress. Body weight gain was slightly reduced in the treated animals. No treatment-related macroscopic abnormalities were observed. The LC_{50} was greater than 2.966 mg/L (Collins, as cited in Morning Star Consulting).

Provided in Table 5 is a summary of other LD_{50} and LC_{50} values for laboratory animals exposed to a single dose of copper naphthenate. Based on the oral LD_{50} values, copper naphthenate is of low to moderate acute oral toxicity. Based on the inhalation LC_{50} value, copper naphthenate is of moderate to high acute inhalation toxicity.

Table 5. Summary Of Acute Toxicity Data For Copper Naphthenate.

Route/organism	LD_{50} Dose	References
Oral/mouse	1900 - 2350 mg/kg	Angerhofer and Taylor, as cited in BIBRA
Oral/rat	>6000 mg/kg bw	Rockhold, as cited in BIBRA
Oral/rat	5800 mg/kg	Lacap and Letizia, as cited in Morning Star Consulting
Oral/rat	4000-6000 mg/kg bw	Chemical Hazard Response Information System, as cited in BIBRA
Oral/rat	2000 mg/kg bw	Farm Chemicals Handbook, as cited in BIBRA
Oral/rat	450 mg/kg bw	Spencer, as cited in BIBRA
Dermal/rabbit	>2000 mg/kg bw	Muni *et al.* , as cited in BIBRA
Dermal/rabbit	>2000 mg/kg bw	Angerhofer and Metker, as cited in BIBRA
Inhalation/rat	LC50 (4-h): >2.966 mg/L	Collins, as cited in Morning Star Consulting.
Inhalation/rat	LC50 (1-h): >5.5 mg/L	British Crop Protection Council, as cited in BIBRA
Oral / mouse	1897 mg/kg	Gigiena Truda I Professional'nye Zabolevaniya. Labor Hygiene and Occupational Diseases, 27(2): 52, 1983, as cited in RTECS
Oral / rat	2000 mg/kg	Farm Chemicals Handbook C81, 1991. (Meister Pub., Willoughby, OH), as cited in RTECS.

Dermal irritation: Contact with neat copper naphthenate on rabbit skin for 24 hours resulted in severe edema. Slight swelling was still visible at day 7 when skin crusting,

cracking, and bleeding were observed. By 21 days post-exposure the skin was normal (Muni et al., cited in BIBRA).

Oily solutions of two different wood preservatives containing 4.8% and 14.5% copper naphthenate were slightly irritating to the skin of guinea-pigs after a probable 24 to 48 hour, covered exposure (Angerhofer and Metker, and Angerhofer and Taylor, both as cited in BIBRA).

Eye irritation: No irritation of the rabbit eye was seen following instillation of a 0.1 mL volume of a 25% solution of a copper naphthenate-containing wood preservative in corn oil, providing 14.5% copper naphthenate (Angerhofer and Metker, cited in BIBRA). However, instillation of a 0.1 mL volume of another wood preservative (neat) containing 48% copper naphthenate was corrosive to the rabbit eye and caused severe damage even when the eyes were washed after a 20-second exposure. This wood preservative also contained 25% of an emulsifier that was a severe skin irritant (Angerhofer and Taylor, cited in BIBRA).

Sensitization: In two studies (Angerhofer and Metker, and Angerhofer and Taylor, both as cited in BIBRA) attempting to induce sensitization with copper naphthenate - containing wood preservatives, groups of 10 guinea pigs were treated once weekly for 3 weeks with a patch (probably 24 or 48 -hr contact) containing a minimally irritating oily solution of wood preservative. The final copper naphthenate concentrations that were applied in the two studies were 4.8 and 14.5%, respectively. After a 2-week rest period, the animals were challenged with a solution of the same preservative at the maximum, non-irritating concentration. The skin reactions to these challenge doses were described as no greater than after the initial application. The preservative formulations were considered to lack sensitizing potential.

