



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

OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

March 18, 2005

**ACTION MEMORANDUM**

**SUBJECT:** Inert Ingredient Tolerance Reassessment – Poly(oxyethylene) Adducts of Mixed Phytosterols

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

**TO:** Lois A. Rossi, Director  
Registration Division

**I. FQPA REASSESSMENT ACTION**

**Action:** Reassessment of one (1) inert ingredient exemption from the requirement of a tolerance.

**Chemical and Use Summary:** See table below.

<b>Tolerance Exemption Being Reassessed</b>				
<b>Tolerance Exemption Expression</b>	<b>CAS Reg No.</b>	<b>40 CFR §</b>	<b>Use Pattern (Pesticidal)</b>	<b>List Classification</b>
Poly(oxyethylene) adducts of mixed phytosterols (such sterols to consist of campesterol, stigmasterol and sitosterol with minor amounts of associated plant sterols) derived from edible vegetable oils; polyoxyethylene content averaging 5-26 moles.		180.920 <sup>1/</sup>	Surfactant, related adjuvants	

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.

**List Reclassification Determination:** Poly(oxyethylene) adducts of mixed phytosterols is uncategorized as to list classification status. Based upon the reasonable certainty of no harm safety finding, the List 4B classification for poly(oxyethylene) adducts of mixed phytosterols is affirmed.

## II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the one (1) exemption from the requirement of a tolerance for the inert ingredient, poly(oxyethylene) adducts of mixed phytosterols and with the List classification affirmation determination, as described above. I consider the one (1) exemption from the requirement of a tolerance for poly(oxyethylene) adducts of mixed phytosterols established in 40 CFR §180.920 [formerly 40 CFR§180.1001(d)] to be reassessed as of the date of my signature, below. A Federal Register Notice regarding this tolerance exemption reassessment decision will be published in the near future.



Lois A. Rossi, Director  
Registration Division

Date: 3.29.05

cc: Debbie Edwards, SRRD  
Joe Nevola, SRRD



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**MEMORANDUM**

SUBJECT: Reassessment of the Exemption from the Requirement of a Tolerance for Poly(oxyethylene) Adducts of Mixed Phytosterols

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

THRU: Pauline Wagner *Pauline Wagner 3/21/05*  
Registration Division (7505C)

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

**Background**

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

**Executive Summary**

This report evaluates poly(oxyethylene) adducts of mixed phytosterols, a pesticide inert ingredient for which an exemption 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 [formerly 40 CFR §180.1001(d)] for use as a surfactant.

A structure activity relationship analysis of poly(oxyethylene) adducts of mixed phytosterols was conducted by the Office of Pollution Prevention and Toxics (OPPT) Structure Activity Team. The OPPT assessment concluded that poly(oxyethylene) adducts of mixed phytosterols are poorly absorbed via all routes of exposure and are of low concern for human health effects, with no identified health concerns. Poly(oxyethylene) adducts of mixed phytosterols are water insoluble and readily degraded in the environment and would not be present in drinking water while also being of low concern for toxicity to aquatic organisms.

Taking into consideration all available information on poly(oxyethylene) adducts of mixed phytosterols, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to poly(oxyethylene) adducts of mixed phytosterols 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 exemptions from the requirement of a tolerance established for residues of poly(oxyethylene) adducts of mixed phytosterols in/on raw agricultural commodities can be considered reassessed as safe under section 408(q) of the FFDCFA.

## **I. Introduction**

This report evaluates poly(oxyethylene) adducts of mixed phytosterols, a pesticide inert ingredient for which an exemption 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 [formerly 40 CFR §180.1001(d)].

Poly(oxyethylene) adducts of mixed phytosterols is a term that refers to the reaction product of phytosterols (primarily campesterol, stigmasterol and beta-sitosterol) with ethylene oxide. Phytosterols, also known as plant sterols, are a naturally occurring class of compounds found in the cells and membranes of plants. Phytosterols have a similar molecular structure to dietary and endogenously secreted cholesterol. The ethoxylation of phytosterols creates a compound that has both a hydrophobic portion (the phytosterol moiety) and a hydrophilic portion (the poly(oxyethylene) moiety), enabling it to function as a surfactant.

## **II. Use Information**

### **Pesticides**

The tolerance exemption for the inert ingredient poly(oxyethylene) adducts of mixed phytosterols is given in Table 1 below.

