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

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

DATE: June 19, 2006

ACTION MEMORANDUM

SUBJECT: Reassessment of the Two Exemptions from the Requirement of a Tolerance for Propyl p-hydroxybenzoate (CAS Reg. No. 94-13-3)

FROM: Pauline Wagner, Chief Pauline Wagner 6/20/06
Inert Ingredient Assessment Branch
Registration Division (7505P)

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

I. FQPA REASSESSMENT ACTION

Action: Reassessment of two inert exemptions from the requirement of a tolerance for Propyl p-hydroxybenzoate (AKA propyl paraben). The reassessment decision is to maintain the inert tolerance exemptions "as-is."

Chemical: Propyl p-hydroxybenzoate

Table 1. Tolerance Exemptions Being Reassessed

40 CFR 180§	Tolerance Exemption Expression	Limits	Use	CAS Registry Number and name
910[a]	Propyl p-hydroxybenzoate	---	Preservative for formulations	94-13-3 Propyl p-hydroxybenzoate
930[b]	Propyl p-hydroxybenzoate (Propyl paraben)	Meets Specifications of Food Chemicals Codex; not to exceed 0.1% in formulations	Preservative	

a. Residues listed in 40 CFR 180.910 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 or raw agricultural commodities after harvest.
b. Materials listed in 40 CFR 180.930 are exempt from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to animals.

Use Summary: Parabens, specifically propyl paraben, have been used as antimicrobial food additives in several food categories such as baked goods, beverages, creams, pastes, jams, jellies, preserves, syrups and other applications for more than 50 years. As indirect food additives, propyl paraben is permitted as antimycotics in food packaging materials with no limit or restriction.

List Reclassification Determination: The current List Classification for propyl p-hydroxybenzoate is 4B and it remains unchanged.

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the two exemptions from the requirement of a tolerance for the inert ingredient propyl p-hydroxybenzoate (CAS Reg. No. 94-13-3), and with the List reclassification determination, as described above. I consider the two exemptions established in 40 CFR part 180.910 and 930 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

Lois A. Rossi, Director
Registration Division

June 26, 2006

Date:

cc: Debbie Edwards, SRRD
Joe Nevola, SRRD

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

June 16, 2006

MEMORANDUM

SUBJECT: Reassessment of the Exemptions from the Requirement of Tolerance for Propyl *p*-hydroxybenzoate (Propyl Paraben) (CAS Reg. No. 94-13-3).

FROM: Elissa Reaves, Ph.D. 6/16/06
Reregistration Branch 2
Health Effects Division (7509P)

Through: William Hazel, Branch Chief
Reregistration Branch 2
Health Effects Division (7509P)

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

BACKGROUND

Attached is the science assessment for propyl *p*-hydroxybenzoate or most commonly referred to as propyl paraben. For convenience, propyl paraben will be used in this document to refer to propyl p-hydroxybenzoate. This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, exposure profile, environmental fate, and ecotoxicity of propyl paraben. The purpose of this document is to reassess the exemptions from the requirement of a tolerance for residues of propyl paraben as required under the Food Quality Protection Act (FQPA).

EXECUTIVE SUMMARY

This document evaluates propyl paraben, a pesticide inert ingredient for which two exemptions from the requirement for a tolerance exists. An inert ingredient is defined by the U.S. Environmental Protection Agency (USEPA) as any ingredient in a pesticide product that is not intended to affect a target pest.

Propyl paraben is one of several alkyl esters of p-hydroxybenzoic acid. As an inert pesticide ingredient, propyl paraben is currently exempt from the requirement for a tolerance when used in pesticide formulations applied to growing crops or to raw agricultural commodities after harvest (40 CFR 180.910). Additionally, propyl paraben is limited to 0.1% in pesticide formulations as an antioxidant or preservative when applied to animals (40 CFR 180.930). Propyl paraben is used as an inert ingredient in agricultural, home yard and garden and animal (insect repellents) pesticide products. Other non-pesticidal uses of propyl paraben include use as preservatives in food, food packaging, cosmetics, and drug formulations.

The antimicrobial properties of the parabens, especially propyl paraben, have been employed in the food industry for more than 50 years. Propyl paraben is generally recognized as safe (GRAS) for direct addition to food (21 CFR 184.1490) up to 0.1% and for indirect addition to packaging materials (21 CFR 181.23). FDA has also approved propyl paraben as a synthetic flavoring substance and adjuvant (21 CFR 172.515) not to exceed 20 ppm. The JECFA and the FEMA (1974) recommended an Acceptable Daily Intake (ADI) for the methyl-, ethyl-, and propyl-esters of p-hydroxybenzoic acid as a group of 0-10 mg/kg body weight/day. Propyl paraben is not considered a high production volume (HPV) chemical.

The available acute toxicity data indicate propyl paraben is practically non-toxic by the oral route. Acute dermal and inhalation data were not located although eye and skin irritation studies suggest propyl paraben is non-irritating. Oral subchronic and chronic animal studies with propyl paraben produced no significant systemic toxicity. Propyl paraben was non-genotoxic in mutagenicity assays and was non-carcinogenic in transplacental carcinogenesis assays and lacked tumor promoting potential in the urinary bladder of mice. Administration of neostigmine, which contains propyl paraben, did not produce behavioral, chemical, or histopathological evidence of neurotoxicity. In addition, the overall available carcinogenicity information indicates the lack of carcinogenic potential for propyl paraben.