Subchronic/Chronic Toxicity:

Tomkins, cited in Morning Star Consulting, used the FIFRA 82-3 Guideline procedure and treated Crl:CD BR rats (10/sex/dose) with dermal applications of copper naphthenate (9.5% copper, purity not specified), 6 hours/day for 13 weeks at doses of 100, 300 and 1000 mg/kg/day. The test material was dissolved in light mineral oil at a concentration of 80% by weight and applied to the clipped, intact dorsal skin of each animal. After application, the test sites were wrapped with a gauze binder and secured with Deriform tape. At the end of each exposure the dressings were removed and the test sites were wiped with paper towels moistened with mineral oil. The concurrent controls were treated with mineral oil only at a dose volume equal to the amount of vehicle received by the high-dose group. Erythema and edema were observed in all dose groups during the study. The frequency and severity of effects were dose-related. The severity of both findings increased during the first four weeks of dosing, then decreased. Histopathology revealed a low incidence of dermal hyperplasia, supportive inflammation and hyperkeratosis in the mid- and high-dose groups. No effects on survival, clinical observations and other parameters of systemic toxicity were seen in any dose group during the study. The NOAEL for systemic toxicity was 1000 mg/kg/day

and the LOAEL was undetermined. The LOAEL for dermal toxicity was 100 mg/kg/day, based on erythema and edema, and the NOAEL was undetermined (Tomkins, cited in Morning Star Consulting).

Genetic toxicity:

Desai et al., cited in Morning Star Consulting, performed an *in vitro* mutagenicity test, using the Ames bacterial/microsomal plate incorporation assay, following Guidelines from TSCA 40 CFR Part 798.5265. *Salmonella* strains TA98, TA100, TA1535 and TA1538 were exposed to doses of copper naphthenate (purity and composition not stated) from 0.05 to 0.5 µg/plate, both with and without activation (activation was with rat liver S-9 microsomes). Dose levels of 1000 µg/plate were reported as cytotoxic. The test material was dissolved in dimethyl sulfoxide (DMSO) and the assays were run in triplicate. A negative control and four positive controls were also included. The test material did not cause any significant increase in the number of histidine revertants and produced results similar to the negative control, so it was considered non-mutagenic in this assay.

Harbell, cited in Morning Star Consulting, used the FIFRA 84-2 Guideline method to carry out a mouse lymphoma mutagenesis assay with L5178Y TK +/- cells. Concentrations of the test material were prepared in acetone and ranged from 3.2 to 42 µg/mL with activation (Aroclor-induced S-9 fraction) and 4.2 to 56 µg/mL without activation. A confirmatory test used concentrations of 7.5 to 36 µg/mL both with and without activation. In both the initial and confirmatory assays, copper naphthenate appeared to be more toxic with metabolic activation. Cytotoxicity was reported to be 100% at a concentration of 100 µg/mL. The copper naphthenate did not induce a significant number of mutations in the absence of activation, but produced a dose-dependent mutation response in the presence of an activating system. Positive results with activation were seen in both the initial and confirmatory assays. In both assays with activation, there appeared to be an increase in the relative proportion of small colonies.

Putman and Morris, cited in Morning Star Consulting, carried out a chromosome aberration study with the test material using Chinese hamster ovary (CHO) cells according to FIFRA 84-2 Guidelines. Acetone was used to dissolve the test material and as a solvent control. Triethylenemelamine and cyclophosphamide were used as positive controls. Test material was tested at concentrations up to 200 µg/mL in an activated system (S-9 fraction from Sprague-Dawley rats induced with Aroclor) and up to 160 µg/mL in an unactivated system. Cytotoxicity was noted at ~60 µg/mL with activation and at ~80 µg/mL without activation. Generally, a minimum of 100 metaphase spreads (50 per duplicate flask) were scored for chromatid- and chromosome-type aberrations. No significant increase in aberrations was seen either with or without activation. While a marginal increase in the number of aberrations was seen in the activated system at a concentration of 60 µg/mL, repeated testing at similar and higher concentrations was negative.