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

Tolerance Exemption Expression	CAS Reg No.	40 CFR §	Use Pattern (Pesticidal)	List Classification
Poly(oxyethylene) adducts of mixed phytosterols (such sterols to consist of campesterol, stigmasterol and sitosterol with minor amounts of associated plant sterols) derived from edible vegetable oils; polyoxyethylene content averaging 5-26 moles.		180.920 <sup>1/</sup>	Surfactant, related adjuvants	

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.

Other Uses

No other uses were identified for poly(oxyethylene) adducts of mixed phytosterols.

**III. Physical and Chemical Properties**

Some of the physical and chemical characteristics of poly(oxyethylene) adducts of mixed phytosterols are found in Appendix A.

**IV. Hazard Assessment**

**A. Hazard Profile**

Poly(oxyethylene) adducts of mixed phytosterols are an amphiphilic form of phytosterols. There are no readily available toxicity data on poly(oxyethylene) adducts of mixed phytosterols. For toxicity endpoints other those related to surfactant effects, phytosterols are suitable analogs for poly(oxyethylene) adducts of mixed phytosterols. Phytosterols are natural constituents of the human diet, with oils, margarine, peanut butter, legumes, sunflower seeds and other fruits and vegetables being the main sources of phytosterols.

Phytosterols are known to lower the concentration of blood cholesterol and have been investigated in a large number of clinical trials (including doses of up to 25 grams per day and durations up to three years). No significant adverse effects have been observed in the decades of medically supervised clinical efficacy testing and the general clinical use of phytosterols (IFST, 2005). The Food and Drug Administration (FDA) had no questions regarding a conclusion by

qualified experts that phytosterols incorporated into vegetable oil spreads at concentrations up to 20% (w/w) are Generally Recognized as Safe (GRAS) (FDA, 2003).

A structure activity relationship analysis of poly(oxyethylene) adducts of mixed phytosterols was conducted by the Office of Pollution Prevention and Toxics (OPPT) Structure Activity Team. The OPPT assessment concluded that poly(oxyethylene) adducts of mixed phytosterols are not absorbed through the skin, poorly absorbed through the gastrointestinal (GI) tract, and moderately absorbed through the lungs based on analog data. The OPPT assessment concluded that poly(oxyethylene) adducts of mixed phytosterols were of a low-moderate concern for human health effects, with a potential concern for inhalation of respirable particles and interference with the natural surfactancy of the lungs, which can affect lung expansion and contraction. The OPPT Structure Activity Team assessment report is included in Appendix A

#### **B. Toxicological Data**

No references to toxicity studies on poly(oxyethylene) adducts of mixed phytosterols were identified in the open literature.

#### **C. Metabolism And Pharmacokinetics**

The OPPT Structure Activity Team assessment noted that poly(oxyethylene) adducts of mixed phytosterols are not absorbed through the skin and are poorly absorbed through the GI tract. Studies on absorption, distribution, metabolism and excretion have shown that phytosterols are poorly absorbed from the intestine (1 - 10%,) and that portion which is absorbed is rapidly eliminated via excretion in the bile (IFST, 2005).

#### **D. Special Considerations for Infants and Children**

Exposures to poly(oxyethylene) adducts of mixed phytosterols by infants and children would be via the dietary route only, a route of exposure by which poly(oxyethylene) adducts of mixed phytosterols are not absorbed and for which there is a low concern for human health effects. Therefore, a safety factor analysis has not been used to assess the risks resulting from the use of poly(oxyethylene) adducts of mixed phytosterols and an additional tenfold safety factor for the protection of infants and children is unnecessary.

#### **V. Exposure Assessment**

Poly(oxyethylene) adducts of mixed phytosterols are not absorbed through the skin, therefore no further dermal exposure assessment is necessary. Since both poly(oxyethylene) adducts of mixed phytosterols and phytosterols are poorly absorbed by the GI tract, and since average dietary intake of phytosterols as natural components of the diet is 200-400 mg/day (levels far exceeding dietary exposures to phytosterols as components of pesticide inert ingredients), no further dietary exposure assessment is necessary. The potential concerns for

surfactant lung effects resulting from inhalation of respirable particles of poly(oxyethylene) adducts of mixed phytosterols would be more commonly associated with exposures to high concentrations of the neat solid material, a scenario that would not be realized in conjunction with the use of poly(oxyethylene) adducts of mixed phytosterols as a pesticide product inert ingredient, where inhalation exposures would be negligible; therefore, 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 poly(oxyethylene) adducts of mixed phytosterols, 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 poly(oxyethylene) adducts of mixed phytosterols.

