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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

**DATE:** April 22, 2005

**ACTION MEMORANDUM**

**SUBJECT:** Inert Reassessment – Three Exemptions from the Requirement of a Tolerance for Cyclohexane (CAS# 110-82-7) and Cyclohexanone (CAS# 108-94-1)

**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 inert exemptions from the requirement of a tolerance. The tolerance exemptions are to be maintained.
**Chemical:** Cyclohexane and cyclohexanone
**CFR:** 40 CFR part 180.920 (both chemicals) and 930 (cyclohexanone)
**CAS #:** 110-82-7 and 108-94-1

**Use Summary:** Cyclohexane and cyclohexanone are used as solvents and co-solvents in a variety of pesticide products, including outdoor yard, garden, and turf products, and agricultural crop products. Cyclohexanone is also found in products applied to animals to control pests such as flies. They are used in the manufacture of a variety of consumer products, including nylon, lacquers, paints, varnishes, and paint removers. Cyclohexane occurs naturally in petroleum crude oil and in volcanic gases.

**List Reclassification Determination:** Currently List 2s, both chemicals can be reclassified to List 4b based on the low risk findings.

## II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the three exemptions from the requirement of a tolerance for the inert ingredients cyclohexane (CAS# 110-82-7) and cyclohexanone (CAS# 108-94-1), and with the List reclassification determinations, as described above. I consider the three exemptions established in

40 CFR part 180.920 (both chemicals) and 930 (cyclohexanone) 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.

Betty Shackleford for

Lois A. Rossi, Director
Registration Division

Date: 5/11/05

CC: Debbie Edwards, SRRD
Joe Nevola, SRRD

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

April 25, 2005

**MEMORANDUM**

SUBJECT: Reassessment of Three Exemptions from the Requirement of a Tolerance for Cyclohexane and Cyclohexanone

FROM: Karen Angulo
Minor Use, Inerts and Emergency Response Branch
Registration Division (7505C)

THRU: Pauline Wagner 5/2/05
Inerts Coordinator
Registration Division (7505C)

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

## I. Background

The attached science assessment for cyclohexane and cyclohexanone summarizes available information on the use, physical/chemical properties, toxicological effects, exposure profile, and environmental fate of these two pesticide inert ingredients. The purpose of this document is to evaluate for reassessment the three existing exemptions from the requirement of a tolerance for residues of the two inert ingredients as required under the Food Quality Protection Act (FQPA) section 408.

## II. Executive Summary

This report evaluates cyclohexane and cyclohexanone, pesticide inert ingredients that each have an exemption from the requirement of a tolerance for pesticide residues when used in

pesticide formulations as a solvent/co-solvent applied to growing crops only under 40 CFR §180.920 [formerly 40 CFR §180.1001(d)]. This assessment also includes one exemption for cyclohexanone when applied to animals under 40 CFR §180.930 [formerly 40 CFR §180.1001(e)].

Cyclohexane and cyclohexanone are volatile, flammable chemicals that are used as solvents and co-solvents in a variety of pesticide products (including outdoor yard, garden, and turf products, and agricultural crop products). They are used in the manufacture of a variety of consumer products, including nylon, plasticizers, lacquers, resins, and paints. Cyclohexane occurs naturally in petroleum crude oil, in volcanic gases, and in cigarette smoke.

Sufficient toxicity data and information on cyclohexane and cyclohexanone are available from a variety of sources. A qualitative assessment for all pathways of human exposure (food, drinking water, and residential) is appropriate given the lack of human health concerns associated with exposure to these chemicals from pesticide products.

