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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

June 28, 2005

ACTION MEMORANDUM

SUBJECT: Inert Ingredient Tolerance Reassessment – Titanium Dioxide

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 two (2) inert ingredient exemptions from the requirement of a tolerance.

Chemical and Use Summary: See table below.

Table 1. Tolerance Exemptions Being Reassessed in this Document

Tolerance Exemption Expression	40 CFR §	Use Pattern (Pesticidal)	CAS Reg No.	List Classification
Titanium dioxide (CAS Reg. No. 13463-67-7)	180.920[1/]	Pigment/coloring agent in plastic bags used to wrap growing banana (preharvest), colorant on seeds for planting	13463-67-7	4B
Titanium dioxide (CAS Reg. No. 13463-67-7)	180.930[2/]	Pigment/colorant in pesticide formulations for animal tag		

1. Residues listed in 40 CFR §180.920 [formerly 40 CFR§ 180.1001(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§ 180.1001(e)] are exempted from the requirement of a tolerance when used as inert ingredients in pesticide formulations when applied to animals.

Additionally, under 40 CFR §180.1195, titanium dioxide is exempted from the requirement of a tolerance for residues in or on growing crops, when used as an inert ingredient (UV protectant) in microencapsulated formulations of the insecticide lambda-cyhalothrin at no more than 3.0% by weight of the formulation. However this tolerance exemption was established after August 3, 1996, and is therefore not subject to the tolerance reassessment provision of FQPA.

List Classification Determination: Titanium dioxide is currently classified as a List 4B inert ingredient. Based on the non-bioavailability of titanium dioxide and lack of concern for adverse human health or nontarget organism effects, titanium dioxide can be reclassified as a List 4A inert ingredient.

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the two (2) exemptions from the requirement of a tolerance for the inert ingredient titanium dioxide, and with the List classification determination, as described above. I consider the exemption from the requirement of a tolerance for titanium dioxide established in 40 CFR §180.920 [formerly 40 CFR§180.1001(d)] and the exemption from the requirement of a tolerance for titanium dioxide established in 40 CFR §180.930 [formerly 40 CFR§180.1001(e)] to be maintained and reassessed as of the date of my signature, below. It should also be noted that while the exemption from the requirement of a tolerance for titanium dioxide established under 40 CFR 180.1195 is not part of this tolerance reassessment decision, the reasonable certainty of no harm safety finding made herein includes consideration of aggregate exposures to titanium dioxide resulting from use under all extant tolerance exemptions under 40 CFR Part 180. A Federal Register Notice regarding this tolerance exemption reassessment decision will be published in the near future.

Lois A. Rossi

Lois A. Rossi, Director
Registration Division

Date: July 11, 2005

cc: Debbie Edwards, SRRD
Joe Nevola, SRRD

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June 28, 2005

MEMORANDUM

SUBJECT: Reassessment of the Exemptions from the Requirement of a Tolerance for Titanium Dioxide

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

THRU: Pauline Wagner, Inerts Coordinator Pauline Wagner 6/28/05
Registration Division (7505C)

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

Background

Attached is the science assessment for titanium dioxide. The purpose of this document is to reassess two existing exemptions from the requirement of a tolerance for residues of this inert ingredient as required under the Food Quality Protection Act (FQPA). This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, and exposure profiles of titanium dioxide. In performing this assessment, the Agency has relied extensively upon reviews of titanium dioxide previously performed by the European Commission Scientific Committee on Food (SCF), the Joint Expert Committee on Food Additives of the Food and Agriculture Organization/World Health Organization (JEFCA), and the European Food Safety Authority (EFSA).

Executive Summary

This report evaluates titanium dioxide (CAS Reg. No. 13463-67-7), a pesticide inert ingredient for which two exemptions from the requirement of a tolerance exists for its residues when used in pesticide formulations applied to growing crops only under 40 CFR §180.920 and in pesticide formulations applied to animals under 40 CFR §180.930. Titanium dioxide is a widely used inorganic white pigment that is produced from mined sources of titanium.

Titanium dioxide pigments are white inorganic pigments used primarily in the production of paints, printing inks, paper and plastic products. Titanium dioxide is also used in many white or colored products including foods, cosmetics, UV skin protection products, ceramics, fibers, and rubber products.

