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

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

DATE: September 14, 2005

ACTION MEMORANDUM

SUBJECT: Inert Reassessment of Methyl p-Hydroxybenzoate

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

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

I. FQPA REASSESSMENT ACTION

Action: Reassessment of two inert exemption(s) from the requirement of a tolerance.

Chemical: Methyl p-Hydroxybenzoate (Benzoic acid, 4-hydroxy-, methyl ester (9CI) (CA Index Name)

CFR: 40 CFR part 180.920 and 40 CFR 180.930

CAS #: 99-76-3

Use Summary: Methyl p-hydroxybenzoate is also known as Methyl paraben is used as a preservative for pesticides, as a preservative in foods, beverages, cosmetics, topical preparations, and parenteral solutions.

List Reclassification Determination:

The current List Classification for methyl p- hydroxybenzoate is 4B; it will retain its current Classification. EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to methyl p-hydroxybenzoate used as inert ingredients in pesticide formulations, the List Classification for methyl p- hydroxybenzoate will keep its 4B classification.

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the two exemptions from the requirement of a tolerance for the inert ingredient methyl p-hydroxybenzoate (CAS REG. No. 99-76-3), and with the List classification determination(s), as described above. I consider the two exemptions established in 40 CFR part 180.920 and 40 CFR 180.930 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.

Donald R Stubbs

Lois A. Rossi, Director
Registration Division

9/15/05

Date:

cc: Debbie Edwards, SRRD
Joe Nevola, SRRD

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

September 7, 2005

MEMORANDUM

SUBJECT: Reassessment of the Two Exemptions from the Requirement of a Tolerance for Methyl p-Hydroxybenzoate (Methyl Paraben)

FROM: Bipin Gandhi
Inert Ingredient Assessment Branch
Registration Division (7505C)

TO: Pauline Wagner, Branch Chief Pauline Wagner 9/15/05
Inert Ingredient Assessment Branch
Registration Division (7505C)

Background

Attached is the science assessment for methyl p-hydroxybenzoatewhich is also known as methyl paraben. The purpose of this document is to reassess two existing exemptions from the requirement of a tolerance for residues of methyl paraben as an inert ingredient, as required under the Food Quality Protection Act (FQPA section 408). This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, environmental and ecological fate, and exposure profile of methyl paraben.

Executive Summary

This report evaluates methyl paraben (CAS Reg. No. 99-76-3), 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. Methyl paraben is used in a variety of pesticide products as an in-can preservative. It is also commonly used as a preservative in foods, beverages, cosmetics, topical preparations, and parenteral solutions (Anonymous Expert Panel, 1984).

This hazard assessment relies upon peer-reviewed assessments of methyl paraben performed by the Anonymous Expert Panel (1984) and reported in the Journal of American College of Toxicology (1984), BIBRA (British Industrial and Biological Research Association (1989), Soni et al. (2002, 2001), and the primary review by Routledge *et al.* (1998). These reviews and other select primary literature are the major sources of information discussed in this assessment.

With the exception of slight skin and eye irritation in animals, few health concerns have been identified in the toxicity studies on methyl paraben. Although most tests have indicated that methyl paraben is not a skin sensitizer, there are some individuals who do develop a sensitization reaction. The chemical is not considered a carcinogen, mutagen or developmental toxin. Although there are no reproductive studies for methyl paraben, results from a screening assay suggest that it may have weak estrogenic activity. Routledge *et al.* (1998) reports that methyl paraben produced a weak positive result in an *in vitro* yeast screen. The results demonstrated that it was 2,500,000 times less active than 17β-estradiol, an endogenous compound. When methyl paraben was administered orally or subcutaneously to immature rats at levels up to 800 mg/kg/day in the *in vivo* uterotrophic assay, the results were negative (Routledge *et al.*, 1998).