Recent *in vitro* and *in vivo* uterotrophic assays produced conflicting estrogenic potential for propyl paraben. Propyl paraben had weak estrogenic activity compared to endogenous estradiol in an *in vitro* yeast-based estrogen assay. Propyl paraben also has been demonstrated as an effective spermicide for human spermatozoa. Additionally, dietary concentrations of 0.01% -1% for four

weeks resulted in decreased daily sperm production and efficiency in young rats. However, these reproductive parameters have not been verified or replicated.

Dietary (food and drinking water) exposure of concern is not anticipated from the use of propyl paraben as an inert ingredient in pesticide products based on the chemical's physical/chemical properties and ready biodegradation. In addition, dietary exposure from animals treated with pesticide products containing propyl paraben is not likely considering the very small amount that can be included in pesticide products (cannot exceed 0.1% in formulation). While dermal exposure to propyl paraben is possible from its inclusion in home-use pesticide products, inhalation exposure from residential use pesticide products is not expected because of the chemical's physical/chemical properties. Propyl paraben has a long history of use in cosmetic products containing parabens intended for use on normal skin is considered safe. Furthermore, products containing 0.2% propyl paraben indicate no reaction indicative of photosensitization. In addition, propyl paraben and its metabolites are generally absorbed from the gastrointestinal tract, metabolized in either the liver or kidney, and quickly excreted via the urine.

Propyl paraben is considered readily biodegradable in terrestrial and aquatic environments. Primary degradation is expected to occur within days followed by mineralization to essentially CO_2 and water in aerobic systems. Under anaerobic conditions in both terrestrial and aquatic environments, degradation will occur much slower. Based on the log K_{ow}, propyl paraben is not expected to bioconcentrate. Propyl paraben may contaminate shallow aquifer groundwater; however, biologically-mediated degradation in both aerobic and anaerobic conditions will limit loadings, thus concentrations. There are no ambient water quality criteria or drinking water maximum contaminant or health advisory levels for propyl paraben.

Taking into consideration available toxicity and exposure information on propyl paraben, including the lack of reproducible reproductive effects reported in only one published study, the Agency has determined that there is reasonable certainty that no harm to any population subgroup will result from aggregate exposure when considering exposure through food commodities and all other non-occupational sources for which there is reliable information. However, it should be noted that the Agency will evaluate any reproductive information for propyl paraben that may become available in the future and amend the exemption as appropriate. Therefore, it is recommended that the exemption from the requirement of a tolerance under 40 CFR 180.910 and 180.930 (0.1%) can be considered reassessed as safe under section 408(q) of the Federal Food, Drug, and Cosmetic Act (FFDCA).

I. Introduction

This report provides a qualitative assessment for propyl paraben, a pesticide inert ingredient with tolerance exemptions under: 40 CFR 180.910 and 180.930 (0.1%). There is sufficient information to conduct this assessment.

II. Use Information

A. Pesticidal Uses

The tolerance exemption for propyl paraben, when used as an inert ingredient in pesticide formulations, is provided in Table 1 below.

Table 1. Tolerance Exemption Being Reassessed in this Document

40 CFR 180§	Tolerance Exemption Expression	Limits	Use Pattern (Pesticidal)	CAS Registry Number and name
910[a]	propyl paraben	--	preservative	94-13-3 propyl p-hydroxybenzoate
930[b]	propyl paraben	0.1%	antioxidant preservative	94-13-3 propyl p-hydroxybenzoate

[a] Residues listed in 40 CFR 180.910 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 or raw agricultural commodities after harvest.
[b]Materials listed in 40 CFR 180.930 are exempt from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to animals.

B. Other Uses

Parabens, specifically propyl paraben, have been used as antimicrobial food additives in several food categories such as baked goods, beverages, creams, pastes, jams, jellies, preserves, syrups and other applications for more than 50 years at concentrations of between 450 ppm and 2000 ppm (Soni et al., 2005). Propyl paraben is considered as generally recognized as safe (GRAS) by the FDA for direct addition to food at concentrations up to 0.1% (21 CFR 184.1490) and by prior sanction for indirect addition via packaging materials (21 CFR 181.23). The FDA has also approved propyl paraben as a synthetic flavor substance and adjuvant for addition to foods at minimum quantity to beverages, in amounts not to exceed 20 ppm (21 CFR 172.515). As indirect food additives, propyl paraben is permitted as antimycotics in food packaging materials with no limit or restriction. In 1974, the JECFA recommended the group Acceptable Daily Intake (ADI) for the methyl-, ethyl-, and propyl-esters of p-hydroxybenzoic acid as 0-10 mg/kg body weight/day (JECFA, 1974). Table 2 summarizes the direct and indirect food additive uses (FDA uses) of propyl paraben.

Likewise, parabens are most active against molds and yeasts and have been successfully used in cosmetics for over a half century. Parabens are routinely used as preservatives in nearly all types of cosmetics (13,200 formulations), with

propyl- and methyl paraben being the most commonly used. Products containing propyl paraben may contact the skin, hair and scalp, lips, mucosae (oral, ocular, and vaginal), axillae and nails.

Additionally, parabens are employed frequently as preservatives in a wide variety of formulations for pharmaceutical uses. Propyl paraben is one of the most effective fungistats used in pharmaceutical preparations. Combinations of parabens are reported to be more active than individual parabens (Soni et al., 2005). The concentration of parabens varies from product to product but seldom exceeds 1%. Methyl- and propyl paraben are used as preservatives in several over-the-counter (OTC) drugs.

