Reregistration Eligibility Decision for Methyl salicylate

November 2005

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

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MEMORANDUM:

Subject: Reregistration Eligibility Document for Methyl Salicylate

From: Janet Andersen, Director
Biopesticide and Pollution
Prevention Division (7511C)

To: Debra F. Edwards, Director
Special Review and
Reregistration Division (7505C)

This Memorandum is to inform you that the Biopesticide and Pollution Prevention Division has completed its review of the available data related to the preliminary risk assessment of the biochemical pesticide active ingredient, Methyl salicylate. Our decision regarding the reregistration eligibility of this active ingredient can be found in the attached document entitled, "Reregistration Eligibility Decision for Methyl Salicylate" which was approved on October 27, 2005.

Attachment:
Reregistration Eligibility Decision for Methyl Salicylate

METHYL SALICYLATE

Reregistration Eligiblity Document

OPP Chemical Code: 076601

Issued: September 27, 2005

METHYL SALICYLATE

I. Chemical Overview:

Methyl salicylate (OPP Chemical Code 076601) is the primary constituent in Oil of Wintergreen, a naturally fragrant oil. It may be characterized as a colorless, yellowish or reddish, oily liquid with the distinct odor and taste of wintergreen or *gaultheria*. Methyl salicylate can also be derived synthetically, and this synthetic variety of methyl salicylate is considered to be structurally and functionally equivalent to the naturally occurring Oil of Wintergreen. Methyl salicylate is manufactured from the steam distillation of macerated leaves from the low growing plant, *Gaultheria procumbens* Lime. (fam. Ericaceae) or from the bark of *Betula lenta* (Sweet Birch).

Common Name: Methyl salicylate

Chemical Names: 2-(methoxycarbonyl) phenol
2-hydroxybenzoic acid methyl ester (CAS Name)
Salicylic acid, methyl ester
Benzoic acid, 2-hydroxy-, methyl ester

Trade and Other Names: Oil of wintergreen (synthetic); Wintergreen oil (synthetic); Gautheria oil (synthetic); Sweet birch oil; Betula oil; Teaberry oil

Chemical Formula: $C_8H_8O_3$

Chemical Family: salicylates

Molecular Weight: 152.15

Percent Composition: C - 63.15%, H- 5.30%,) - 31.55%

Melting Point: mp -8.6^0

Boiling Point: bp 220-224
Flash point: Flash pt, closed cup: 210^0F (99^0C)

CAS Registry Number: 119-36-8

OPP Chemical Code: 076601

Basic Manufacturers:

Bakers's 18 Corporation
5003 Brittany South, Suite 3 Drive
St. Petersburg, FL 33715

Caraustar Industries, Inc.
7960 Lorain Avenue
Cleveland, OH 44102

I. Regulatory History:

The active ingredient methyl salicylate was first registered as a pesticide by the Agency in 1972 for use as an animal repellent in impregnated twist tabs hung on plants to repel dogs and cats from flower gardens. In 1996, the Agency registered methyl salicylate as an insect repellent to be used as a constituent of food and feed packaging material to repel insects in stored commodities (i.e., Indianmeal moths). This registration is considered to be a "food use", since it entails use in stored food commodities and thus necessitated the establishment of an exemption from the requirements of a tolerance, see 40 CFR §180.1189.

II. Use Profile:

The following is information the uses of methyl salicylate with an overview of currently registered use sites and application methods.

Type of Pesticide:

Biochemical insect repellant and animal repellent. Both the biochemical insect repellent and animal repellent have "non-toxic" or more appropriately, non-lethal modes of action to the target pest.

Use Sites:

Methyl salicylate has a long history of use in consumer products as a counterirritant and as an analgesic in the treatment and temporary management of aching and painful muscles and joints. Methyl salicylate is also used in suntan lotions (as an UV-absorber) and perfumery as a modifier of blossom fragrances. The pesticidal uses of methyl salicylate include vertebrate repellent on terrestrial and greenhouse food crops and as an insect repellent when incorporated into a coating on the internal and outer surfaces of cartons used to store consumer products like human and pet foods, animal feeds and nonfood items such as clothing and textiles.

Target pest:

Insects (e.g., Indianmeal moth) that infest stored commercial and consumer food and feed products. Animal repellent (e.g., dogs and cats) for use on ornamental plants in residential garden plots.