This hazard assessment relies upon peer-reviewed assessments of titanium dioxide performed by thye European Commission Scientific Committee on Food (SCF), the Joint Expert Committee on Food Additives of the Food and Agriculture Organization/World Health Organization (JECFA), and the European Food Safety Authority's (EFSA) Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food. Based on its evaluation of the available data on titanium dioxide, JECFA concluded that the establishment of an acceptable daily intake was unnecessary. In its safety review of certain food colorants, the SCF reaffirmed an earlier determination regarding the use of titanium dioxide as a colorant in foodstuffs and concluded that titanium dioxide was acceptable for general food use without the need for establishment of an acceptable daily intake. In its most recent evaluation of titanium dioxide, EFSA concurred with the JECFA assessment of titanium dioxide and concluded that the use of titanium dioxide would not pose any safety concerns. Both the JECFA and EFSA evaluations of titanium dioxide noted there is no absorption or tissue storage of titanium dioxide.

Titanium dioxide is not bioavailable as it is not absorbed via the gastrointestinal tract or through the skin. Inhalation exposure to high concentrations of titanium dioxide particles has been shown to result in pulmonary effects in rats, but these effects may be a rat-specific threshold phenomenon, possibly of little relevance to humans. Epidemiological data suggest that there is no carcinogenic effect associated with workplace exposure to titanium dioxide dust. Titanium dioxide is not carcinogenic in mice or rat dietary studies and no adverse effects were observed in chronic rat studies at concentrations up to 5% in the diet.

Based on the insoluble nature of titanium dioxide in water and the low acute toxicity of titanium dioxide to freshwater fish, there are no nontarget aquatic species risk concerns resulting from the use of titanium dioxide as an inert ingredient. Based on the lack of absorption, as well as no identified toxicological effects of concern in animal testing, there are no risk concerns for nontarget terrestrial organisms resulting from the use of titanium dioxide as an inert ingredient.

Taking into consideration all available information on titanium dioxide, it has been determined that there is a reasonable certainty that no harm to any population subgroup will

result from aggregate exposure to titanium dioxide when considering dietary exposure and all other nonoccupational sources of pesticide exposure for which there is reliable information. Therefore, it is recommended that the exemptions from the requirement of a tolerance established for residues of titanium dioxide in/on raw agricultural commodities and animals can be considered reassessed as safe under section 408(q) of the FFDCA.

I. Introduction

This report evaluates titanium dioxide (CAS Reg. No. 13463-67-7), a pesticide inert ingredient for which two exemptions from the requirement of a tolerance exist for its residues when used in pesticide formulations applied to growing crops only under 40 CFR §180.920 and in pesticide formulations applied to animals under 40 CFR §180.930. An exemption from the requirement of a tolerance was established for titanium dioxide under 40 CFR §180.1195 for use as an inert ingredient (UV protectant) in microencapsulated formulations of lambda-cyhalothrin on March 25, 1998 (EPA 1998), however that rule did not specifically address the reassessment of the two above-noted tolerance exemptions for titanium dioxide.

Titanium dioxide is a widely used inorganic white pigment that is produced from mined sources of titanium, with 98% of all mined titanium used in the production of titanium dioxide. The most commercially significant mineral forms of titanium dioxide are rutile and anatase (Terran 1997). The production of titanium dioxide pigment in the United States in 2003 was 1.4 million metric tons (Gambogi 2003).

II. Use Information

Pesticides

The two tolerance exemptions for titanium dioxide being reassessed in this document are given in Table 1 below.

Table 1. Tolerance Exemptions Being Reassessed in this Document

Tolerance Exemption Expression	40 CFR §	Use Pattern (Pesticidal)	CAS Reg No.	List Classification
Titanium dioxide (CAS Reg No. 13463-67-7)	180.920[1/]	Pigment/coloring agent in plastic bags used to wrap growing banana (preharvest), colorant on seeds for planting	13463-67-7	4B
Titanium dioxide (CAS Reg. No. 13463-67-7)	180.930[2/]	Pigment/colorant in pesticide formulations for animal tag		

1. Residues listed in 40 CFR §180.920 [formerly 40 CFR§ 180.1001(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§ 180.1001(e)] are exempted from the requirement of a tolerance when used as inert ingredients in pesticide formulations when applied to animals.