In two dominant lethal assays carried out by Angerhofer and Metker and Angerhofer and Taylor, both as cited in BIBRA, groups of ten male mice were treated with doses of copper naphthenate up to ~470 mg/kg/day by stomach tube for 5 day. When the males were mated with untreated females, there was no reduction in reproductive efficiency and it was concluded that copper naphthenate showed a lack of mutagenic activity. However, it should be pointed out that only the most mature male germ cells (spermatozoa and late spermatids) were being sampled in this test.

An unscheduled DNA synthesis (UDS) test was carried out according to Guideline method FIFRA 84-2 and OECD 482 by Curren, cited in Morning Star Consulting. Rat (Sprague-Dawley) primary hepatocyte cultures were treated with the test material, dissolved in acetone, at concentrations from 0.5 to 50 µg/mL. UDS was assessed by the incorporation of ^{3}H-thymidine into the cells. Cells exposed to 15 µg/mL exhibited signs of toxicity, with some cells having small and irregularly shaped nuclei. Only nuclei with acceptable morphology were evaluated for UDS. The copper naphthenate caused no significant increase in mean net nuclear grain counts (an increase of at least 5 counts over solvent control was considered significant) at concentrations that were not cytotoxic (0.15 to 5.0 µg/mL). All criteria for a valid test were met and it was concluded that the copper naphthenate gave a negative result in the UDS study.

An *in vitro* mutagenesis study of copper naphthenate by Angerhofer and Taylor, cited in BIBRA, using the Ames test in *Salmonella typhimurium*, found no evidence of mutagenicity either with or without activation.

In tests for chromosome aberrations in hamster ovary cells and mutagenicity in mouse cells, with and without activation, Angerhofer and Taylor, cited in BIBRA, found that copper naphthenate had no activity.

Carcinogenicity:

No relevant carcinogenicity data for copper naphthenate have been identified. A Shell 1982 study, cited in BIBRA, reported that repeated dermal applications (twice weekly for 2 years) of calcium naphthenate produced skin tumors in female mice.

Developmental toxicity / Reproductive Toxicity and Teratogenicity:

A teratology/developmental toxicity study was carried out by Nemec, cited in Morning Star Consulting, according to the FIFRA 83-3 Guideline. The copper naphthenate (9.5% copper, purity not specified) was dissolved in corn oil and administered by gastric gavage (dose volume: 10 mL/kg) to pregnant Sprague-Dawley rats (25 positively mated females/dose group) from day 6 through day 15 of gestation at doses of 30, 100 and 300 mg/kg/day. Control females received only corn oil. Animals were sacrificed on day 20 of gestation and the uteri and ovaries were examined. The location and number of fetuses, early and late resorptions, total implantations and corpora lutea were recorded. Fetuses were weighed, sexed and examined for external, skeletal and soft tissue malformations and developmental variations. Clinical signs of maternal toxicity were

seen in the mid- and high-dose groups that included reduced food consumption and reduced body weight. Post-implantation loss was slightly increased in the high-dose group due to one female with an entire litter resorbed. However, this was the only developmental effect that was considered to be possibly treatment-related. The LOAEL for maternal toxicity was 100 mg/kg/day, based on clinical signs, reduced food consumption and reduced body weight, and the LOAEL for developmental toxicity was 300 mg/kg/day. The NOAEL for maternal toxicity was 30 mg/kg/day and the NOAEL for developmental toxicity was 100 mg/kg/day (Nemec, cited in Morning Star Consulting).