III. Science Assessment:

The mammalian toxicology and ecological effects data requirements for methyl salicylate have been fulfilled through literature citations. The product analysis data requirements have been reviewed and determined to be adequately satisfied. Several product registrations have been issued under Section 3(c)(5) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) based on the information submitted to the Agency. In granting these product registrations, the Agency did not foresee any unreasonable adverse effects to humans and the environment from the use of methyl salicylate when used as directed by the product labeling. After re-evaluating this information and other pertinent data, the Agency maintains this position, and does not foresee any unreasonable adverse effects to humans and the environment from the use of methyl salicylate when used as the active ingredient in insect and animal repellents.

A. Physical/Chemical Properties Assessment:

The product chemistry data requirements for methyl salicylate are fully satisfied.

Product Identity:

Methyl salicylate (Pesticide Chemical Code 076601) is the major constituent of oil of wintergreen which is a natural fragrant oil. Methyl salicylate is a colorless, yellowish or reddish, oily liquid with the odor and taste of wintergreen. Synonyms for methyl salicylate include: Oil of Wintergreen (synthetic), Wintergreen Oil (synthetic), *Gautheria* Oil (artificial), Sweet Birch oil, Betula Oil, and Teaberry Oil.

Chemical names for Methyl salicylate include; 2-(methoxycarbonyl) phenol, 2-hydroxybenzoic acid methyl ester, benzoic acid, 2-hydroxy-, methyl ester, salicylate acid, methyl ester. The CAS Registry number for Methyl salicylate is 119-36-8; its Pesticide Chemical Code is 076601; and its RTECS and FEMA numbers are V04725000 and 2745, respectively.

The molecular chemical formula for Methyl salicylate is $C_8H_8O_3$. The molecular weight for Methyl salicylate is 152.15 with a percent composition of: C = 63.15%, H = 5.30%, O = 31.55%.

B. Acute Toxicity:

The Acute oral and dermal LD_{50} values are summarized from the published literature in TABLE 1 listed on the next page:[1]

Table 1: Summary of acute oral and dermal toxicity studies with Methyl salicylate.

Study	LD_{50} (mg/kg)	Toxicity Category	MRID Number
Acute Oral			
-rat	887 (715-100)	III	44213005
-rat	1250	III	44213006
-mouse	1110	III	44213007
-guinea pig	1060 (836-1300)	III	44213005
-guinea pig	700	III	44213006
-rabbit	1300	III	44213006
-rabbits	2800	III	44213009,-10
-dogs	2100	III	44213009,-10
Acute Dermal			
-rabbit	>5000	IV	44213006

:[1] Memorandum, Consideration of uncondictional registration of methyl salicylate as a new active ingredient. Signed, Janet L. Andersen, Director, Biopesticide and Pollution Prevention Division, Dec. 30, 1997. pp. 15.

Methyl salicylate is a liquid that is not expected to result in appreciable inhalation exposure under the conditions of formulation or use. The end use products are prepared from slow release matrices impregnated with the insect repellent which release small amounts of methyl salicylate vapors over extended periods of time (>1 month). Similarly with the animal repellent twist tie products, the active ingredient, methyl salicylate, is impregnated into a plastic matrices twist ties and the vapors are released in small amounts over an extended time period. Based on the low anticipated exposures from this use and taking into consideration the results indicated in a subchronic inhalation toxicity study (discussed below) and other acute and chronic toxicity data, the requirement for an acute inhalation study was waived.

Toxic signs observed in the acute studies with rats included depression soon after dosing, and deaths were observed 4 to 18 hours after treatment. Guinea pigs exhibited convulsions and gastrointestinal irritation; deaths occurred in these animals from 1 hour to 3 days following treatment. In single dose studies in dogs (MRID 44213006), oral (gavage) doses of 0.6-4.7 g methyl salicylate/kg caused emesis, intense hyperpnea, excitation of the central nervous system and diarrhea. Two dogs initially recovered these effects but died later at 8 and 18 hours after dosing. Three anesthetized dogs given 0.6-5 g/kg showed an increase in respiratory amplitude without change ins in arterial pressure. An oral dose of 700 mg methyl salicylate/kg body weight given to dogs reduced blood pressure and cardiac output with a slight increase in heart rate within 5 hours. According to the report (MRID 44213006), the myocardial failure produced by this dose was related to hyperkalemic cardiomyopathy and uncoupling of oxidative phosphorylation. Elevated creatine-phosphokinase levels in the coronary effluent, an increase in

arterial lactate, potassium ion and oxygen and an increase in arterial epinephrine and norepinephrine were noted. Similar results were obtained following infusion of 700 mg methyl salicylate/kg into hindlimb muscle of dogs (MRID 44213006).