The acute LD_{50} in rodents is greater than 2000 mg/kg and the chronic oral NOAEL for rats of 1050 mg/kg for a 96 week exposure. A body weight gain less than that of the controls was the only reported adverse effect.

For the general population, exposure to methyl paraben can occur using a variety of consumer products, including food, beverages, medicines, cosmetics and as an antifungal agents. Methyl paraben has been classified as GRAS by Food and Drug Administration (FDA) and listed as such under 21 CFR 184.1490.

For methyl paraben, a qualitative assessment for all pathways of human exposure (food, drinking water, and residential) is appropriate given that it is a direct food additive with a use limit of 0.1% w/w in food as a preservative (FDA), and the lack of human health concerns associated with exposure to methyl paraben when used as an inert ingredient in pesticide formulations.

There are no ecotoxicity data available in the Environmental Protection Agency's Ecotox database for methyl paraben. However, some secondary data have been found from a Danish Environmental Protection Agency review (Madsen, 2001) and estimated data using structure activity relationships (SAR) Meylan (2000, 1998). The Danish Agency concluded that methyl paraben is readily biodegradable in terrestrial and aquatic environments. Based on the log K_{ow}, methyl paraben is not expected to bioconcentrate. Movement in the environment in the dissolved phase is expected to be significant based on its solubility and low estimated adsorption coefficients. Based on its SAR, methyl paraben is considered slightly to high toxic to aquatic

organisms depending on taxa, has low toxicity to fish, aquatic vertebrates and aquatic plants. But, because of the rapid abiotic and biotic degradation of the methyl paraben, concentrations are not expected to reach levels to elite effects unless applications exceed more than 2 pounds per acre in close proximity to surface water.

Taking into consideration available information on methyl paraben, there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to methyl paraben when considering dietary exposure through food commodities and all other nonoccupational sources of dermal and other sources of exposures for which there is reliable information. Therefore, it is recommended that the exemptions from the requirement of a tolerance established for residues of methyl paraben when used as a preservative in pesticide formulations applied to growing crops only, and to animals, can be considered reassessed as safe under section 408(q) of the FFDCA.

It is recommended that a limit of 0.1% be applied to methyl paraben when it used as an inert ingredient in the pesticide formulations applied to growing crops only under 40 CFR 180.920. This recommendation will be considered at a later date.

I. Introduction

This report evaluates methyl paraben (CAS Reg. No. 99-76-3), the 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 applied to animals under 40 CFR §180.930. Methyl paraben is also commonly used as a preservative in foods, beverages, cosmetics, topical preparations, and parenteral solutions (Anonymous Expert Panel, 1984).

Methyl p-hydroxybenzoate is most commonly referred to as methyl paraben. Other synonyms in use for methyl p-hydroxybenzoate are:

Methylben
Metaben
Methyl p-oxybenzoate
Solbrol M
Preserval M

II. Use Information

A. Pesticides

The two exemptions from the requirement of a tolerance for methyl paraben that are being reassessed in this document are provided in Table 1 below.

Table 1. Exemptions from the Requirement of a Tolerance Being Reassessed in this Document for Methyl p-Hydroxybenzoate (Methyl Paraben)

Tolerance Exemption Expression	40 CFR §	Use Pattern (Pesticidal)	Limits	CAS Reg No.
Methyl p-hydroxybenzoate	180.920[1/]	Preservative for formulations	- - -	99-76-3
Methyl p-hydroxybenzoate (methyl paraben)	180.930[2/]	Preservative	Meets specifications of Food Chemicals Codex; not to exceed 0.1% in formulations.	

1. Residues listed in 40 CFR §180.920 are exempted from the requirement of a tolerance when used as inert ingredients in pesticide formulations applied to growing crops only.
2. Residues listed in 40 CFR §180.930 are exempted from the requirement of a tolerance when used as inert ingredients in pesticide formulations applied to animals.

B. Other Uses

Methyl paraben is commonly used as a preservative in foods, beverages, cosmetics, topical preparations, and parenteral solutions (Anonymous Expert Panel, 1984).