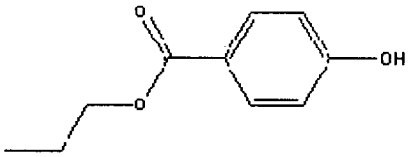
Table 2. FDA Direct / Indirect Food Additive Uses for Propyl Paraben

Name	21 CFR	Use Pattern
Propyl paraben	184.1490	GRAS, direct addition to food up to 0.1%
Propyl paraben	181.23	Indirect addition via packaging materials
Propyl paraben	172.515	Synthetic flavoring substance and adjuvant to foods at minimum quantity, and beverages no to exceed 20 ppm
Propyl paraben	556.550	A tolerance of zero for residues in milk from dairy animals

III. Physical and Chemical Properties

Some of the physical and chemical characteristics of propyl paraben, along with its structure and nomenclature, are found in Table 3.

Table 3. Physical and Chemical Properties of Propyl Paraben

Parameter	Value	Reference
Structure		ChemFinder
CAS Number	94-13-3	HSDB

CAS Name	propyl p-hydroxybenzoate	HSDB
Synonyms	Propyl paraben, propyl 4-hydroxybenzoate, propyl parasept, protoben p, propyl chemosept, preseval p	HSDB
Empirical Formula	$C_{10}H_{12}O_3$	HSDB
Molecular Weight	180.2	Golden et al., 2005
Physical State	Small colorless crystals or crystalline powder with virtually no odor or taste	FAO 1967, HSDB Merck Index 1996
Melting Point (°C)	96.2-96.8	HSDB, Soni et al., 2005 Merck Index 1996
Boiling Point (°C)	285.14 °C	Meylan, 2000
Water Solubility	463 mg/L in water at 20°C	HSDB
Other Solubility	NA	
Refractive Index	1.505	Soni et al., 2005
Relative Density (water=1)	1.0630	HSDB
Vapor Pressure	3.07×10^{-4} mm Hg @ 25°C	Meylan, 2000
pKa	8.35	Soni et al., 2005
log K_{ow}	2.71-3.04	Toxnet SIS, 2005 Golden et al., 2005 HSDB
Henry's Law Constant	1.375×10^{-7} atm-m^3/mole @ 25°C	Meylan, 2000

NA = Not Available.

IV. Hazard Assessment

Propyl paraben is being evaluated as part of the US EPA's tolerance reassessment process of inert ingredients. This hazard assessment consists of a summary hazard profile for propyl paraben followed by available data and finally special considerations for infants and children. The toxicity data base for propyl paraben is limited but adequate for the characterization of hazard. Literature information from peer reviewed articles such as Soni et al., 2001 and 2005, Golden et al., 2005, Oishi 2002, FAO 1967, WHO 1974, and BIBRA 1989 provide support for the hazard evaluation of propyl paraben.

A. Hazard Profile

The parabens, including propyl paraben, are generally absorbed from the gastrointestinal tract and metabolized either in the liver or kidney, and excreted via the urine. The clearance of metabolites of the parabens is rapid, with approximately 86% cleared within 24 hours (rabbits). Dermal penetration studies indicate a significant amount of propyl paraben (up to 30%) may be absorbed in the intact form.

The available acute toxicity data indicate propyl paraben is practically non-toxic by the oral route. Acute dermal and inhalation data were not located although eye and skin irritation studies suggest propyl paraben is non-irritating.

Oral subchronic and chronic animal studies with propyl paraben produced no systemic toxicity. Propyl paraben was non-genotoxic in mutagenicity assays and

was non-carcinogenic in transplacental carcinogenesis assays and lacked tumor promoting potential in the urinary bladder of mice.

Currently there are no reliable reproductive or developmental toxicity studies with propyl paraben. However, developmental studies exist for the chemical analog, methyl paraben, in which developmental effects were not observed in rabbits, rats, mice, or hamsters.

Recent studies indicate propyl paraben has weakly estrogenic effects *in vitro* and *in vivo*. However, the estrogenic activity of propyl paraben is orders of magnitude less potent (30,000-fold) than endogenous estrogen in an *in vitro* yeast-based estrogen assay. Propyl paraben was also demonstrated as an effective spermicide for human spermatozoa. *In vivo* studies produced conflicting responses on estrogenic potential depending on the species and route of exposure explored. However, the most recent literature study indicates significant decreases in daily sperm production and efficiency in the testes of male Wistar rats after exposure to propyl paraben in the diet (0.1%-1%) for 4 weeks. To date, this study has not been repeated or corroborated by another laboratory. A reproductive toxicity study is currently not available for propyl paraben.