The minimum lethal subcutaneous (sc) dose in guinea pigs was reported as 1500 mg/kg (MRID 44213008), while other results quoted were 2700-2750, 4250-4350 and 2250 mg/kg for the lethal sc doses in the guinea pig, rabbit and dog, respectively (MRID 44213006).

A primary skin irritation test in rabbits evaluated methyl salicylate in four vehicles (MRID 44213011). The test material was suspended in water or dissolved in PEG 400, 70% ethanol, or 70% ethanol plus emollients at concentrations of 1, 3 or 6% and was applied to shaved and depilated intact skin of test rabbits. No irritation was observed at sites treated with the 1% water suspension at 24 or 72 hours following application of the test material. Primary irritation indexes were summarized in the report as follows:

Table 2:[2] Methyl Salicylate in Various Vehicles; Rabbit Primary Irritation Indices On Intact Skin

	Methyl Salicylate (%)		
	1	3	6
Vehicle	Irritation Index		
H_2O*	0.0	0.83	1.83
PEG 400	0.33	0.50	0.50
70% Ethanol	1.17	4.17	4.00
70% Ethanol + emollients	2.17	3.00	3.00

*Suspensions

*[2] Memorandum, Consideration of uncondictional registration of methyl salicylate as a new active ingredient. Signed, Janet L. Andersen, Director, Biopesticide and Pollution Prevention Division, Dec. 30, 1997. pp. 17.

These results indicate mild irritation for all three concentrations of methyl salicylate in PEG 400 and the 1% concentration in 70% ethanol. The two higher concentrations in 70% ethanol were moderate irritants which produced necrosis in all three animals that were treated at each concentration. The ethanol plus emollient solutions were all moderately irritating. According to the report, the 1% solution was the least reactive, but all concentrations elicited necrosis and intradermal and subcutaneous hemorrhage.

In a summary table (MRID 44213010), methyl salicylate was listed as a severe skin and eye irritant in guinea pigs which indicates a Toxicity Category II.

The requirement for a hypersensitivity study with methyl salicylate is waived based on the following factors. Occupational exposure is likely to be intermittent and it will be significantly reduced by use of personal protective equipment such as rubber gloves, splash-proof goggles and/or face shield. Also insect repellent packaging materials that contain Methyl salicylate in stable chemical matrices which will minimize the release or migration of extremely low doses from the packaging materials. Additionally, the level of methyl salicylate in packaging materials will be substantially less than levels found in topical ointments/liniments.

C. Subchronic Toxicity Studies:

Since methyl salicylate has food uses, the requirement for subchronic toxicity is required for registration.

Groups of 10 male and 10 female weanling Osborne-Mendel strain rats were fed diets containing 0, 1,000, and 10,000 ppm methyl salicylate for 17 weeks (MRID 44213014). A statistically significant decrease in mean body weight gain ($p \leq 0.001$) was observed in males given the 10,000 ppm methyl salicylate diet (375.6 for controls and 286. g for the treated group). Females showed a similar decrease in body weight gain (controls gained an average of 197.9 g and the 10,000 ppm dose group females gained 143.2 g; ≤ 0.001). No other effects were noted following gross and microscopic examinations of test animals according to the report. The NOEL was established at 1,000 ppm (-50mg/kg/day), and the LOEL was established at 10,000 ppm (-500mg/kg/day) based on the decreased body weight gain in both sexes of rats.

Groups of one male and one female beagle dogs were given oral doses (by capsule) of 50, 100, 500, 800, or 1200 mg methyl salicylate per kg body weight daily, six days each week for 59 days (MRID 44213014). Emesis was observed in two dogs receiving 1200 mg/kg/day and in one dog receiving 800 mg/kg/day 3-4 hours following the administration of each dose.

Dogs given 500 mg/kg/day dosage had diarrhea and weakness during the last 3-4 days and lost weight. At this and higher dose levels, dogs lost weight and were sacrificed *in extremis* or died within a month on the experiment.

The only treatment-related microscopic change in the test animals noted was in the livers of two dogs given the 1200 mg/kg/day dose and in one dog at the 800 mg/kg/day dose level (moderate to marked fatty metamorphosis). Based on the results reported for this study, a NOEL was established at 250 mg/kg/day, and the LOEL was 500 mg.kg.day based on decreased body weight.

Groups of three rabbits (mixed males and females) were given dermal applications of 0.5, 1,2,or 4 ml methyl salicylate per kg body weight per day for 5 days each week for up to 96 days (MRID 44213014). The application sites were clipped weekly, and the test animals were restrained during the 6½ hour daily exposure periods to prevent oral ingestion of the test material. The authors noted that the test compound was absorbed by the end of each exposure, so application sites were not wiped before the rabbits were returned to their cages.