Hardin *et al.* (1981) carried out what they described as "preliminary studies" on the teratogenic potential of copper naphthenate. While the i.p. route of exposure used in this study is not a human route of exposure, data on the developmental toxicity of copper naphthenate is limited and this study does give some supporting evidence that copper naphthenate is not likely a developmental toxicant to humans. The maximum tolerated dose (MTD) was established for copper naphthenate by injecting non-pregnant rats with different doses of the test material. The MTD was defined as the highest dose at which there was no mortality, no marked signs of toxicity (e.g., unconsciousness) and less than a 10% reduction in body weight gain relative to the control within two weeks following 15 daily intraperitoneal (i.p.) injections of the test material. After establishing an MTD of 10 mg/kg for copper naphthenate (dissolved in corn oil), the investigators gave i.p. injections to between 10 and 15 pregnant Sprague-Dawley rats on day 1 through day 15 of gestation. Controls received corn oil injections only. On day 21 of gestation the females were killed and individual fetuses were weighed, measured for crown-rump length, sexed and examined for externally visible malformations. A half or more of each litter was preserved in Bouin's fixative for internal examination by the Wilson method of free-hand sectioning and the balance of each litter was preserved in ethanol for clearing and skeletal staining with alizarin red. The internal organs of the maternal rats were examined grossly, and the brain, heart, lungs, liver, spleen, kidneys, adrenals and ovaries were weighed and preserved in 10% formalin for histopathological examination. There were no signs of maternal toxicity as measured by reduced body weight gain or altered weights (absolute or relative) of two or more organs (statistical significance was set at $p < 0.05$). No fetal toxicity was noted as measured by reduced pre- or post-implantation survival, reduced fetal body weight or length. No developmental effects were noted as measured by grossly visible external or internal (visceral or skeletal) malformations. While the i.p. route of exposure used in this study is not a human route of exposure, data on the developmental toxicity of copper naphthenate is limited and this study does give some supporting evidence that copper naphthenate is not likely a developmental toxicant to humans (Hardin *et al.*, 1981).

Neurotoxicity:

No neurotoxicity studies on copper naphthenate were identified. Exposure to naphthenic acids increases the permeability of membranes to potassium, which could affect nerve transmission (National Library of Medicine, 1995).

C. Metabolism and Pharmacokinetics

Little information on the metabolism of copper naphthenate has been reported. Copper is generally cleared from the body unless in acutely toxic quantities. Copper is stored in the liver and marrow (National Library of Medicine, 1995).

D. Special Considerations for Infants and Children

Copper naphthenate is likely of low toxicity for human health effects endpoints (including developmental and reproductive effects) based on available rodent information. In a developmental toxicity study, developmental NOAELs and LOAELs were greater than maternal NOAELs and LOAELs. The results suggest that offspring do not have greater sensitivity to copper naphthenate than adults.

Based on this information there is no concern, at this time, for increased sensitivity to infants and children to copper naphthenate 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 and Drinking Water Considerations

Copper napthenate is composed of copper and napthenic acid. Copper naphthenate functions in pesticide formulations as a mercaptan scavenger, which likely binds copper naphthenate to the other moieties. This function serves to greatly reduce the potential for exposure. Considering this mercaptan scavenger function and limited allowable use in pesticide products (not more than 2.5% in pesticide formulation; applied before the edible portions of plants begin to form), contributions to drinking water are not anticipated.

Copper

As an element, copper will continue to cycle through geochemical processes without degradation once introduced into the environment. The eventual environmental sink is soil or sediment. Availability and toxicity of copper in these (and other) media is driven by physico-chemical parameters such as pH, redox potential, and amount of organic matter in the media.

The availability of copper in the formulated product is governed by the stability constant of copper napthenate and the stability constants of compounds it may form with the mercaptans and/or other ligands in the formulation. As these may not be readily available, the most conservative estimate of availability is to assume that 100% of the copper used in the product is free to move through the environment upon application. Assuming copper to be approximately 19% (by weight) of copper napthenate (Equation 1), application of 1 pound (lb) of formulated product would contain approximately 0.0048 lb copper (Cu) (Equation 2).