B. Toxicological Data

Acute Toxicity

Table 4. Summary of Acute Toxicity Data for Propyl Paraben

Parameter	Toxicity Value	Reference
Oral LD_{50}	6322 to >8,000 mg/kg (mouse) >8,000 mg/kg (rat) 6000 mg/kg (rabbit)[a] 4000 mg/kg (dog)[a]	WHO Food Additive Series 5 Soni et al., 2005
Dermal LD_{50}, rabbit	NA	
Inhalation LC_{50}, rat	NA	
Eye Irritation, rabbit	(0.1-0.8%) no signs of irritation	Soni et al., 2005
Skin Irritation, rabbit	10%, no irritation after 48 hrs.	Soni et al., 2005

[a] LD_{100} or lethal dose; NA = Not Available

Subchronic Toxicity

Short-term and subchronic dermal studies provided by the Cosmetic, Toiletry and Fragrance Association (CFTA) were reviewed by the Cosmetic Ingredient Review (CIR) expert panel (1994). Daily dermal exposure for up to 3 months to product formulations containing up to 0.2% methyl- and 0.2% propyl paraben did not cause significant alterations on food consumption, body weight gains, hematology, blood chemistry, and urinary analysis of the exposed rabbits compared to controls. In another dermal toxicity study, 13 weeks of exposure to 0.7% methyl- and 0.3% propyl paraben caused mostly changes to the treated skin site. Body weight gain was significantly decreased in the treated rats

compared to control rats. The report concluded there was no cumulative systemic toxic effect from the formulation (review in Soni et al., 2005).

An oral gavage study with rats, propyl paraben (0.2%; 0, 40, or 200 mg/kg/day) in corn oil (dose volume 2 ml/kg) was administered daily for one month. No signs of toxicity were noted with body weight gain and food consumption, and organ weights unaffected. There were no treatment-related changes in histological examination of tissues and slight changes noted in hematological and blood chemistry values were not biologically significant (reviewed in Soni et al., 2005).

Chronic Toxicity

Chronic oral studies indicate temporary and reversible decreases in body weight gains only at high concentrations. Daily exposure of propyl paraben in the diet at 2% (0.9 to 1.2 g/kg/day) for 96 weeks did not cause any toxic effects in rats (24/sex/group). Propyl paraben at 8% (5.5 to 5.9 g/kg/day) did not cause any toxic signs or reduce body weight gains or food consumption (reviewed Soni et al., 2005). Weanling dogs (3/group) fed 0.5 or 1.0 g/kg/day by capsule 6 days/week for about one year did not produce any toxic signs. Six organs (liver, kidney, heart, lung, spleen pancreas) were examined at the end of the experiment and were reported normal (reviewed Soni et al., 2005). The 8% propyl paraben in the diet for 96 weeks did cause an increase in tumors.

Neurotoxicity

Examination of neostigmine formulations, which contain methyl- and propyl paraben as preservatives, revealed no evidence of neurotoxicity in rats and sheep from intra-thecal injection of neostigmine. Administration of neostigmine containing glucose, methyl paraben, and propyl paraben did not produce behavioral, chemical, or histopathological evidence of neurotoxicity (as cited in Soni et al., 2001 and 2005).

Mutagenicity

Mutagenicity testing reviewed by Soni et al. 2005 including the Ames test, cytogenetic assays, dominant lethal assay and host-mediated assay indicate propyl paraben is not genotoxic. Propyl paraben was non-carcinogenic in a transplacental carcinogenesis assay and a urinary tumor-promoting study.

Carcinogenicity

A review by Soni et al. 2005 of chronic and carcinogenicity studies available indicate that overall propyl paraben is not carcinogenic. Equivocal results have been documented after exposure to high concentrations of propyl paraben for the labeling index of hyperplasia in the prefundic forestomach and epithelium of the urinary bladder. For example, 3% propyl paraben administered for 20 weeks to

hamsters caused an increased labeling index in the urinary bladder epithelium. However, Fischer 344 rats administered 3% propyl paraben for 4 weeks resulted in no significant increase in labeling index of the urinary bladder. Similarly, increased labeling index of hyperplasia was observed in the prefundic forestomach of 3-4 week old rats after dietary exposure to 4% propyl paraben for 9 days. However, 3% propyl paraben in the diets of adult rats for 8 weeks failed to increase labeling in the forestomach and glandular epithelium of the stomach mucosa. It should be noted, however, that the increases in labeling index or hyperplasia of the prefundic forestomach questions the relevance of these observations to humans. Humans do not posses a prefundic forestomach.

Developmental and Reproductive Toxicity

Currently there are no reliable reproductive or developmental toxicity studies with propyl paraben. However, developmental studies exist for the chemical analog, methyl paraben, in which developmental effects were not observed in rabbits (GD 6-18, 300 mg/kg/day), rats (GD 6-15, 500 mg/kg/day), mice (GD6-15, 500 mg/kg/day), or hamsters (GD6-10, 300 mg/kg/day) (FDRL 1972 and 1973 as cited in Soni et al., 2005). A multi-generational reproductive toxicity study would be useful for the elucidation of possible developmental or reproductive effects from potential exposure to propyl paraben.

Estrogenic Activity

Recent studies in the literature with parabens indicate the potential for a weak estrogenic effect *in vitro* and *in vivo* (Lemini et al., 2003 and 2004). *In vitro*, the parabens typically demonstrate a positive correlation between estrogen receptor binding affinity and paraben chain length. An increase in chain length results in increased relative binding affinity for the estrogen receptor. However, this affinity of the parabens for the estrogen receptor must be placed into proper context. As indicated, the magnitude of the estrogenic response increases with alkyl group size, but the methyl-, ethyl-, and propyl-paraben response is approximately 2,500,000-fold, 150,000-fold, and 30,000-fold LESS potent than endogenous 17β-estradiol (E2) (Routledge et al., 1998; Soni et al., 2005). It is currently hypothesized that the parabens have estrogen-receptor dependent estrogenic activities, but that their effects on the intra-cellular signaling pathway may be different from that of endogenous E2.