Three rabbits receiving the 4 ml/kg/day dose died (one each at 6, 8, and 28 days), and anorexia, weight loss, depression were observed in these animals before their deaths. Slight sloughing of epidermal scales was noted by the investigators in two of the three rabbits at the 2.0 ml/kg/day dose level at day six. The remaining animals showed no skin abnormalities.

According to the report, microscopic changes in the rabbits at the 4 ml/kg/day dose level included dilation, desquamation, and formation of new atypical epithelium of the renal tubules with the distal portions of the nephrons more affected. Foci of moderate necrosis and slight calcification of voluntary muscles, marked vacuolation of pancreatic acinar cells, slight hepatitis were also noted in the animals receiving the highest dose tested. The investigators indicated that there was an increased incidence of spontaneous nephritis and mild hepatitis over that in rabbits on other experiments, and there was slight to very slight dermatitis.

The study did not have a control group, and the incidence of microscopic effects in the kidneys were not presented for the surviving test animals. Therefore, a NOEL for systemic toxicity can not be demonstrated from the results as presented from this study. A NOEL for Subchronic dermal toxicity was established at 2 ml/kg/day (~2368 mg/kg/day), and a LOEL was observed at 4.0 ml/kg/day (~4736 mg/kg/day) based on dermal effects and lethality.

In a Fragrance Materials Monograph on Methyl salicylate (MRID 44213006), a study was described in which rats were exposed for 20 days to a saturated atmosphere (~700 mg/m^3) for 7 hours per day without any reported effects.

The requirement for immune response studies with methyl salicylate was waived based on very low anticipated exposures and low toxicity indicated by submitted study reports. Occupational exposure is likely to be significantly reduced by the use of personal protective equipment such as rubber gloves, splash proof goggles and/or face shield. Insect repellent packaging materials will contain impregnated methyl salicylate stable chemical matrices that minimize release or migration from the packaging into the food contents. Also, the level of methyl salicylate in packaging materials will be much less than levels found in topical ointments, liniments, lotions, oral mouth rinses, and certain foods (e.g., baked goods, beverages, chewing gum and candies). Finally, mutagenicity and chronic toxicity, discussed later, as well as acute subchronic, developmental, and reproduction studies have not indicated significant effects on relaxant endpoints at low dose levels.

D. Chronic Toxicity and Carcinogenicity:

Groups of 25 female and 25 male weanling rats were fed diets containing 0, 1000, 5000, 10,000, and 20,000 ppm methyl salicylate (approximately 0, 50, 250, 500, and 1000 mg/kg/day) for 2 years (MRID 44213014). The reports stated that rats given the 10,000 and 20,000 ppm diets had rough hair coats and significantly decreased growth. Half of the animals in the 20,000 ppm dose group died after 8 weeks of treatment, and the remaining test animals all died by 49 weeks.

According to the investigators, the data pertaining to organ weight and hematological results did not indicate any dose related or toxicologically significant changes in treated groups in study.

The reported incidence of gross lesions in rats on the 5000 ppm diets differed from that in the control rats. The investigators noted that pituitary lesions (no further details given) were observed in 10 rats on the 5000 ppm diet and in only 4 control rats; no gross lesions of the pituitary in rats from the 10,000 ppm dose group were mentioned in the report so it was assumed that those animals also had a 100% incidence. Other gross observations such as pneumonia, nephritis, and tumors were seen in similar numbers of rats on all diets with the exception of those animals given 20,000 ppm. diet.

According to the investigators, microscopic examination revealed an increased amount of cancellous bone (in metaphysis) of rats given the 20,000 ppm diet when compared to those of the control rats of the same age. The report noted bone changes were moderate in 5 and marked in 4 of 9 bones examined from the highest dose group. At the 10,000 ppm dose, 2 of 11 bones examined showed slight changes. Affected bones had fewer osteoclasts as the degree of change increased.

The investigators noted similar kinds of incidences of tumors occurred in rats on all diets except the 20,000 ppm diet which contained no survivors after the first year. The most commonly observed tumor according to the report was mammary tumors of the female rats. Based on the reported results, a NOEL for systemic toxicity was established in the study at 1000 ppm (~50 mg/kg.day) and the LOEL was observed at 5,000 ppm (~250 mg/kg/day) based on the incidences of rough hair coat, decreased growth, gross lesions of the pituitary gland, bone changes, and mortality.