Equation 1:
% Cu in Copper napthenate = (MW Cu/(MW Cu + mean MW Napthenic Acid))*100%
MW Cu = 63.54 g/mole
Mean MW napthenic acid = (180 +350)/2 g/mole = 265
(63.54 g/mole/(63.54 g/mole +265 g/mole))*100% = 19%

Equation 2:
1 lb formulated product *2.5 % copper napthenate *19% Cu = 0.0048 lb Cu

Napthenic Acid

The napthenic acid was also assumed to be 100% available. Assuming copper to be approximately 19% (by weight) of copper napthenate (Equation 3), application of 1 lb of formulated product would contain approximately 0.020 lb napthenic acid (Equation 4). Application of 10 lbs of product would release 0.2 lbs of Cu.

Equation 3:
% Napthenic Acid in Copper napthenate =
(MW Napthenic Acid/(MW Cu + mean MW Napthenic Acid))*100%
MW Cu = 63.54 g/mole
Mean MW napthenic acid = (180 +350)/2 g/mole = 265 g/mole
(265 g/mole/(63.54 g/mole +265 g/mole))*100% = 81%

Equation 4:
1lb formulated product *2.5 % copper napthenate *81% napthenic acid =
0.020 lb napthenic acid

VI. Exposure Assessment

Commercial uses of copper naphthenate include use as a preservative in canvas, rope, tents, tarpaulins, gun covers, and varnishes. In addition, copper naphthenate is a registered pesticide active ingredient for use as a wood preservative, a mildewcide in textiles, and fouling-inhibitor in boat paints. It is also approved by FDA as an indirect food additive, and for use in veterinary topical treatments to the surface of horse and pony hooves that have Thrush.

This use of copper naphthenate as an inert ingredient in pesticide products is greatly limited by the amount that can be applied and when it can be applied. The tolerance exemption's limitation states that not more than 2.5% copper naphthenate can be present in the pesticide formulation. In addition, products containing copper naphthenate can only be applied before the edible portions of plants begin to form, which effectively limits the number of applications. These limitations on use significantly reduce the likelihood of residues on food or of residential exposures (inhalation and dermal), and contributions to drinking water are not anticipated. Copper naphthenate

functions in pesticide formulations as a mercaptan scavenger, which likely binds copper naphthenate to the other moieties. In addition to its limited use, this scavenger function serves to, and greatly reduces, the potential for dietary and residential exposures. Therefore, dietary and residential exposures of concern are not likely from the use of copper naphthenate as an inert ingredient in pesticide formulations.

VII. Aggregate Exposures

In examining aggregate exposure, the FFDCA section 408 directs EPA to consider available information concerning exposures from the pesticide residue in food and all other nonoccupational 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 copper naphthenate, 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 the low levels of exposure to this chemical when used as an inert ingredient in pesticide formulations.

VIII. Cumulative Exposure

Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency considers "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 copper naphthenate and any other substances and, this material does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that copper naphthenate 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

Copper naphthenate appears to have low acute oral and dermal toxicity with rodent LD_{50} values in excess of 2000 mg/kg. Acute inhalation studies demonstrate low toxicity with LC_{50} values of > 5.5 mg/L. Copper naphthenate also was not genotoxic in non-mammalian cells *in vitro*, however, one study with mammalian cells indicated a positive

response when in the presence of an activating system. In a developmental toxicity study, developmental NOAELs and LOAELs were greater than maternal NOAELs and LOAELs, which suggests that offspring do not have greater sensitivity to copper naphthenate than adults. No repeat dose oral studies were identified except for the developmental study discussed above.

Although no oral repeat dose studies were found (except for developmental toxicity), the toxicity information available on copper naphthenate is sufficient to make the safety finding. Exposure to copper naphthenate as an inert ingredient is unlikely because the process of treating ("scavenging") corrosive mercaptans results in the binding of copper naphthenate to other moieties, which greatly reduces the amount of unchanged copper napthenate that remains available. In addition, registrants will add only the minimum amount of copper napthenate necessary to complete the mercatptan scanenger purpose. The tolerance exemption limits the amount of copper napthenate that can be added to no more than 2.5% in pesticide formulations, and only in pesticide products that are only applied to growing crops prior to the formation of the edible parts of the plant. Therefore, dietary (food and drinking water) and residential (inhalation and dermal) exposures of concern are unlikely with copper naphthenate when used as an inert ingredient in pesticide products.