In vivo studies indicate conflicting responses on estrogenic potential depending on the species, dose, and route of exposure explored. Currently there is no evidence of estrogenic activity *in vivo* in uterotrophic assays following oral administration. For example, a mouse uterotrophic assay with immature B6D2F1 mice, neither oral nor subcutaneous dose levels up to 100 mg/kg/day for 3 consecutive days produced any estrogenic response on uterus weight (Hossaini et al., 2000 as reviewed by Soni et al., 2005).

Recently, a single study reported that propyl paraben reduced sperm concentrations without treatment-related effects on the sex organ weights in immature male rats (Oishi 2002). More specifically, propyl paraben (purity 99%) was administered in phytoestrgoen-free diets (AIN93G) with corn oil (vehicle) at 0%, 0.01% (12.4±3.04 mg/kg)), 0.1% (125±30 mg/kg), or 1% (1290±283 mg/kg) for 4 weeks to immature (19-21 days) male Crj:Wistar rats (N=8) (Oishsi, 2002). A positive estrogen control group was not included in the study. Propyl paraben was administered at the onset of spermatogenesis. Daily sperm production (DSP) and sperm counts in the cauda epididymis of treated males were compared with vehicle controls males. Likewise, testosterone concentrations were evaluated after treatment and compared to controls. Testosterone concentration was not tested before and after treatment. No biologically relevant body weight loss was observed even at the high dose. However, propyl paraben at 0.1% produced a dose-related statistical ($p<0.05$) decrease in sperm reserves of the cauda epididymides (↓41% at 0.1%; ↓48% at 1%). In addition, the DSP (↓30%, ↓28%, ↓31%) and efficiency (↓31%, ↓25%,↓28%) were statistically reduced ($p<0.05$) at comparable rates in all treated males, respectively. Testosterone concentration measured from the serum was decreased 9%, 21%, and 35% ($p<0.05$) compared to controls.

There are several issues regarding the hazard characterization for the decreased daily sperm production rates from the Oishi 2005 study. First, individual animal data are not available for analysis. There was also no positive control for comparison of changes to an estrogenic chemical. Secondly, the decreased sperm levels have not been corroborated in another laboratory under similar testing scenarios. Additionally, there is the possibility that the sperm effects may have been the result of the direct toxicity of propyl paraben. *In vitro* experiments suggest propyl paraben may exert spermatocidal activity by impairment of the sperm membrane function (Song et al., 1989, 1991). However, the tissue concentration of propyl paraben in the study was not reported. Finally, the decreased sperm production and efficiency may have resulted from a hormonal imbalance or a delayed maturation (delayed sperm development), since no effect on testes or epididymal weights were affected in the study. It should also be noted that the rats used in the study were immature and at the onset of spermatogenesis.

In the past several years, potential endocrine disrupting chemicals, including data for the parabens, has been published. Parabens and other estrogenic chemicals have been detected in nanogram (ng) quantities in human breast tumors and is hypothesized they may contribute to the development of breast cancer (Golden et al., 2005; Dabre et al, 2004; Soni et al., 2005). However, there have been no published epidemiological studies to support or refute the hypothesis for a link between the use of cosmetics containing parabens or other products and the increased incidence of breast cancer. In addition, studies evaluating other weakly estrogenic chemicals have demonstrated that although a chemical may

bioaccumulate in breast tissue, bioaccumulation does not always correlate to an etiological link with increased risk of breast cancer (Golden et al., 2005).

B. Mode of Action, Metabolism, and Pharmacokinetics

Propyl parabens known mode of action is the uncoupling of oxidative phosphorylation, inhibiting NAD+ and FAD linked mitochondrial respiration and reducing mitochondrial membrane potential (Nakagawa and Moldeua, 1998 as cited in Soni et al., 2001). This mitochondrial dysfunction is likely the cause of the cytotoxicity observed in *in vitro* assays with propyl paraben.

As for absorption and metabolism, the parabens are generally absorbed from the gastrointestinal tract, metabolized in either the liver or kidney, and excreted via the urine (SCOGS, 1972; Soni et al., 2005). Esterases located in the liver and kidneys are known to efficiently hydrolyze parabens to p-hydroxybenzoic acid (Soni et al., 2005). Neither the methyl- nor the propyl parabens accumulate in the body. The major metabolites excreted in the urine, in decreasing order, were reported as p-hydroxybenzoic acid (25-39%) and the glycine (25-29%), glucuronic acid (10-18%) and sulfuric acid conjugates (7-12%) of p-hydroxybenzoic acid. The clearance of metabolites via the urine is rapid, with metabolites appearing in the urine within 30 minutes and majority (86%) cleared in 24 hrs (rabbits). However, it is reported that as the alkyl chain length increases, the rate of urinary excretion of p-hydroxybenzoic acid decreases.

An elimination study in which dogs were fed 1000 mg/kg bw propyl paraben excreted 58% of the parent in the urine. In comparison, dogs given 50 mg/kg bw by intravenous injection excreted 94% in the urine. The ester was the only detectable component in the plasma shortly after administration (FAO/WHO 1967).