Although most of the effects noted in this chronic feeding study occurred in a group of rats receiving an excessively toxic dose (as indicated by the previously described high mortality), a supplemental study was conducted to evaluate the effects of Methyl salicylate on bone (MRID 44213014). Groups of 3 male and 3 female weanling rats were fed diets containing 0, or 20,000 ppm methyl salicylate for 71 days. (The duration of the study was limited because of the mortality induced by methyl salicylate in treated animals). According to the report, results of the chronic and special studies indicate that at 20,000 ppm methyl salicylate in the diets of rats, chrondroclastic and especially osteoclastic activity are blocked or diminished. Because of this, the ends of the bones are filled with an excessive lattice of persistent primary trabeculae. The articular cartilage was also delayed in resorption and production of primary trabeculae which persists longer than expected. In addition to the bone changes, focal gastric hemorrhages were observed in the glandular portion of the stomachs of 3 of 6 treated rats.

Groups of 2 male and 2 female beagle dogs were given methyl salicylate orally in capsules containing 0, 50, 150, or 350 mg/kg/day for 6 days each week for 2 years (MRID 44213014). One high dose female died of canine infectious hepatitis after 33 days, and its replacement died 19 weeks later of canine distemper. There were no other deaths in the study.

Dogs given the 150 and 350 mg/kg/day doses showed retarded growth. Dogs given the 150 mg.kg/day dose gained 0.5 kg, dogs in the 350 mg/kg/day group lost 1.9 kg and the control group animals gained 1.85 kg during the study. Absolute and relative (to body weight) organ weights for the liver in dogs given the two highest dose levels were increased, and hepatocellular hypertrophy was observed in these treated animals, while none was seen in control group dogs. The NOEL established by this study was 50 mg/kg/day, and the LOEL was 150 mg/kg/day based on reduced body weight gain, increased absolute and relative liver weights, and an increased incidence of hepatocellular hypertrophy.

According to the information presented in the abstract (MRID 44213018), groups of 25 male and 25 female weanling rats were given test diets containing 0, 0.07 or 0.21% natural oil of sweet birch (U.S.P. XV) for two years. There were no effects noted on survival, growth, food consumption, and general condition of animals in the two treated groups hen they were compared with control animals. There were also no treatment related effects noted at necropsy or microscopic examinations of test animals. A smaller group that was given a diet containing 0.06% "butter yellow" as a positive control (hepatic carcinogen) was also included, but no results were reported in the abstract .

Developmental Toxicity:

Groups of pregnant rats received dermal applications of methyl salicylate (in a petroleum based grease [PBG]) at dose of 0, 1, 3, or 6 g/kg/day on gestation days 6-15 (MRID 44213016). Undiluted methyl salicylate was applied to positive control group at a dose of 2 g/kg/day and was reduced to 1 g/kg/day on gestation days 10-15 because of maternal mortality (25%) and severe dermal irritation.

The positive control group exhibited a 100% incidence of total resorptions. Urinalysis revealed very high concentrations of salicylic acid (unspecified in report) in these animals.

According to the abstract of these studies, a significant proportion of the dermally applied methyl salicylate was absorbed. However, the urinary concentrations of salicylic acid in PBG treated animals were far below the toxic levels observed in the positive control group (no data included in the report). There were no effects noted on food consumption, body weight, clinical signs, and reproductive parameters in any group treated with methyl salicylate in PBG, and no increased incidences of fetal malformations or variations were reported in these groups. On the basis of the results, the investigators, concluded that the developmental toxicity of methyl salicylate is confirmed and that methyl salicylate in PBG was not teratogenic under the conditions of the study. The maternal and developmental NOEL's for the test materials in rats was established at >6 kg/day when applied dermally in petroleum based grease.

Groups of virgin female hamsters were given a single oral and dermal dose of 0 and 175 mg methyl salicylate per 100 g body weight at day 7 and 9 hr. of gestation (MRID 44213015). The dermal doses were applied to areas of shaved skin on the back of the neck, and these animals were anesthetized with 13 mg nembutal during a 2 hour exposure period in order to prevent grooming of the treatment site. After the dermal exposure period, treated skin was thoroughly-

washed with running water. Blood samples were collected from all groups (under light anesthesia) following treatment. These samples were analyzed spectrophotometrically for salicylate concentrations.

The report indicated that most of the embryos were recovered after 9 days of gestation, although some were not harvested at that time. However, those embryos only survived to gestation day 12.

The incidence of neural tube defects was summarized in the report as follows:

Incidence of neural tube defects in 9-day Hamster embryos

Treatment

				Methyl salicylate (mg/100g)		
Observation	Oral Control	Topical control	Nembutal control	175 oral	350 topical	525 topical
Number of Litters	17	6	9	35	6	19
% neural Tube Defects	11	0	0	72	6	53

The report described the defects produced by methyl salicylate treatment as failure of closure of the neural tube with resulting cranium bifidum and/or spina bifida which typically involved the midbrain region. These defects most frequently involved both the cranium and spine rather than the spine alone. Malformations observed in embryos in orally or topically treated groups were similar.