Taking into consideration all available information on copper naphthenate, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to copper naphthenate when considering exposure through food commodities and all other non-occupational sources for which there is reliable information. Therefore, it is recommended that the one exemption from the requirement of a tolerance established for residues of copper naphthenate when used on growing crops can be considered reassessed as safe under section 408(q) of the Federal Food, Drug, and Cosmetic Act (FFDCA).

X. Ecotoxicity and Ecological Risk Characterization

Copper

Toxicity of copper in aquatic ecosystems is greatly influenced by water chemistry, especially pH, alkalinity, and the amount of dissolved organic carbon. Systems with low concentrations of any or all of these chemical constituents are high toxicity situations for copper. Toxicity values for aquatic organisms presented in Table 6 will vary by site depending on the water chemistry of that specific waterbody. Toxicity values for freshwater organisms have been normalized to a standard laboratory water chemistry using the Biotic Ligand Model (EPA 2003).

Table 6. Aquatic Toxicity of Copper

Common Name	Scientific Name	LC_{50} (g/L) Dissolved Cu	Toxicity Rating	Reference
Freshwater				
Green Alga	*Selenastrum capricornutum*	3.1	Not applicable	MRID 43363603
Water Flea (Invertebrate)	*Daphnia*	3.6	Very highly toxic	EPA 2003
Salmonids (Fish)	*Onchorynchus*	29.1	Very highly toxic	EPA 2003
Saltwater				
Marine Diatom	*Skeletonema costatum*	250	Not applicable	MRID 43363605
Mussel	*Mytilus*	6.2		EPA 2003
Summer Flounder	*Paralichthys dentatus*	12.7	Very highly toxic	EPA 2003

Copper is moderately toxic to terrestrial organisms (Table 7). Copper toxicity appears to vary depending on the ligand attached to the copper atom, and the dietary matrix.

Table 7. Copper Toxicity to Terrestrial Organisms

Common Name	Type of Study	LC_{50} (mg/kg)	Toxicity Rating	Reference
Bobwhite quail	Acute oral	98	Moderately toxic	MRID 00067456
Bobwhite quail	Acute dietary	991	Moderately toxic	MRID 00811103
Rat (female)	Acute oral	114	Moderately toxic	MRID 43396201

Napthenic Acid

Napthenic acids are slightly-to-moderately toxic to aquatic organisms (Table 8), and practically non-toxic to mammals (Table 9) on an acute basis. Some mammalian studies noted reproductive effects such as reduced fertility at an oral dose of 60 mg/kg/day (MorningStar 2005).

Table 8. Freshwater Aquatic Toxicity of Napthenic Acid

Common Name	Scientific Name	LC_{50} (mg/L)	Toxicity Rating	Reference
Alga	*Navicula seminulum*	30.5-80.5	Slightly toxic	MorningStar 2005
Invertebrate	*Nitocra spinipes*	4.8	Moderately toxic	
Zebra Fish[1]	*Brachydanio rerios*	16.3	Slightly toxic	
Zebra Fish embryo	*Brachydanio rerios*	3.5	Moderately toxic	
Three-spine Stickleback	*Gasterosteus aculeatus*	5.0	Moderately toxic	
Bluegill	*Lepomis macrochirus*	5.6	Moderately toxic	

[1] Reported as TLm in text, and 96-h LC_{50} in supporting table

Table 9. Napthenic Acid Toxicity to Terrestrial Organisms

Common Name	Type of Study	LC_{50} (g/kg)	Toxicity Rating	Reference
Rat	Acute oral	5.9	Practically non-toxic	MorningStar 2005
Mouse	Acute oral	3.6	Practically non-toxic	

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