Cyclohexane and cyclohexanone have low acute and chronic toxicity for endpoints of concern based on the available information, and are not considered to be genotoxic or carcinogenic. They are slight to moderate eye, skin, and respiratory irritants, but they do not induce sensitization. Central nervous system (CNS) effects can result from exposure to these chemicals, but at doses higher than are expected to occur from pesticidal uses. Reproductive and developmental studies show no toxicity or sensitivity issues of concern. Based on their biodegradability and volatile nature combined with the outdoor use pattern, these chemicals are not expected to be present in the diet or drinking water at levels that would be of concern to EPA. In addition, ecological risk concerns are not likely to occur from the use of cyclohexane and cyclohexanone as pesticide inert ingredients.

Taking into consideration all available information on cyclohexane and cyclohexanone, it is determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to these chemicals 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 three exemptions from the requirement of a tolerance established for residues of cyclohexane and cyclohexanone in/on raw agricultural commodities and animals can be considered reassessed as safe under section 408(q) of the FFDCA.

## III. Introduction

This report evaluates the pesticide inert ingredients cyclohexane and cyclohexanone, which each have an exemption from the requirement of a tolerance when used in pesticide formulations as a solvent/co-solvent when applied to growing crops only under 40 CFR §180.920 [formerly 40 CFR §180.1001(d)]. This assessment also includes one exemption for cyclohexanone when applied to animals under 40 CFR §180.930 [formerly 40 CFR §180.1001(e)].

The assessments of cyclohexane and cyclohexanone have been grouped together in this document because they are structurally related, share similar use patterns and potential routes of exposure.

## IV. Use Information

### A. Pesticide Uses.

Cyclohexane and cyclohexanone are used as solvents and co-solvents in a variety of pesticide products, including outdoor yard, garden, and turf products, and agricultural crop products. Cyclohexanone is also found in products applied to animals to control pests such as flies. The three tolerance exemptions for the three chemicals are given in Table 1 below.

**Table 1. Tolerance Exemption Being Reassessed in this Document**

| Tolerance Exemption Expression | CAS Reg No. | 40 CFR § | Use (Pesticidal) | List Classification |
|---|---|---|---|---|
| Cyclohexane | 110-82-7 | 180.920[1] | solvent/cosolvent | 2 |
| Cyclohexanone | 108-94-1 | 180.920[1] | solvent/cosolvent | 2 |
| | | 180.930[2] | solvent/cosolvent | |

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.

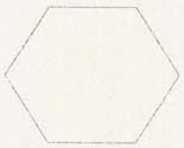
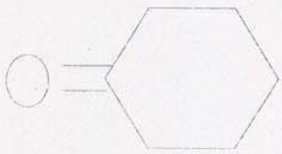
2. Residues listed in 40 CFR §180.930 [formerly 40 CFR§ 180.100(e)] are exempted from the requirement of a tolerance when used as inert ingredients in pesticide formulations when applied to animals only.

### B. Other Uses.

Cyclohexanone and cyclohexane are used in the manufacture of a variety of consumer products, including as an intermediate in the production of nylon, plasticizers, and other chemicals, and as a solvent for materials such as lacquers, resins, polymers, paints, varnishes, and paint removers. Cyclohexane occurs naturally in petroleum crude oil, in volcanic gases, and in cigarette smoke.

## V. Physical and Chemical Properties

Table 2

| Physical/Chemical | Cyclohexane | Cyclohexanone |
|---|---|---|
| CAS # | 110-82-7 | 108-94-1 |
| Molecular formula | C6-H12 | C6-H10-O |
| Structural formula |  |  |
| Molecular weight | 84.16 | 98.14 |
| Physical state | Liquid | Liquid |
| Vapor Pressure | 77 mm Hg at 68°F (20°C) | 5 mm Hg at 68°F (20°C) |
| Flash Point | -4°F (-20°C) | 111°F (43.9°C) |
| Water Solubility | Insoluble, 55 mg/L @ 25$^0$C | Soluble, 8.7g/ml @ 25$^0$C |
| Henry's Law constant | 0.195 atm.m$^3$/mol @ 25$^0$C | 9.00E-06 atm.m$^3$/mol @ 25$^0$C |
| Log KOW | 3.44 | 0.81 |

## VI. Hazard Assessment

### A. Hazard Profile

This hazard assessment was developed using robust summaries of information and data that have been reviewed by qualified scientists that are provided in reports from EPA's Integrated Risk Information System (IRIS), European Commission's Joint Research Centre (EU JRC), National Library of Medicine's Hazardous Substances Database (HSDB), and Organization for Economic Cooperation and Development's SIDS Initial Assessment Report (OECD SIAP).