C. Regulations and Standards:

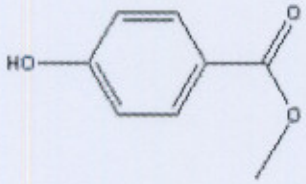
FDA has affirmed methyl paraben as generally recognized as safe (GRAS) for direct addition to food in concentrations up to 0.1% (21 CFR 184.1490). The Joint FAO (Food and Agricultural Organization) /WHO (World Health Organization) Expert Committee on Food Additives (WHO, 1974, as cited in BIBRA) has approved the use of methylparaben in food (group Average Daily Intake [ADI] for methyl, ethyl and propyl esters of p-hydroxybenzoic acid is 0-10 mg/kg bw/day).

III. Physical and Chemical Properties

Some of the physical and chemical characteristics of methyl paraben are given in Table 2 below.

Table 2. Methyl p-Hydroxybenzoate (Methyl Paraben) - Physical and Chemical Properties

Parameters	Value	Reference
Chemical Name	Methyl p-hydroxybenzoate	chemfinder.com
Molecular Formula	$C_8H_8O_3$	chemfinder.com
Molecular Weight	152.15	chemfinder.com

Structural Formula		chemfinder.com
Color/form	Solid – colorless crystal-, white powder or white crystalline powder	Bingham et al. 2001
Odor	Faint, Characteristic	Soni et al. 2002
Taste	Slight burning	Soni et al. 2002
Melting Point	131°C	Bingham et al. 2001
Boiling Point	275°C	Bingham et al. 2001
Density/Specific gravity	Not reported	
Solubility	0.3% in water	Bingham et al. 2001
Log K_{ow}	1.96	Meylan, 2000
Vapor Density	Not reported	Bingham et al. 2001
Vapor pressure	0.034 mm Hg @ 25°C	Bingham et al. 2001
Henry Law Constant	2.862×10^{-8} atm-m^3/mole @25°C	Meylan, 2000

IV. Hazard Assessment

A. Hazard Profile

This hazard assessment relies upon peer-reviewed assessments of methyl paraben performed by the Anonymous Expert Panel and reported in the Journal of American College of Toxicology (1984), BIBRA (1989), Soni et al. (2002), as well as the primary review by Routledge *et al.* (1998). These reviews as well as select primary literature were the major source of the information discussed in this assessment.

B. Toxicological Data

Acute Toxicity

Data on acute toxicity, skin and eye irritation, and sensitization are briefly summarized in Table 3. More detailed information on selected studies is provided below.

Oral LD_{50} values of 2000 to >8000 mg/kg depending on the form of the chemical have been reported for rats and mice (Soni et al., 2002). Fatal doses produced a rapid onset of ataxia, CNS depression, and death. Recovery from nonfatal doses was rapid. Matthews et al. (1956)

showed the free ester of methylparaben was less toxic than the sodium salt. Saline suspensions have been shown to be less acutely toxic than saline solutions (Soni et al., 2002).

Skin Irritation

Sokol (Soni et al., 2002) applied 10% methyl paraben to the shaved backs of 50 albino rats for 48 hours. Only mild iritation was observed. Analysis of the kidney tissue at the end of study did not reveal the presence of the parent compound or its degradation products.

Eye Irritation

Saturated aqueous solutions may be moderately irritating to the eyes; however, lower concentrations are used in eye drops as a preservative (Grant and Schuman, 1993). Simonelli and Marri (Soni et al., 2002) and Elder (Soni et al., 2002) reported that methyl paraben was slightly irritating to the eyes of rabbits.