Dermal penetration and occlusion studies indicate a significant amount of propyl paraben may be absorbed in the intact form with absorption varying from 30% to 100% (Soni et al., 2001 and 2005). Factors contributing to the amount of propyl paraben absorbed were mainly dependent upon the lipid solubility of the paraben, the partition coefficient, the presence of solubilizers, and the vehicle used in the study (Soni et al., 2005). Treatment of skin with an esterase inhibitor, diisopropyl fluorophosphates, is reported to inhibit the appearance of the metabolite, but failed to inhibit the penetration of propyl paraben itself.

C. Special Considerations for Infants and Children

The database for propyl paraben is limited. With regards to special considerations for infants and children, there are currently no Agency guideline developmental or reproductive toxicity studies for propyl paraben. The published literature does provide a developmental and reproductive study for methyl

paraben, a chemical analog, and these studies do not indicate any qualitative or quantitative susceptibility concerns.

However, a male reproductive development study does exist in the literature, which describes the significant decrease of daily sperm production and efficiency at 0.01% (12 mg/kg/day) of the diets of young male rats. After careful review of this literature study, it has been determined that this study is not reliable and therefore the scientific merit of the study does not allow for its formal use in risk assessment. This assessment of merit was based on the lack of available raw data for individual animals, lack of data for repetition of statistical analysis, and the lack of verification and corroboration. In addition, *in vitro* studies indicate propyl paraben is orders of magnitude less potent (30,000-fold) than endogenous estrogen (in a yeast based estrogen assay). Furthermore, the exposure to propyl paraben as an inert ingredient when limited to 0.1% in formulation to either raw agricultural commodities or animals is expected to be several orders of magnitude less than 12 mg/kg/day and therefore below levels of concern.

Therefore, based on the predicted exposure to propyl paraben from an inert use, there is no concern at this time, for increased sensitivity to infants and children to propyl paraben. 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

The Office of Pesticide Programs Environmental Fate and Effects Division (EFED) summarized the fate of the four paraben compounds by reviewing the available data and considering Structure Activity Relationships (SAR). The ester and phenol classes were used to estimate environmental behavior. The parabens, methyl-, ethyl-, propyl-, and butyl-paraben are essentially indistinguishable in terms of their environmental behavior. Table 5 provides a summary of the estimated environmental behavior of propyl paraben, relying on abiotic and biotic transformation processes and sorption characteristics. In summary, propyl paraben is considered readily biodegradable in terrestrial and aquatic environments. Primary degradation will occur within days followed by mineralization to essentially CO_2 and water in aerobic systems. Under anaerobic conditions in both terrestrial and aquatic environments, degradation will occur much slower. Abiotically, propyl paraben will undergo base-catalyzed hydrolysis especially above pH 8; as pH increases so does the rate of hydrolysis to the corresponding carboxylic acid. Occurrence in air via spray drift and volatilization (a minor route of dissipation) will undergo rapid hydroxyl radical reaction. Photolysis is not expected to be a major transformation route except under alkaline aqueous conditions. Partitioning to air from water is not expected to contribute much to the dissipation of propyl paraben. Based on the log K_{ow}, propyl paraben is not expected to bioconcentrate. Movement in the environment

in the dissolved or sorbed phase is expected to be significant based on the solubility and low estimated adsorption coefficient.

Table 5. Environmental Transformation Properties of Propyl Paraben

Parameter	Value[1]
	Propylparaben
Structure	
Aerobic Ready Biodegradability	Yes, >90% Theoretical oxygen demand
Biodegradation Results	Primary in days; ultimate in weeks
Atmospheric Oxidation ($T_{1/2}$)	Hydroxyl radical: ~9 hours Reaction with nitrate radicals may be important
Hydrolysis	Base-catalyzed hydrolysis important at ≥ pH 8
Soil Adsorption (K_{oc})	~425
Log BCF	1.6
Level III Fugacity	Air: <<1% Water: ~17% Soil: ~82% Sediment: <1%

[1](Meylan, 2000)

Movement of these molecules into surface water will be dependent on the proximity of environmental releases (applications to land and spray drift), occurrence of runoff producing rainfall relatively shortly after applications, and microbial health of the environment. A delay in transport to surface water will substantially limit concentrations in ambient water. Once in surface water, further degradation of the parabens will occur as they move through the system to drinking water intakes. Once at drinking water intakes, removal during treatment will be controlled mainly by the pH of the various steps. Since most publicly owned drinking water utilities maintain a pH of approximately 8 to reduce copper pipe corrosion, base-catalyzed hydrolysis is expected to impact final concentrations at consumer taps.

All four parabens may contaminate shallow aquifer groundwater; however, biologically-mediated degradation in both aerobic and anaerobic conditions will limit loadings, thus concentrations. There are no ambient water quality criteria or drinking water maximum contaminant or health advisory levels for any of the four parabens reviewed.

According to a report published by the Danish Environmental Protection Agency (2001), propyl paraben was readily biodegradable under aerobic conditions with partial degradation in anaerobic screening tests (ISO 11734) with ultimate biodegradability ranging from 18% to 40% of the theoretical gas production. It is possible that the parabens inhibit the anaerobic bacteria at the applied test concentration (20 mg of C/l) and that ethyl- and propylparaben were more toxic than methylparaben. The potential for bioaccumulation is low to moderate as judged from the QSAR estimated log Kow values of 3.04.