### B. Metabolism and Pharmacokinetics

Regarding metabolism and pharmacokinetics, cyclohexane is readily distributed to all tissues with a preference for adipose tissues. Cyclohexane is rapidly metabolized in the liver, leading to the formation of various quantities of cyclohexanol, cyclohexanone, and 1,2- and 1,4-cyclohexanediols. In humans, the main metabolic pathway leads to the formation of a majority of 1,2- and 1,4-cyclohexanediols excreted unchanged for 1,4-cyclohexanediol and in glucuronide form for 1,2-cyclohexanediols. Elimination via the lungs is the major route of excretion (higher with increasing doses of cyclohexane) as unchanged cyclohexane or $CO_2$. Elimination of metabolites is quite slow in the urine, and biological half-lives in humans is estimated to be 5 hours by inhalation. No additional information on metabolism was found for cyclohexanone beyond what is summarized above for cyclohexane.(EU JCR, 2004)

### C. Toxicological Data for Cyclohexane

In EPA's Office of Pollution Prevention and Toxics' Chemical Summary for Cyclohexane (EPA OPPT, 1994), acute toxicity in humans was described as being low, producing eye irritation in humans. Undiluted cyclohexane is irritating to the skin. No dose levels were provided. In animals, neurological symptoms and organ effects were seen at lethal levels. The oral LD50 in rats ranges from 8.0 to 39 mL/kg (both greater than 5 g/kg) depending upon the age of the animals. The oral LD50 for mice is 1.3 g/kg. Rats exposed by inhalation to 2,500 ppm of cyclohexane for 9 to 10 hours/day, 5 days/week for up to 30 weeks exhibited no adverse effects.

The EU's JRC reported that available LD50s and LC50s show that the chemical is of low toxicity via all routes of administration. Neurobehavioral toxicity studies performed on rats and humans show that cyclohexane has narcotic properties, with No Observable Adverse Effect Levels (NOAEL) of 400 ppm (1,400 $mg/m^3$) in rats and 250 ppm (860 $mg/m^3$) in humans. In addition, cyclohexane is almost completely absorbed by the oral and inhalation routes. Elimination via the lungs is the major route of excretion. Dermal absorption of pure liquid cyclohexane is expected to be 5%, and is a minor route of exposure for cyclohexane. Long-term and repeat exposure to liquid cyclohexane can result in defatting of the skin. (EU JRC, 2004).

The following summarizes several of the toxicological studies evaluated in the cyclohexane risk assessment developed by the European Commission's Joint Research Center (EU JRC, 2004):

- In repeat dose inhalation studies in mice and rats, slight liver effects were induced after sub-acute and sub-chronic exposure; the NOAEL for hepatic effect is estimated to be 2,000 ppm (6,880 $mg/m^3$).
- Neurobehavioral toxicity studies show that cyclohexane has narcotic properties, with a NOAEL of 400 ppm (1,400 $mg/m^3$) in rats and 250 ppm (860 $mg/m^3$) in humans.

- No developmental effects were observed in two developmental studies performed in rats and rabbits. The highest dose tested (7,000 ppm [24,080 mg/m$^3$]) was considered the NOAEL for fetuses, and a NOAEL of 500 ppm (1,720 mg/m$^3$) for dams.