Sensitization

Methyl paraben was injected intradermally (0.1%) into the dorsal skin of four guinea pigs 5 days a week for 8 weeks. Sites were scored 24 hour after each injection. No sensitization reactions were observed (Soni et al., 2002)

TABLE 3. Summary of Acute Lethality, Eye and Dermal Irritation and Sensitization Data

Form	Species	Route	Dose/Exposure	Endpoint	Reference
free ester in suspension	Mouse	Oral	>8000 mg/kg	LD_{50}	Matthews et al., 1956
sodium salt	Mouse	Oral	2000 mg/kg	LD_{50}	Matthews et al., 1956
0.85% saline	Rat	Oral	2100 mg/kg	LD_{50}	Litton Bionetics, as cited in Soni et al., 2002
37-79% in saline suspension	Rat	Oral	>5600 mg/kg	LD_{50}	Litton Bionetics, as cited in Soni et al., 2002
hydrophilic ointment	Rabbit	Dermal	10% 48 hr	No effect	Sokol, as cited in Soni et al., 2002
parent compound	Rabbit	Dermal	0.1 ml 24 hr	Slightly irritating; score: 0.67/4.0	Elder, as cited in Soni et al., 2002
Not reported	Rabbit	Ocular	0.2%	Slight transient conjunctival hyperemia	Simonelli and Marri, as cited in Soni et al., 2002
In isotonic saline	Rabbit Guinea pig	Ocular	0.1-0.2%	Not irritating	Soehring et al., as cited in Soni et al., 2002

TABLE 3. Summary of Acute Lethality, Eye and Dermal Irritation and Sensitization Data					
Form	**Species**	**Route**	**Dose/Exposure**	**Endpoint**	**Reference**
Not reported	Rabbit	Ocular	Not reported	Slight transient irritation; score 1/110	Elder, as citred in Soni et al., 2002
Not reported	Mouse	Dermal	5, 10, 25%	Not sensitizing	Basketter et al., 1994,
saline and Freund's adjuvant	Guinea pigs	Intracutan.	0.1% every other day for 3 wks: 0.1% intracutan, and 5% patch challenges	Not sensitizing	Maurer et al., 1980.

Basksetter et al. (1994) concluded that methyl paraben is not a skin sensitizer in the mouse local lymph node assay when tested at concentrations of 5, 10, and 25%. It was also negative in the guinea pig maximization test.

Subchronic/Chronic Toxicity

Rats maintained for 96 wks on diets containing 2 or 8% methyl paraben (equivalent to dose levels of 0.9-1.2 g/kg/day and 5.5-5.9 g/kg/day, respectively) exhibited a lower body weight gain at the higher exposure level (Matthews et al., 1956). No treatment-related microscopic effects were observed in the liver, kidney, spleen, heart, pancreas, or lung. No specific information was provided as to whether other organs were evaluated histologically. There was no indication that hematology or clinical chemistry were evaluated.

Rodrigues et al. (Soni et al., 2002) studied the short term effects of various phenols and acids, including methyl paraben, on the F344 rat forestomach epithelium. Methyl paraben (4%) was fed to 8 rats for 9 days to determine effects on the [^{3}H]thymidine labeling index and the histological appearance of the forestomach. Methyl paraben feeding did not affect the labeling index in the prefundic and mid-region of the rat forestomach. Similarly, histopathology observations did not show mucosal changes after methyl paraben feeding.

Genetic Toxicity

Mortelmans and Griffin (1981) reported that methyl paraben demonstrated no evidence of mutagenicity in the bacterium *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100, (Ames test) either in the presence or absence of a liver metabolizing fraction. Similar tests with *Escherichia coli WP 2 (uvrA)* also produced negative results. Kawachi et al. (1980), Prival et al. (1991, 1982), and Blevins and Taylor (1982) presented the same conclusions in Ames testing with *E. Coli.*

In vivo studies in rats (cytogenetic using bone marrow; dominant lethal) at doses of 5 to 5000 mg/kg methylparaben demonstrated no chromosome aberration or dominant lethal effects. The authors concluded that the compound was not mutagenic (Soni et al., 2002).