## **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 poly(oxyethylene) adducts of mixed phytosterols 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 poly(oxyethylene) adducts of mixed phytosterols 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/>

## **VIII. Environmental Fate Characterization/Drinking Water Considerations**

The OPPT Structure Activity Team assessment of poly(oxyethylene) adducts of mixed phytosterols noted that they are dispersible in water, but do undergo aerobic biodegradation along with strong sorption to soils and sediments, resulting in slow migration to ground water.

Based on these conclusions, poly(oxyethylene) adducts of mixed phytosterols are not be expected to be present in drinking water sources as a result of pesticide inert ingredient use. Some estimated environmental fate properties of poly(oxyethylene) adducts of mixed phytosterols are given in Appendix A.

### **IX. Human Health Risk Characterization**

Poly(oxyethylene) adducts of mixed phytosterols are an ethoxylated form of phytosterols that are not absorbed by the skin and are, like phytosterols themselves, poorly absorbed through the GI tract. The OPP Structure Activity Team has identified poly(oxyethylene) adducts of mixed phytosterols as being of low- moderate concern for human health effects, with the only effect of concern being surfactant lung effects resulting from respiration of the neat solid material—a scenario that would not be realized from use of poly(oxyethylene) adducts of mixed phytosterols as a pesticide inert ingredient. Phytosterols are natural components of human diets and clinical trials utilizing doses of up to 25 g of phytosterols as food additives and dietary supplements have not resulted in any documented adverse effects.

Taking into consideration all available information on poly(oxyethylene) adducts of mixed phytosterols, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to poly(oxyethylene) adducts of mixed phytosterols when considering dietary exposure and all other non-occupational sources of pesticide exposure for which there is reliable information. Therefore, it is recommended that the exemption from the requirement of a tolerance established for residues of poly(oxyethylene) adducts of mixed phytosterols in/on raw agricultural commodities can be considered reassessed as safe under section 408(q) of the FFDCA.

### **X. Ecotoxicity and Ecological Risk Characterization**

There are no available aquatic toxicity studies on poly(oxyethylene) adducts of mixed phytosterols (ECOTOX, 2002). The OPPT Structure Activity Team rated poly(oxyethylene) adducts of mixed phytosterols as high concern for toxicity to fish, algae, and aquatic invertebrates with a concern concentration of 2 ppb (Appendix A).

### **References:**

ChemIDplus 2005. ChemIDplus Advanced. U.S. National Library of Medicine. National Institutes of Health. Department of Health and Human Services. Online Search Database <http://chem.sis.nlm.nih.gov/chemidplus/>  
Search terms: Poly(oxyethylene) adducts of mixed phytosterols; phytosterol; campesterol; stigmasterol; sitosterol (February 21, 2005)



ECOTOX 2002. U.S. Environmental Protection Agency. 2002. ECOTOX User Guide: ECOTOXicology Database System. Version 3.0. <http://www.epa.gov/ecotox/>  
Search terms: Poly(oxyethylene) adducts of mixed phytosterols; phytosterol; campesterol; stigmasterol; sitosterol (February 21, 2005)

FDA 2003. Center for Food Safety and Applied Nutrition. Agency Response Letter--GRAS Notice No. GRN 000112. Letter from A. Rulis to C. Gund, February 4, 2003.  
<http://www.cfsan.fda.gov/~rdb/opa-g112.html>

IFST 2005. IFST: Current Hot Topics– Phytosterol Esters (Plant Sterol and Stanol Esters). The Institute of Food Science and Technology. London, UK. <http://www.ifst.org/hotspot29.htm>

OPPT 2004. Office of Pollution Prevention and Toxics Structure Activity Team Report: Plant-derived sterols, ethoxylated. December 14, 2004.

TOXNET. 2005. Hazardous Substance Data Bank (HSDB). On-line Scientific Search Engine, National Library of Medicine, National Institute of Health. <http://www.toxnet.nlm.nih.gov>.  
Search term: Poly(oxyethylene) adducts of mixed phytosterols; phytosterol; campesterol; stigmasterol; sitosterol (February 20, 2005)