In EPA's IRIS (2003) report, a two-generation inhalation reproduction toxicity study in rats conducted with cyclohexane was selected as the principal study in determining the inhalation Reference Concentration (RfC). Male and female rats were exposed by whole body inhalation to cyclohexane vapor at 0, 500, 2,000 or 7,000 ppm (0, 1,721, 6,886, or 24,101 mg/m$^3$). After 10 weeks of exposure, the animals were bred within their respective treatment groups and allowed to deliver and rear their offspring until weaning. At weaning, F1 rats were treated to the same exposure schedule as the P1 generation. At least 11 weeks after weaning, the F1 rats were bred to produce the F2 litters. The study's authors concluded that inhalation exposure of rats to 24,101 mg/m$^3$ (Lowest Observable Adverse Effect Level [LOAEL]) cyclohexane vapors produced significant reductions in body weights in P1 and F1 females and F1 males, and significant reductions in pup weights from lactation days 7 to 25 for F1 and F2 litters. The NOAEL of 6,886 mg/m$^3$ (2,000 ppm) was determined, and an inhalation RfC of 6 mg/m$^3$ was calculated using an uncertainty factor of 300, including a factor of 10 for database deficiencies (no chronic or lifetime animal studies). An additional factor was not used to account for the extrapolation from endpoints in less-than-chronic studies to chronic effects because developmental toxicity (reduced pup weight during lactation) was used as the critical effect. (Table 3) (IRIS 2003)

**TABLE 3. IRIS (2003) Inhalation RfC Summary for Cyclohexane**

| Critical Effect | Experimental Doses[1] | Uncertainty Factor | RfC[2] |
|---|---|---|---|
| Rat, 2-generation inhalation reproductive toxicity study – Reduced pup weights in the F1 and F2 generations | NOAEL: 6,886 mg/m$^3$ (2,000 ppm)<br>LOAEL: 24,101 mg/m$^3$ (7,000 ppm) | 300 | 6 mg/m$^3$ (1.74 ppm) |

1. Exposure concentrations were reported in ppm and converted to mg/m$^3$ using the following formula: mg/m$^3$ = (ppm)(MW)/24.45; where the molecular weight (MW) used for cyclohexane was 84.2 g/mol.
2. The RfC was derived by dividing the Human Equivalent Concentration (HEC) benchmark concentration limit of 1,822 mg/m$^3$ by the product of uncertainty factors (UFs) or 300, equaling 6 mg/m$^3$.

In reproductive toxicity studies on cyclohexane, a slight decrease in rat pup weight was observed at 7,000 ppm, but was accompanied by slight maternal toxicity. A NOAEL of

6,880 mg/m$^3$ (2,000 ppm) was determined for pups, whereas a NOAEL of 1,720 mg/m$^3$ (500 ppm) was derived for maternal toxicity. (EU JRC, 2004)

In an inhalation developmental toxicity study of cyclohexane with rats, adult maternal body weights were significantly reduced at 24,101 mg/m$^3$. While developmental toxicity was not detected, the standard prenatal developmental study does not extend into the lactation period, which is where the reduced pup weight effect was found in the two-generation reproductive toxicity study. Maternal and fetal effects were not detected in a similar developmental toxicity study of rabbits. (IRIS 2003)

EPA's IRIS (2003) concluded that there are inadequate studies for characterizing human carcinogenicity potential. Genotoxicity studies are generally negative. The EU JRC (2004) reported "It was demonstrated in a questionable study that cyclohexane might have a weak promotion potential. Despite the lack of a conventional two-year carcinogenicity test, cyclohexane is not considered likely to be carcinogenic." Available mutagenicity studies do not indicate that cyclohexane has genotoxic properties.

**D. Toxicological Data for Cyclohexanone**

OECD's SIAP (1996) concluded that cyclohexanone exhibited low to slight acute toxicity by the oral and inhalation routes. It is an eye and skin irritant, however, it did not induce skin sensitization. No study results were provided. Fact sheet-type summary publications from New Jersey (2001) and the International Programme on Chemical Safety (2004) give similar acute toxicity summary information, adding cough, nose and throat irritation, and that exposure to high concentrations can cause dizziness and light-headedness. No acute exposure levels were identified.