Carcinogenicity

No cancer studies are currently available for the methyl paraben. However, no observations of tumor incidence were reported in the 96 week rat studies (Matthews et. al., 1956).

Developmental Toxicity

FDRL (Food and Drug Research Labs., Inc.) performed teratology studies in mice, rats, hamsters (FDRL, 1972) and rabbits (FDRL, 1973). Groups of 21-25 animals were given four dose levels (5.5, 25.5, 118, 550 mg/kg for mice and rats and 3, 14, 65, 300 mg/kg for hamsters and rabbits) of methyl paraben, orally. Mice and rats, were administered methyl paraben on gestation days (GD) 6 through 15. Hamsters received methyl paraben on GD 6 to 10, whereas rabbits received the doses on GD 6 to 18. Animals were observed for signs of toxicity and body weights were recorded. On GD 17 (mice), 20 (rats), 14 (hamsters) or 29 (rabbits), animals were subjected to caesarian section. The number of implantation sites, resorptions, live and dead fetuses, and live pup body weights were noted. All fetuses were examined grossly; one-third underwent detailed visceral examination and the remaining two-thirds were examined for skeletal defects following staining with Alizarin Red S. The administration of up to 550 mg/kg (maximum dose studied) of methyl paraben to pregnant mice or rats (10 consecutive days) and up to 300 mg/kg (maximum dose studied) to hamsters (5 days) or rabbits (13 days) had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls. Methyl paraben was not embryotoxic or teratogenic under these study conditions.

Reproductive Toxicity

Although there are no reproductive studies for methyl paraben, *per se,* results from an *in vitro* assay suggest that methyl paraben may have weak estrogenic activity. Routledge *et al.* (1998) reports that methyl paraben is 2,500,000 times less active than 17β-estradiol, an endogenous compound, in the *in vitro* a yeast-based estrogen assay. Additionally, methyl paraben, administered orally or subcutaneously to immature rats at levels up to 800 mg/kg/day did not yield a positive response in an *in vivo* uterotrophic assay. The study included the four most used parabens – methyl-, ethyl-, propyl-, and butyl- (Routledge *et al.*, 1998).

C. Metabolism and Pharmacokinetics

Studies suggest that parabens administered orally are rapidly absorbed, metabolized and excreted (Routledge *et al.,* 1998). The rate of absorption by the skin increases with the ester chain length (Routledge et al., 1998). It appears the metabolism and elimination rates may be dose, route, and perhaps species-dependent (Kiwada *et al.,* 1979 as cited in Routledge *et al.,* 1998). Methyl paraben is more water soluble and more rapidly absorbed and metabolized in the

GI tract than the higher alkyl chain analogues (Soni et al., 2001). Thus the limited availability of the parent compound may, in part, account for the negative result in the *in vivo* uterotrophic assay.

D. Special Considerations for Infants and Children

Overall, the toxicity of acute and chronic toxicity of methyl paraben is quite low; with oral LD_{50} values in rodents greater than 2000 mg/kg, and with chronic oral NOAEL for rats of 1050 mg/kg for a 96 week exposure. This chemical is not considered a carcinogen, mutagen or developmental toxin. There is no information on reproductive toxicity. The *in vitro* and *in vivo* studies designed to identify potential estrogenic-like compounds have yielded only a weak response *in vitro* and a negative response *in vivo*. Metabolic studies suggest that methyl paraben is rapidly metabolized and excreted thus potentially reducing the residence time *in vivo*. Given these results, at this time there is no concern for potential sensitivity to infants and children resulting from exposure to methyl paraben when used as an inert ingredient in pesticide formulations. For the same reason, a safety factor analysis has not been used to assess risk and, therefore, the additional tenfold safety factor for the protection of infants and children is also unnecessary.