## APPENDIX A

### OPPT SAT Review of Plant-derived sterols, ethoxylated

<b>STRUCTURE ACTIVITY TEAM REPORT</b> ver. 04/98		CBI? (YES/NO) <span style="border: 1px solid black; border-radius: 50%; padding: 2px;">NO</span>	
<b>Case #:</b> Z-05-0008	<b>DCN:</b>		
<b>SAT Date:</b> 12/14/2004	<b>SAT Chair:</b> Beckie Jones		
<b>Submitter:</b>			
<b>Chemical Name:</b>			
Plant-derived sterols, ethoxylated			
<b>CAS RN:</b> None		<b>Trade Name:</b>	
<b>Structure</b>			
<b>Molecular Formula:</b> C <sub>98</sub> H <sub>170</sub> O <sub>9</sub>			
<b>Molecular Wt.</b> 635	<b>WT%&lt;500:</b>	<b>WT%&lt;1000:</b>	
<b>MP:</b>	<b>BP:</b>	<b>Eq. Wt:</b>	
<b>H<sub>2</sub>O Sol (g/L):</b> Dispersible		<b>V.P.:</b> <0.000001	
<b>Max. Prod. Volume (kg/yr):</b>		<b>Physical State:</b> Solid	
<b>USE:</b>			
Pesticide inert ingredient.			
<b>Related Case Numbers</b>		<b>Case Role</b>	
<b>Related Case Numbers</b>		<b>Case Role</b>	
<b>Related Case Numbers</b>		<b>Case Role</b>	
<b>Related Case Numbers</b>		<b>Case Role</b>	
<b>FOCUS</b>	<b>Date:</b>	<b>Results:</b>	

Page of

STRUCTURE ACTIVITY TEAM REPORT

CASE NUMBER: Z05-0008

RELATED CASES:

CONCLUSIONS/DISCUSSIONS

TYPE OF CONCERN:	HEALTH	ECOTOX
LEVEL OF CONCERN:	1-2	3

KEYWORDS:

LUNG  
AQUATOX-A,C

SUMMARY OF ASSESSMENT

FATE: Solid  
S = Disp.; VP @ 25C (mm) < 1.0E-6(E); H < 1.00E-8(E)  
POTW removal (%) = 90 via sorption and biodeg  
Time for complete ultimate aerobic biodeg = mo  
PBT Potential: P1B1T1  
Sorption to soils/sediments = strong  
\*CEB FATE: Migration to ground water = slow

HEALTH: Absorption is nil through the skin, poor through the GI tract, and moderate through the lungs based on analogs. There is concern for lung effects if respirable particles are inhaled based on the surfactant properties of this material. It can interfere with the natural surfactancy of the lungs which can affect the expansion and contraction of the lungs.  
\*CEB HEALTH: Low moderate concern.

ECOTOX: Predicted (P) and measured (M) toxicity values in mg/L (ppm) are:

fish 96-h LC50	>=	0.110 P
daphnid 48-h LC50	>=	0.110 P
green algal 96-h EC50	>=	0.110 P
fish chronic value	>=	0.020 P
daphnid ChV	>=	0.020 P
algal ChV	>=	0.030 P

Predictions are based on SARs for nonionic surfactants-alkylethoxylates-C21-E05; SAR chemical class = surfactant-nonionic-sterolethoxylate-sterol-E05; log Kow of the hydrophobe = sterol is = 11.9 (ClogP) which is equivalent to 21 linear carbons based on Kow; MW1492; pH7; effective concentrations based on 100% active ingredients and mean measured concentrations; hardness <150.0 mg/L as CaCO3; and TOC <2.0 mg/L;  
high concern for toxicity;  
assessment factor = 10.0

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concern concentration = 0.002 mg/L (ppm)  
\*CEB ECOTOX: All releases to water with CC = 2 ppb

Becky Jones 564-8919

NCSAB SAT REPORT		CBI? (Y/N)	
PMN:	Z-05-0008	CAS RN:	None
Chemical Name:		Analog:	
Plant-derived sterols, ethoxylated		Production Volume:	
Structure:			
Use:			
Pesticide inert ingredient.			
Formula:	$C_{98}H_{170}O_9$	Eq Wt:	
Mol Weight:	1492.44	Wt% < 500:	Wt% < 1000
MP:		BP:	VP: < 0.000001
H2O Sol (g/L):	Dispersible	Physical State:	Solid
			Log P:
Endpoint (mg/L)	Est. Value	Meas. Value	Comments
Fish 96-h	< 0.11		
Daphnid 48-h	< 0.11		
Algal 96-h	< 0.11		
Fish ChV	< 0.020		AcR5
Daphnid ChV	< 0.020		AcR5
Algal ChV	< 0.030		EC50 / 4
BCF			
CHEMICAL CLASS:		SAR: <i>leaf-non-sterid-ethoxylate</i>	
ECOTOX CONCERN	<input checked="" type="checkbox"/> H <input type="checkbox"/> M <input type="checkbox"/> L	CONCERN CONCENTRATION <i>0.002</i>	
DATE	<i>12/14/04</i>	ASSESSOR:	