Upon repeated administration to rats in drinking water, the NOAEL was 4,700 ppm after 25 weeks, and the LOAEL was 3,300 ppm after two years. Effects at higher concentrations were primarily body weight decreases. The NOAEL in repeated dose inhalation studies was 100 to 190 ppm. Those values were based on either gray mottling of the lungs or ocular irritation and degenerative changes in the liver and kidney at higher concentrations (no dose levels were given). However, the NOAEL in those studies was not confirmed in more conclusive and GLP inhalation studies for reproductive and developmental effects (NOAEL = 650 to 1,000 ppm). (OECD SIAP)

An oral Reference Dose (RfD) was determined for cyclohexanone in IRIS (1987). While this IRIS report was developed in 1987, a literature search in 2002 did not identify any critical new studies that warranted changing the assessment. The study that was used in calculating the RfD is a chronic toxicity study of cyclohexanone in rats and mice conducted by the National Cancer Institute in which cyclohexanone was administered via drinking water. Rats were dosed at 3300 or 6500 ppm levels, male mice at 6500 or 13,000 ppm, and female mice at 6500, 13,000 or 25,000 ppm levels. Survival and weight gain were similar to the controls in both

sexes of either species treated with the lowest dosage of cyclohexanone, but weight gain was depressed at all of the higher doses. Female mice treated with doses of 13,000 ppm or 25,000 ppm and male mice treated with a dose of 13,000 ppm exhibited increased mortality as compared with controls; 50% of the females treated with 25,000 ppm cyclohexanone survived beyond one year. Based on these effects, the 3300 ppm cyclohexanone (converted to 462 mg/kg/day) in rats is considered the NOAEL, whereas the high dose (6500 ppm or 910 mg/kg/day) that causes decreased body weight gain was considered the LOAEL in rats. (Table 4)

**TABLE 4: IRIS (1987) Oral RfD Summary for Cyclohexanone**

| Critical Effect | Experimental Doses | Uncertainty Factor | RfD |
|---|---|---|---|
| Chronic Rat Oral Study -- Body weight depression | NOAEL: 3300 ppm (462 mg/kg/day)<br>LOAEL: 6500 ppm (910 mg/kg/day) | 100[1] | 5 mg/kg/day |

1. An uncertainty factor of 100 was applied; 10 for interspecies extrapolation and 10 for intraspecies variability among the human population.

The OECD SIAP assessment reports that inhalation studies in rats produced a NOAEL of 500 ppm for reproductive and NOAELs of 650 - 1000 ppm for developmental effects. Developmental studies indicate that fetal toxicity was present only at concentrations that were maternally toxic, and no malformations were detected. (OECD SIAP)

International Programme on Chemical Safety's International Agency for Research on Cancer (1989) reported that cyclohexanone was tested for carcinogenicity by oral administration in the drinking water in one strain of mice and one stain of rats. In mice, there was a slight increase in the incidence of tumors that occur commonly in that strain, but only in animals given the low dose. In rats, a slight increase in the incidence of adrenal cortical adenomas occurred in males treated with the low dose. The chemical induced chromosomal aberrations and ploidy changes in cultured human cells and in rats, but it did not induce mutation in bacteria. The report concluded that there is inadequate evidence for the carcinogenicity of cyclohexanone in experimental animals. No dose levels were provided in this report.

### E. Conclusions

Sufficient data are available to assess the hazard of both cyclohexane and cyclohexanone. Both are well absorbed through oral and inhalation routes, with inhalation being the major route of exposure, and both chemicals are metabolized by the body. They are slight to moderate eye, skin, and respiratory irritants, but they do not induce sensitization. Reproductive

and developmental effects occur at doses higher than what are relevant for pesticide uses. CNS effects also are reported at high doses and are reversible once the exposure is removed. No neurotoxicity was reported in any of the studies other than CNS depression. They are not considered to be carcinogenic.