VI. Exposure Assessment

Propyl paraben is used in cosmetics, foods, food packaging, and pharmaceuticals. The use of propyl paraben as a direct food additive (0.1%) is considered GRAS by the US FDA (21 CFR 184.1490) as well as a synthetic flavoring substance and adjuvant not to exceed 20 ppm (21 CFR 172.515). A survey by the FDA/CFSAN estimated consumption of all parabens unlikely to exceed 1 mg/day with the Select Committee on GRAS Substances (SCOGS) estimating a daily average intake of both methyl and propyl paraben combined to be 0.15 mg (SCOGS, 1972 as cited in Soni et al., 2001).

As an inert ingredient in pesticides, propyl paraben is used as a preservative in agricultural and home yard and garden products. It is also used as a preservative in pest control pesticide products applied to animals (such as insect repellents), but the quantity cannot exceed 0.1% in formulation. Dietary (food and drinking water) exposure of concern is not anticipated from the use of propyl paraben as an inert ingredient in pesticide products based on the chemical's physical/chemical properties and ready biodegradation. In addition, dietary exposure from animals treated with pesticide products containing propyl paraben is not likely considering the very small amount that can be included in pesticide products (cannot exceed 0.1% in formulation). While dermal exposure to propyl paraben is possible from its inclusion in home-use pesticide products, inhalation exposure from residential use pesticide products is not expected because of the chemical's physical/chemical properties. Propyl paraben has a long history of use in cosmetic products containing parabens intended for use on normal skin is considered safe. Furthermore, products containing 0.2% propyl paraben indicate no reaction indicative of photosensitization. In addition, propyl paraben and its metabolites are generally absorbed from the gastrointestinal tract, metabolized in either the liver or kidney, and quickly excreted via the urine.

Taking into consideration all available information on propyl paraben, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to propyl paraben when considering exposure through food commodities and all other non-occupational sources for which there is reliable information. Therefore, it is recommended that the two exemptions from the requirement of a tolerance established for residues of propyl paraben when used as preservative in pesticide formulations under 40 CFR 180.910 and 930 can be considered reassessed as safe under section 408(q) of the FFDCA.

VII. Aggregate Exposures

In examining aggregate exposure, the Federal Food, Drug, and Cosmetic Act (FFCDA) 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 propyl paraben, a qualitative assessment for all pathways of human exposure (food, drinking water, and residential) is appropriate given the exposure via these pathways is orders of magnitude less than the effect observed in reproductive studies of rats.

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 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 propyl paraben and any other substances, and propyl paraben does not appear to produce toxic metabolites produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that propyl paraben 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

Propyl paraben is used in cosmetics, foods, food packaging, and pharmaceuticals. The antimicrobial properties of the parabens, especially propyl paraben, have been employed in the food industry for more than 50 years. Propyl paraben is generally recognized as safe (GRAS) for direct addition to food (21 CFR 184.1490) up to 0.1% and for indirect addition to packaging materials (21 CFR 181.23). FDA has also approved propyl paraben as a synthetic flavoring substance and adjuvant (21 CFR 172.515) not to exceed 20 ppm. The JECFA and the FEMA (1974) recommended an Acceptable Daily Intake (ADI) for the methyl-, ethyl-, and propyl-esters of p-hydroxybenzoic acid as a group of 0-10 mg/kg body weight/day.

Propyl paraben is practically non-toxic by various route of administration. Oral subchronic and chronic studies in rats produced no significant systemic toxicity. Propyl paraben was negative in genotoxicity and mutagencicity assays, failed to induce growth in transplacental carcinogenesis assays, and lacked tumor promoting potential in the urinary bladder of mice. Propyl paraben failed to

produce behavioral, chemical, or histopathological evidence of neurotoxicity. Recent *in vitro* and *in vivo* uterotrophic assays produced conflicting estrogenic potential for propyl paraben. Propyl paraben had weak estrogenic activity compared to endogenous estradiol in an *in vitro* yeast-based estrogen assay. Propyl paraben also has been demonstrated as an effective spermicide for human spermatozoa. Additionally, dietary concentrations of 0.01% -1% for four weeks resulted in decreased daily sperm production and efficiency in young rats. However, these reproductive parameters have not been verified or replicated.

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X. Ecotoxicity and Ecological Risk Characterization

The EFED previously reviewed the ecotoxicity of the four parabens. Table 6 lists the estimated toxicity of propyl paraben based on both an ester and phenol class analysis. In addition, EFED was provided with summaries of toxicity estimates for three of the four parabens for fish, aquatic invertebrates and aquatic plants (Madsen, 2001). The data for the propyl paraben is also provided in the table.

Table 6. Ecological Effects of Propyl Paraben

Taxa	Endpoint/ECOSAR Class[1]
	Propylparaben
Fish	96-hr LC_{50} = 8 ppm (esters) 96-hr LC_{50} = 7 ppm (phenols) Chronic = 2 ppm (esters) Chronic = 1.0 ppm (phenols)
Invertebrates	48-hr LC_{50} = 18 ppm (esters) 48-hr LC_{50} = 4ppm (phenols) Chronic = 0.7 ppm (phenols)
Green Algae	96-hr EC_{50} = 0.6 ppm (esters) 96-hr EC_{50} = 12 ppm (phenols)
	Literature Reported Values
Green Algae (*Pseudokirchneriella subcapitata*) (Madsen, 2001)	72-hr EC_{50} = 15(15-16) ppm
Daphnia magna (Madsen, 2001)	48-hr LC_{50} = 15.4 (8-32.3) ppm
Golden orfe (*Leuciscus idus*) (Madsen, 2001)	48-hr NOEC = 5 ppm

[1] All reported values are based on ECOSAR and are rounded estimates.