V. Environmental Fate Characterization/Drinking Water Considerations

The Agency summarized the fate of the paraben compounds by reviewing the available data and considering Structure Activity Relationships (SAR). The ester and phenol classes were used to estimate environmental behavior. Table 4 below provides a summary of methyl paraben's estimated environmental behavior relying on abiotic and biotic transformation processes and sorption characteristics. In summary, it 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, methyl 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 the methyl paraben. Based on the log K_{ow}, methyl paraben is not expected to bioconcentrate. Movement in the environment in the dissolved or sorbed phase is expected to be significant based on its solubility and low estimated adsorption coefficient.

Table 4. Environmental Transformation Properties of Methyl p-Hydroxybenzoate (Methyl Paraben)	
Parameter	Value - Methyl Paraben
Aerobic Ready Biodegradability	Yes, >90% Theoretical oxygen demand
Biodegradation Results	Primary in days; ultimate in weeks
Atmospheric Oxidation ($T_{1/2}$)	Hydroxyl radical: ~12 hours Reaction with nitrate radicals may be important
Hydrolysis	Base catalyzed hydrolysis important at pH $\geq$ 8
Soil Adsorption (K_{oc})	~125
Log BCF	0.8
Level III Fugacity	Air: <<1% Water: ~23% Soil: ~76% Sediment: <<1%

Movement of methyl paraben 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 the 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 methyl paraben will occur as it moves 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 treatment 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.

Methyl paraben is stable in acidic solutions. Hydrolysis occurs above pH 7. In strong alkaline solutions methyl paraben hydrolyzes to the corresponding carboxylic acid (4-methyl benzoic acid). As the carbon number of the alkyl chain increases, anti-microbial activity increases but water solubility decreases. Methyl paraben has the least anti-microbial activity compared to other alkyl parabens. Methyl paraben is not expected to be found in drinking water at levels above 1 ppb based on its environmental fate profile and Tier I modeling in vulnerable aquatic systems (Madsen, 2001).

Methyl 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 methyl paraben.

VI. Exposure Assessment

For the general population, exposure to methylparaben can occur using a variety of consumer products, including food, beverages, medicines, and cosmetics. Methy paraben is widely used as cosmetic preservative in a variety of products, including creams (hand, face, body), lotions and moisturizers; eye makeup products, foundation and other makeup products, night creams and lotions, cleansing products; hair conditioners, bubble baths; shampoos; mud packs; under arms deodorants; skin lighteners; and sachets. Methyl paraben in cosmetics is commonly used at 0.3%, however, its use may range up to 1.0%. Methyl paraben has been classified as GRAS by Food and Drug Administration and listed as such under 21 CFR 184.1490. The FDA limits the use of methyl paraben in foods to 0.1% w/w. The daily intake of methyl paraben from its use in foods has been estimated to be 1 – 16 mg/kg for infants and 4 - 6 mg/kg for persons 2 years and older (Elder, 1984). These levels are orders of magnitude below any effects observed in animal studies.

Methyl paraben has been used in a variety of pesticide products as an in-can preservative. Therefore, exposure is possible from residential uses (inhalation and dermal) and through crop uses (40 CFR 180.920). The use on animals is not expected to contribute to diet because of the very small amount that is allowed (0.1%) (40 CFR 180.930). Methyl paraben is not expected to be present in significant amounts in drinking water from its use as an inert ingredient.

VII. Aggregate Exposure

In examining the 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 methyl paraben, a qualitative assessment for all pathways of human exposure (food, drinking water, and residential) is appropriate as a direct food additive, in many foodstuffs, drugs and cosmetics and the lack of human health concerns associated with exposure to methyl paraben when used as an inert ingredient in pesticide formulations.