According to the report, plasma salicylate levels reached a peak of 125 mg/100 ml at about 2 hours after oral treatment and returned and returned to control levels during the next 8-10 hours. Peak plasma concentrations of 50 mg/100ml were observed 5-6 hours following dermal application of methyl salicylate, and the investigators noted that levels similar to oral control values were also observed during the next several hours following dermal treatment. The study authors further noted that increasing the dermal dose to five times the 175 mg/100g oral dose resulted in a peak plasma salicylate level of 120 mg/100g (similar to that following oral treatment). However, the higher dose was difficult to apply and too stressful for the animals to continue being treated.

Comparisons of material and fetal salicylate levels were presented in the study as follows:

Comparison of maternal and fetal salicyate levels after oral Methyl salicylate treatment

Time after Treatment (hr)	Salicylate levels (Mg/100 ml fluid)	
	Maternal	Fetal
1	40.2	21.6
2	56.3	29.8
2.5	44.8	39.8

Reproduction Toxicity:

A three generation reproduction study (MRID44213020) was conducted in rats with two litters per generation. The animals were fed diets containing methyl salicylate at levels of 0, 500, 1500, 3000, and 5000 ppm (approximately 0, 25, 75, 150, and 250 mg/kg/day) for the entire study. Separate groups F_{2b} rats (first litter of second generation) from each dose level were fed 1500 ppm calcium carbonate in addition to the methyl salicylate. Those animals were mated, and their first and second litters were evaluated along with the other offspring in the study.

No mention was made of parental toxicity observations other than reproductive findings.

According to the report, there were decreases in fertility in 5000 ppm dose group. Overall fertility in the control group was 100% compared with 92% at the 5000 ppm dose level for the first mating in the study, and the values reported for the second matings in the study were 97% and 88% in the control and 500 ppm level in the first and second matings of the second generation (10.8 compared to 6.2 pups/litter in the first mating for control and treated groups, respectively). The average litter sizes for the second mating of the second generation at the 3000 ppm level were also decreased (11.9 and 9.4 in the control and 3000 ppm groups, respectively). Since these differences were not observed consistently (i.e., they were not seen in the first and third generations) in the study, there may be causes other than administration of methyl salicylate for the differences reported for these parameters.

Statistically significant decreases in viability (number of live pups born/liter) were observed in both matings at 3000 and 5000 ppm dose levels in the second generation, but these changes are related to the initial decrease in the total number of pups per litter noted above. Calculated viability indexes (number of live pups born/total pups) for these litters are comparable to controls with the largest difference being 0.85 in the first mating of the second generation at

5000 ppm compared with a 1.00 value for controls. Survival to lactation Day 4 and weaning showed similar results, but these results were also related to the increased number of stillborn pups noted in fertility and viability results Again, differences noted for viability and survival were only noted for the second generation at the 3000 and 5000 ppm group females were 32.9 - 44.7 g and 34.8 - 425 g, respectively.

The livers and kidneys of weaned pups from the last litters of the 0, 3000, and 5000 ppm dose groups were examined microscopically and no signs of toxicity were noted.

The authors concluded that the most significant effects were evident by day 4 *post partum*. They further noted that methyl salicylate exhibited its effects mainly on fertility, reduced litter size viability and survival indexes at the 3000 and 5000pp dose levels during the second of three generations. Based on the reported results, a reproductive NOEL was established at 500 ppm (~75 mg/kg/day), and an LOEL was observed at 3000 ppm (~150 mg/kg/day) based on decreased fertility and viability.

Groups of eleven week old male and female mice were given gavage doses of 0, 01., 0.25, and 0.5 g methyl salicylate per kg body weight for a 7-day premating period, and were then randomly grouped as mating pairs and cohabited and treated continuously for 100 days. After the 100-day cohabitation. The pairs were separated but continued on treatments. During the next 21 days, final litters were delivered and kept for at least 21 days (weaning).

No treatment related mortalities or signs of toxicity were observed, and no effects on male or female body weights were noted.

At the 0.5 g/kg/day dose level, the investigators noted significant decreases in the mean number of litters per pair (4.92 and 4.30 litters/pair in the 0 and 0.5 g/kg/day dose groups, respectively), the average number of pups per litter (11.3 and 7.8 for control and treated groups, respectively), the proportion of pups born alive (0.97 in the control group and 0.91 in the 0.5 g/kg/day dose group), and mean live pup weights (1.62 and 1.57 g/kg/day for controls and treated groups, respectively).