### F. Special Considerations for Infants and Children

Based on the low toxicity via oral, inhalation, and dermal routes of exposure in animals, both cyclohexanone and cyclohexane are not of toxicological ceoncern for human expsore. For cyclohexane, no developmental effects were detected in several studies summarized in EPA's IRIS report (2003). A NOAEL of 6,886 $mg/m^3$ (2,000 ppm) was determined for reproductive effects, and an inhalation RfC of $6mg/m^3$ was calculated. For cyclohexanone, the OECD SIAP assessment reports that inhalation studies produced a NOAEL of 500 ppm for reproductive and NOAELs of 650 - 1000 ppm for developmental effects. Developmental studies indicate that fetal toxicity was present only at concentrations that were maternally toxic, and no malformations were detected. Based on this available information, a safety factor analysis has not been used to assess the risks resulting from the use of cyclohexanone and cyclohexane as inert ingredients in pesticide products, and an additional tenfold safety factor for the protection of infants and children is unnecessary.

## V. Environmental Fate Characterization/Drinking Water Considerations

Cyclohexane and cyclohexanone are expected to rapidly volatilize in air and will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals within 1 to 2 days.

Cyclohexane will readily partition to air from surface water, while cyclohexanone will do so at a much lower rate. Estimated volatilization half-lives for a model river and model lake are approximately 1 hour and 3.6 days, respectively, for cyclohexane. If released in water, cyclohexanone would be slowly lost by volatilization; its estimated half-lives in a model river and model lake are 3 and 33 days, respectively. (EPI Suite™, Version 3.12. http://www.epa.gov/oppt/exposure/docs/episuitedl.htm)

Cyclohexane and cyclohexanone are expected to volatilize readily from surface layers of soil. Both molecules exhibit high mobility in soil and would be expected to leach. Both chemicals readily biodegrade in soil. Considering their volatilization from surface soils and ready biodegradation, neither cyclohexane or cyclohexanone are likely to be present in drinking water sources at substantial concentrations as a result of their use as pesticide inert ingredients. Based on their biodegradability and potential to volatilize during standard treatment processes, both compounds are unlikely to be present in drinking water at measurable concentrations.

## VI. Exposure Assessment

For the general population, exposure to cyclohexane and cyclohexanone can occur from using a variety of consumer products (including adhesives, paints, varnishes, resins, nylon,

polishes), from the environment (water, air) after the chemicals have been released from manufacturing or spills, from engine exhaust, and from cigarette smoke. In addition, the chemicals occur naturally in the environment. Cyclohexane occurs naturally in crude oil and is also released into the atmosphere from volcanos. The general public's exposure to cyclohexane and cyclohexanone from natural sources and a wide variety of consumer products is expected to be much greater than exposure from their use in pesticide products.

Cyclohexane and cyclohexanone are used in a variety of pesticide products, including those for outdoor yards, gardens, turf, and agricultural crops. Cyclohexanone is also found in products applied to animals to control pests such as flies. Both chemicals readily volatilize when released, especially cyclohexane. The volatile nature of the chemicals limit the amount that will remain on food crops, and any residue that enters the body is metabolized. In addition to volatilization from soil surfaces, both chemicals readily biodegrade in soil, which means that run-off into surface water from pesticidal uses is not expected. Therefore, dietary exposures of concern from food (crops and meats, including fish) and drinking water are not likely from the use of these chemicals in pesticide products.

Many of the pesticide products that contain these chemicals are used outdoors, which limits inhalation exposure. Dermal exposure is also not expected to be of concern because of the chemicals' volatile properties. Therefore, inhalation and dermal exposures from residential uses are expected to be small. In addition, the amount of these chemicals used in consumer and pesticides products is limited by their high flammability potential. Product labels typically warn of fire hazard and instruct users to provide adequate ventilation or work outdoors, and doing so has the added benefit of limiting inhalation exposure potential.