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 methyl paraben and any other substances, and this substance 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 methyl 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

With the exception of slight skin and eye irritation, few health concerns have been identified in the toxicity studies on methyl paraben. The acute and chronic oral toxicity of methyl paraben is quite low; with oral LD_{50} values in rodents greater than 2000 mg/kg, and with a chronic oral NOAEL for rats of 1050 mg/kg for a 96 week exposure. A body weight gain less than that of the controls was the only reported adverse effect. However, *in vitro* and *in vivo* studies on a series of parabens have demonstrated that methyl paraben has weak estrogenic acitivity in vitro, but is negative when tested in *in vivo*. The rapid metabolism and excretion of methyl paraben may decrease the parent compound's residence time in the body and thus mitigate, in part, any potential estrogenic activity.

Exposure to methyl paraben is possible through consumer products, and its use as an inert ingredient in residential, agricultural crop, and animal pesticide products. Methyl paraben is rapidly absorbed, metabolized, and excreted after oral and dermal exposures. For dietary exposure, the use on animals is not expected to contribute to diet because of the very small amount that is allowed (0.1%). As a food additive, estimated exposure levels are orders of magnitude below levels where effects are observed in animal studies. Methyl paraben is readily biodegradable and is not expected to be found in drinking water at levels of concern from agricultural or animal pesticide uses. Low levels of exposure may occur as a result of applications to crops and from residential uses, nevertheless, considering the rapid metabolism and excretion from the body and the overall low toxicity, dietary (food and drinking water) and residential exposures are not expected to result in any levels of concern.

Taking into consideration all available information on methyl paraben, EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to methyl paraben used as an inert ingredient when considering dietary exposure and all other nonoccupational sources of pesticide exposure for which there is reliable information. Overall exposure due to the inert use of methyl paraben is expected to result in human exposure below any dose level that would produce any adverse effect. Therefore, it is recommended that the exemption from the requirement of a tolerance established

for residues of methyl paraben when used on the growing crops and use on animals can be considered reassessed as safe under section 408(q) of FFDCA.

X. Ecotoxicity and Ecological Risk Characterization

EPA has summarized the toxicity estimates for methyl paraben for fish, aquatic invertebrates and aquatic plants in table 5 (Madsen, 2001). Based on the available estimates, methyl paraben may be of concern to aquatic primary producers (algae), the base of the food web, and to aquatic invertebrates and fish dependent on primary producers as food sources and habitat quality. Based on a limited Tier I analysis using the Generic Estimated Environmental Concentration model, (GENEEC), application of greater than 22 pounds per acre may exceed the endangered species level of concern (LOC) for methyl paraben. Aquatic invertebrate LOCs may be exceeded for methyl paraben with applications greater than 8 pounds per acre.

Table 5. Ecological Effects Methyl Paraben

Parameters	Endpoint/ECOSAR Class[1] Estimated Data
Fish	96-hr LC_{50} = 23 ppm (esters) 96-hr LC_{50} = 22 ppm (phenols) Chronic = 9 ppm (esters) Chronic = 3 ppm (phenols)
Invertebrates	48-hr LC_{50} = 120 ppm (esters) 48-hr LC_{50} = 8 ppm (phenols) Chronic = 2.5 ppm (phenols)
Green Algae	96-hr EC_{50} = 2 ppm (esters) 96-hr EC_{50} = 76 ppm (phenols)
Literature Reported Values	
Green Algae (*Pseudokirchneriella subcapitata* (Madsen, 2001)	72-hr EC_{50} = 91(90-93) ppm
Daphnia magna (Madsen, 2001)	48-hr LC_{50} = 11.2 (5.7-22.0) ppm
Golden orfe (*Leuciscus idus*) (Madsen, 2001)	48-hr NOEC = 50 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 methyl paraben (Madsen, 2001). Parabens showed estrogenic activity between 100 and 300 mg/kg with methyl paraben being the least active. The major metabolite of the methyl paraben, *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 rat, no activity was observed (Madsen, 2001).

XI. Proposed Regulatory Action

The Agency will be recommending a limit of 0.1% for methyl paraben when it is used as an inert ingredient in the pesticide formulations applied to growing crops only under 40 CFR 180.920. This recommendation will be considered at a later date.

References

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