According to the report, fertility and mating indexes in the control group were considerably lower than expected (5/17), and the experiment was repeated. In the repeat study, fertility in all three groups (Control Male vs Control Female; 0.5 g/kg/day Male vs Control Female; Control male vs 0.5 g/kg/Female) was low and similar in all three groups. These results are summarized from the report as follows:

Treatment Group	No. with Copulatory plug/No. cohabited	Mating index(%)[a]	No. fertile/No. Cohabited	Fertility index(%)[b]
Control male vs. control female	10/17	59	7/17	41
0.5g/kg male vs control female	7/18	39	8/18	44
Control male vs 0.5 G/kg female	10/18	56	11/18	61

a: Mating index (%) = (No. with copulatory plugs ÷ No. cohabited) x 100
b: Fertility index (%) = (No. fertile ÷ No. cohabited) x 100

The reproductive performance of animals in the second trial was evaluated by observation of the numbers of live male and female pups per litter, proportion of pups born alive, sex ratio, and pup weights, and there was no effect on those observed.

Based on the results of the continuous breeding studies in mice, the NOEL for reproductive effects was established at 0.25 g/kg/day. and the LOEL is 0.5 g/kg/day based on the decreased number of litters per pair and reduced live litter size.

Mutagenicity:

A modified Ames assay was conducted with *Salmonella typhimurium* strains TA98 and TA100 and a single dose of ~10 mg methyl salicylate per plate without metabolic activation or with activation systems prepared from polychlorobiphenyl (PCB) generated liver in rats, mice, guinea pigs or hamsters. Mutagenic activity was noted in cultures with the hamster activation system. The numbers of revertant colonies in the TA98 strain were 38± 7 and 74± 4in the control and treated cultures, respectively, and the respective values for strain TA100 cultures were 182± 33 and 400± 41 revertants per plate. No significant increase in the numbers of revertant colonies were observed in cultures with the other metabolic systems from the other three species, and no increases were observed in the absence of metabolic activation.

A more complete Ames assay was conducted with *Salmonella typhimurium* strains TA1535, TA1537,TA98, and TA100 with and without Aroclor 1254-induced rat and hamster metabolic activation systems (MRID 44213012). Methyl salicylate was added to each bacterial culture in DMSO at concentrations of 0, 1,3,.3, 10,33.3, 100, and 333.3 µg/plate. No mutagenic activity was observed at the concentrations tested in the absence or presence of metabolic activation.

In a third bacterial assay (MRID 44213013), the potential of methyl salicylate to damage DNA was evaluated in Bacillus subtillus strains H17(Rec^+) and M45 (Rec^-). The inhibition zones of cell growth around discs containing 5 mg of methyl salicylate were compared for each

of the two strains, and when the difference in the zones was 2mm or more, the test material would be considered capable of damaging cellular DNA. Methyl salicylate was not found to cause DNA damage, since the difference in zones observed was 1.2± 0.3 mm.

The results of these three assays taken together do not suggest that methyl salicylate has mutagenic potential in bacteria unless very high doses are used (>5,000 μg/plate).

The requirement for additional mutagenicity studies with methyl salicylate is waived based on the following factors. Occupational exposure is likely to be significantly reduced by use of personal protective equipment such as rubber gloves, splash-proof goggles, and/or face shield. Insect repellent packaging materials will contain methyl salicylate in stable chemical matrices that minimize the biochemical's release or migration from packaging into food contents. Also, the level of methyl salicylate in packaging materials will be much less than levels found in topical ointments, oral mouth rinses, and certain foods (e.g. baked goods, beverages, chewing gum and candies). Finally, developmental, reproduction and chronic toxicity studies of methyl salicylate have not indicated significant effects on relevant endpoints.