## VII. 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).

In developing this assessment for cyclohexanone and cyclohexane, 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 expected from these chemicals.

## VIII. Cumulative Exposure

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning

the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to cyclohexanone and cyclohexane 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 cyclohexanone and cyclohexane 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/

## IX. Human Health Risk Characterization

Sufficient toxicity data and information on cyclohexane and cyclohexanone are available from a variety of sources. For cyclohexanone and cyclohexane, 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 expected from the inert ingredient pesticide use of these chemicals.

Cyclohexane and cyclohexanone have low acute and chronic toxicity based on the available information. They are slight to moderate eye, skin, and respiratory irritants, but they do not induce sensitization. They are not considered to be carcinogenic, and both chemicals are metabolized by the body. Reproductive and developmental effects occur at doses higher than what are relevant for pesticide uses. CNS effects also are reported at high doses and are reversible once the exposure is removed. No neurotoxicity was reported in any of the studies other than CNS depression. Based on their biodegradability and volatile nature combined with the outdoor use pattern, these chemicals are not expected to be present in the diet or drinking water at levels that would be of concern to EPA.

Taking into consideration all available information on cyclohexane and cyclohexanone, there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure 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 three exemptions from the requirement of a tolerance established for residues of cyclohexane and cyclohexanone in/on raw agricultural commodities and animals can be considered reassessed as safe under section 408(q) of the FFDCA.

## X. Ecotoxicity and Ecological Risk Characterization

There is limited measured toxicity information to characterize the effects of cyclohexane and cyclohexanone on aquatic and terrestrial organisms. The data available show that toxicity values range from non-toxic to moderately toxic to aquatic and terrestrial organisms. Both chemicals have a limited potential for bio-accumulation in the aquatic food chain. A short summary of the toxicity data and information is given below.

- Cyclohexane is practically non-toxic to moderately toxic to aquatic organisms in acute tests, and is expected to be of low toxicity to terrestrial organisms (EPA's OPPT and OPP). Acute toxicity test results for cyclohexane are reported in the EU JRC for fish, aquatic invertebrates, algae, and microorganisms. The lowest 96-hour $LC_{50}$ reported for fish is 4.53 mg/l (*Pimephales promelas*). The lowest 48-hour $EC_{50}$ for invertebrates is 0.9 mg/l (*Daphnia magna*). The lowest 72-hour $EC_{50}$ for algae (*Selenastrum capricornutum*) is 3.4 mg/l (inhibition of biomass). No longer-term studies have been performed. EPA's Ecotox Database reports toxicity results for a number of aquatic species. Results were consistently higher than those reported in the EU JRC.

- Cyclohexanone is characterized as practically non-toxic to slightly toxic based on information contained in the EPA's Ecotox Database. The most sensitive plant species tested was blue-green algae with an LOEC of 52 mg/L, the most sensitive invertebrate was *Daphnia magna* with an $EC_{50}$ of >500 mg/L, and the most sensitive fish tested was rainbow trout with a 24h $LC_{50}$ of 5 mg/L. Chronic studies were not available. The low Kow value (0.805) indicates that cyclohexanone is unlikely to bioconcentrate in aquatic organisms. (OECD SIAP)

While toxic effects can occur for these chemicals, especially in industrial spill situations (which are not part of this assessment), their use in pesticide products is not expected to present risks of concern. Applications to the environment would need to exceed 5 pounds per acre based on the most sensitive species listed above, which is well above expected application rates for their use as inert ingredients in end-use products. Both chemicals will readily volatilize when released, especially cyclohexane. In addition to volatilization, both chemicals will readily biodegrade in soil, which means that run-off into surface water from pesticidal uses is likely to be low. Therefore, ecological risk concerns are not likely to occur from the use of cyclohexane and cyclohexanone as pesticide inert ingredients.

**References**:

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EPA's Ecotox Database is available at (http://www.epa.gov/cgi-bin/ecotox_quick_search)

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