Additionally, under 40 CFR §180.1195, titanium dioxide is exempted from the requirement of a tolerance for residues in or on growing crops, when used as an inert ingredient (UV protectant) in microencapsulated formulations of the insecticide lambda-cyhalothrin at no more than 3.0% by weight of the formulation (EPA 1998). Since this tolerance exemption was established after August 3, 1996, it is not subject to the tolerance reassessment provision of FQPA.

Other Uses

Titanium dioxide pigments are white inorganic pigments used primarily in the production of paints, printing inks, paper and plastic products. Titanium dioxide is also used in many white or colored products including foods, cosmetics, UV skin protection products, ceramics, fibers, and rubber products. Titanium dioxide provides opacity and imparts whiteness and brightness to the products in which it is used, as well as affording protection from UV degradation (CEFIC 2002).

Titanium dioxide is approved by the Food and Drug Administration (FDA) as a color additive exempt from certification for the following uses: under 21 CFR §73.575 for coloring foods at levels up to one percent by weight; under 21 CFR §73.1575 for coloring ingested and externally applied drugs generally; and under 21 CFR §73.2575 for use in cosmetics, including cosmetics intended for use in the area of the eye.

III. Physical and Chemical Properties

Some of the physical and chemical characteristics of titanium dioxide are given in Table 2. below.

Table 2. Titanium Dioxide Physical and Chemical Properties

Parameter	Value	Source
Structure		ChemIDplus 2005
Physical Form	Solid	HSDB 2005

Table 2. Titanium Dioxide Physical and Chemical Properties		
Parameter	**Value**	**Source**
Molecular Weight	79.865	ChemIDplus 2005
Water Solubility	none	IPCS 1993
Melting Point	1843 ° C (M)	HSDB 2005
Vapor Pressure	Not applicable	
Henry's Law Constant	Not applicable	
Octanol-Water Partition Coefficient (K_{OW})	Not applicable	

IV. Hazard Assessment

A. Hazard Profile

This hazard assessment primarily relies upon peer-reviewed assessments of titanium dioxide performed by European Commission Scientific Committee on Food (SCF), the Joint Expert Committee on Food Additives of the Food and Agriculture Organization/World Health Organization (JECFA), and the European Food Safety Authority's (EFSA) Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food.

The JECFA evaluation of titanium dioxide states that "Titanium dioxide is a very insoluble compound. The studies in several species, including man, show neither significant absorption nor tissue storage following ingestion of titanium dioxide." Based on its evaluation of the available data on titanium dioxide, JECFA concluded that the "Establishment of an acceptable daily intake[1] for man is considered unnecessary" (JECFA 1969).

In its safety review of certain food colorants, the SCF reaffirmed an earlier determination regarding the use of titanium dioxide as a colorant in foodstuffs and concluded that titanium dioxide was acceptable for general food use with no established ADI (SCF 1977). The responsibilities for European Commission risk assessments for food additives is now the responsibility of the EFSA which, in its most recent evaluation of titanium dioxide, concurred with the JECFA assessment of titanium dioxide and concluded that the use of titanium dioxide would not pose any safety concerns (EFSA 2004).

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[1]ADI (Acceptable Daily Intake): An estimate by JECFA of the amount of a food additive, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk

Titanium dioxide is not dermally absorbed by humans (Plfucker et al 2001). Titanium dioxide is a frequently used compound in lung clearance studies, where a biologically inert substance is required, however inhalation of high concentrations of fine or ultrafine titanium dioxide particles has been shown to result in pulmonary inflammation, fibrosis, and lung tumors in rats (Lee et al 1985). In contrast to the results in rats, inhalation effects were not observed in mice and hamsters and may be a rat-specific threshold phenomenon, dependent upon lung overloading at high exposure concentrations and possibly of little relevance to humans. Epidemiological data suggest that there is no carcinogenic effect associated with workplace exposure to titanium dioxide dust (Hext et al 2005).