The estrogenic effects of the parabens were investigated in juvenile rainbow trout. Yolk protein (vitellogenin) was used as the estrogen-specific marker (endpoint) following repeated injections of ethyl-, propyl- and butyl-paraben (Madsen, 2001). Parabens showed estrogenic activity between 100 and 300 mg/kg with butylparaben being the most active. The major metabolite of the parabens, *p*-hydroxybenzoic acid, was also tested, but was reported to show no activity. Some estrogenic activity was also demonstrated in laboratory rats, a surrogate species for wild mammals, however, when given orally to immature rate, no activity was observed (Madsen, 2001).

Using the rat and mouse as surrogates for wild mammals, the parabens are classified as practically non-toxic when given orally, LD_{50} exposure generally $\geq$3000 mg/kg-body weight. On a chronic basis, exposures to propyl-paraben did not result in effects until doses reached 1600 mg/kg-day, generally the more toxic of the two assessed in this summary review. Effects noted were growth retardation. This effect may or may not be important ecologically.

REFERENCES:

Anonymous Expert Panel. 1984. Final report on the safety assessment of methylparaben, ethylparaben, propylparaben, and butylparaben. J. American College Toxciologists 3:147-209.

BIBRA 1989. Toxicity profile: Propyl paraben. British Industrial Biological Research Association, Surrey, UK 8 pp.

Cosmetic Ingredient Review 1994. Final report on the safety assessment of methylparaben, propylparaben, and butylparaben. Journal of the American College of Toxicology 3(5):14-209.

Dabre et al., 2004. Concentrations of parabens in human breast tumours. Journal of Applied Toxicology 24:5-13.

Danish Environmental Protection Agency 2001. Environmental and Health Assessment of Substances in Household Detergents and Cosmetic Detergent Products. Preservatives: Parabens, Environmental Project, 615: 119-123.

FAO 1967. Toxicological evaluation of some antimicrobials, antioxidants, emulsifiers, stabilizers, flour-treatment agents, acids and bases. FAO Nutrition Meetings, Report Series No. 40A, B, C WHO/Food Add./67.29

FDRL (Food and Drug Research Labs), 1972. Teratologic evaluation of FDA 71-38 (methyl paraben) US NTIS report (PB 221785), 42 pp.

FDRL (Food and Drug Research Labs), 1973. Teratologic evaluation of FDA 71-38 (methyl paraben) US NTIS report (PB 223817), 14 pp.

Golden et al., 2005. A review of the endocrine activity of parabens and implications for potential risks to human health. Critical Reviews in Toxicology. 35:435-458.

HSDB (Hazardous Substances Data Bank). 2006. U.S. National Library of Medicine, National Institutes of Health, Bethesda, MD. Searched through TOXNET. http://toxnet.nlm.nih.gov/.

Lemini et al., 2003. In vivo and in vitro estrogen bioactivities of alkyl parabens. Toxicology and Industrial Health 19:69-79.

Lemini et al., 2004. Morphometric analysis of mice uteri treated with the preservatives methyl, ethyl, propyl, and butylparaben. Toxicology and Industrial Health 20:123-132.

Madsen, Torben; Boyd, Helle Buchardt; Nylen, Dorthe; Pedersen, Anne Rathmann; Petersen, Gitte I.; Simonsen, Flemming. 2001. Environmental and Health Assessment of Substances in Household Detergents and Cosmetic Products. Environmental Project, 615. Danish Environmental Protection Agency, Ministry of Environment and Energy. Copenhagen, Denmark. http://www.mst.dk/udgiv/publications/2001/87-7944-596-9/html/default_eng.htm

Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. Twelfth Edition. 1996. Propyl Paraben #8051.

Meylan, 2000. Mylan, W. and P. Howard, 2000. Estimation Program Interface, Version 3.10. Syracuse Research Corporation, Syracuse, N.Y. For: U.S. Environmental Protection Agency, Office of Pollution prevention and Toxics, Washington, D.C.

Oishi S. 2002. Effects of propyl paraben on the male reproductive system. Food and Chemical Toxicology 40:1807-1813.

Routledge et al., 1998. Some alkyl hydroxyl benzoate preservatives (parabens) are estrogenic. Toxicology and Applied Pharmacology 153:12-19.

Soni et al., 2001. Safety assessment of propyl paraben: a review of the published literature. Food and Chemical Toxicology 39:513-532.

Soni et al., 2005. Safety assessment of esters of p-hydroxybenzoic acid (parabens). Food and Chemical Toxicology 43:985-1015.

Song et al 1989. In vitro spermatocidal activity of parabens against human spermatozoa. Contraception. 39: 331-335.

Song et al., 1991. Evaluation of the effect of butyl p-hydroxy-benzoate on the proteolytic activity and membrane function of human spermatozoa. Journal of Reproduction and Fertility 91:435-440.

TOXNET. On-line Scientific Search Engine, National Library of Medicine, National Institute of Health. http://toxnet.nlm.nih.gov. Search term: 94-13-3; Hazardous Substance Databank (last revised; 3/5/2003); accessed 2005.

WHO 1974. Toxicological evaluation of some food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers, and thickening agents. WHO Food Additives Series 5. Geneva.