B. Toxicological Data

The EFSA evaluation of titanium dioxide noted the toxicological database considered by JECFA and referenced additional key toxicological data on chronic toxicity and carcinogenicity. The EFSA evaluation of the additional toxicological data reported "a NCI carcinogenicity study was conducted in groups of 50 per sex of Fischer 344 rats and B6C3F1 mice dosed at 0, 25000 and 50000 mg titanium dioxide /kg diet for 103 weeks (NCI, 1979). Increased incidences of thyroid C-cell adenomas or carcinomas were observed in female rats but these increases were neither statistically significant nor considered to be related to administration of the test compound. Tumour incidences in the other groups were not significantly higher than in controls. A chronic dietary study administration of titanium dioxide coated mica at 0, 1, 2 and 5% in Fischer 344 rats for 130 weeks showed no toxicological or carcinogenic effects (Bernard et al., 1990)."

C. Metabolism And Pharmacokinetics

Both the JECFA and EFSA evaluations of titanium dioxide noted that there is no absorption or tissue storage of titanium dioxide. The World Health Organization (WHO) Environmental Health Criteria for titanium, an evaluation of the effects of titanium on human health and the quality of the environment, states that "titanium compounds are poorly absorbed from the gastrointestinal tract, which is the main route of exposure for the general population" (WHO 1982).

There is no dermal absorption of titanium dioxide. Inhalation effects resulting from titanium dioxide are limited to localized lung effects Adverse effects resulting from inhalation studies of titanium dioxide have been confined to the respiratory tract and lung-associated lymphatic tissues (NAS 1999).

D. Special Considerations for Infants and Children

Based on the lack of absorption, history of safe use as a pigment and food additive, low toxicity, and lack of concern for human health effects, a safety factor analysis has not been used

to assess the risks resulting from the use of titanium dioxide as a pesticide inert ingredient and an additional tenfold safety factor for the protection of infants and children is unnecessary.

V. Exposure Assessment

Titanium dioxide is not absorbed via the oral or dermal routes of exposure, therefore no further oral or dermal exposure assessment is necessary. Exposures to high concentrations of fine or ultrafine titanium dioxide particles have been shown to result in pulmonary effects in rats but is likely a rat-specific threshold phenomenon, dependent upon lung overloading at high exposure concentrations and possibly of little relevance to humans. Since the pesticide inert ingredient use of titanium dioxide is as a pigment in which the titanium dioxide is bound in a polymeric matrix and not present as particulate titanium dioxide, there would be no inhalation exposure to titanium dioxide particles resulting from its use as a pesticide inert ingredient and no further inhalation exposure assessment is necessary.

VI. Aggregate Exposures

In examining aggregate exposure, FFDCA section 408 directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures, including drinking water from ground water or surface water and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

For titanium dioxide, a qualitative assessment for all pathways of human exposure (food, drinking water, and residential) is appropriate given the general lack of bioavailability of titanium dioxide, its insolubility in water, and the lack of human health concerns associated with exposure to titanium dioxide.

VII. Cumulative Exposure

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to titanium dioxide 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 titanium dioxide 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 concerning common mechanism determinations and

procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/

VIII. Environmental Fate Characterization/Drinking Water Considerations

Titanium dioxide is a stable compound that is insoluble in water and therefore would not be expected to be present in drinking water sources as a result of pesticide inert ingredient use.

IX. Human Health Risk Characterization

Evaluations of titanium dioxide by JECFA, SCF, and EFSA have each concluded that there are no safety concerns associated with the use of titanium dioxide as a food additive at levels ranging up to 3%. Taking into consideration all available information on titanium dioxide, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to titanium dioxide when considering dietary exposure and all other nonoccupational sources of pesticide exposure for which there is reliable information. Therefore, it is recommended that the exemptions from the requirement of a tolerance established for residues of titanium dioxide 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

The available ecotoxicity data on titanium dioxide are primarily limited to acute aquatic toxicity studies. The acute aquatic LC_{50} of titanium dioxide in fathead minnows is >1000 mg/L (ECOTOX 2002). Based on the insoluble nature of titanium dioxide in water and the low acute toxicity of titanium dioxide to freshwater fish, there are no nontarget aquatic species risk concerns resulting from the use of titanium dioxide as an inert ingredient. Based on the lack of absorption as well as no identified toxicological effects of concern in animal testing, there are also no risk concerns for nontarget terrestrial organisms resulting from the use of titanium dioxide as an inert ingredient.

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