SUMMARY OF EFFECT LEVELS FOR SUBCHRONIC TOXICITY, CHRONIC TOXICITY, REPRODUCTIVE TOXICITY AND CARCINOGENICITY, AND MUTAGENICITY STUDIES CONDUCTED WITH METHYL SALICYLATE

Type of Study	NOEL	LOEL	Basis for establishment fo effect level
Subchronic dietary exposure in Rats	1000ppm (~50mg/kg/day)	10,000 ppm (~500mg/kg/day)	Decreased body weight gain in both sexes.
Subchronic dietary exposure in Beagle Dogs	250mg/kg/day	500 mg/kg/day	Decreased body weight gain.
Subchronic dermal Toxicity in Rabbits	2ml/kg/day (~2368 mg/kg/day)	4.0 ml/kg/day (~4736 mg/kg/day)	Dermal effects and Lethality.
Chronic Toxicity (Systemic toxicity In Rats)	1000 ppm (~50 mg/kg/day)	5000 ppm (~250 mg/kg/day)	Incidences of rough hair coat, decreased growth, gross lesions of pituitary gland, bone changes and mortality.
Chronic Feeding Study In Beagle Dogs	50 mg/kg/day	150 mg/kg/day	Reduced body weight gain, increase absolute and relative liver weight and an increase in incidences of hepatocellular hypertrophy.
Maternal and Development Toxicity In Rats	>6 mg/kg/day		No effect in food consumption, body weight, clinical signs and Reproductive parameters
Reproductive Toxicity in Rats	1500 ppm (~75 mg/kg/day)	3000 ppm (~150 mg/kg/day)	Decreased fertility and viability.
Reproductive Effects in Mice	0.25 mg/kg/day	0.5 mg/kg/day	Decreased number of liters per pair and reduced live litter size.
Mutagenicity Studies Ames assays conducted with *Salmonella typthimurium*	>5,000 µg/plate		Results of assays do not suggest Methyl salicylate has mutagenic potential in bacteria unless at very high doses.

Dose Response Assessment

Sensitivity in Children

There were several studies considered as support for retaining the uncertainty factor for sensitivity of infants and children (UF = 10). These include chronic, subchronic, developmental and reproductive toxicity studies in rats, a continuous breeding study in mice and developmental toxicity study in hamsters. In addition, published estimates of toxicity in human adults and children that are based on reports of incidental over exposures indicated that children are more sensitive to methyl salicylate' toxicity. There is also uncertainty associated with the animal studies and estimates of human LD_{50} values because all of the data considered in this assessment are found in published literature available before Good laboratory Practices and testing guidelines were established by the Agency. This means that information on methyl salicylate's toxicity may not always be reported in detail, adequate for a reliable comparison of the sensitivity of adult animals with that observed in their offspring.

Postnatal exposure adversely affected bone growth in young rats at excessive subchronic doses (1,000 mg/kg/day: MRID 44213014). The single dose oral developmental toxicity study in hamsters (MRID 44213015) indicate that methyl salicylate has the potential to reduce litter size and cause total litter loss at a very high single dose level (1.75 g/kg). Similar effects were observed in other species after repeated doses in a rat multigeneration reproduction study (MRID 44213020) and in a continuous breeding study in mice (MRID 44213019) a doses ≥250 mg/kg/day. The NOELs for reduced litter sizes indicated in both the multigeneration and continuous breeding studies are 75 and 250 mg/kg/day in rats and mice, respectively, and respective LOELs are 150,and 250 mg/kg/day.

Finally, a report (MRID44213009) has suggested the LD_{10} has been estimated to be 0.17 g/kg for children and 0.5 g/kg for adults which supports the use of at least a three-fold uncertainty factor to consider the sensitivity of infants and children (see additional considerations in the discussion of acute dietary endpoints). However, the uncertainty factors should be applied in a risk assessment of acute exposures to infants and children as follows; the 1750 mg/kg/day LOEL from the hamster single dose study should be modified by uncertainty factors of 10 for interspecies extrapolation; 10 for intraspecies variability; 10 for the severity of the effect; and 3 because a LOEL is used (total UF = 3000). It should be noted that the 10-fold uncertainty factor for intraspecies variability adequately accounts for the 3-fold factor suggested by the information on human children and adults.

Reference Dose

The toxicological information considered above provided the no-observed-effect levels (NOELs) and the lowest-observed-effect levels (LOELs) summarized in the **Chart - - SUMMARY OF EFFECT LEVELS FOR SUBCHRONIC TOXICITY, CHRONIC TOXICITY, REPRODUCTIVE TOXICITY AND CARCINOGENICITY, AND MUTAGENICITY STUDIES CONDUCTED WITH METHYL SALICYLATE** listed on page 16. It should be noted that many of the NOELs are above limit doses, particularly for

page 16. It should be noted that many of the NOELs are above limit doses, particularly for studies administering methyl salicylate dermally (> 1,000 mg/kg/day and by inhalation (saturated atmosphere).

Although a reference dose (RfD) has not been established for methyl salicylate by the Agency, the toxicity data summarized in the **Chart - - SUMMARY OF EFFECT LEVELS FOR SUBCHRONIC TOXICITY, CHRONIC TOXICITY, REPRODUCTIVE TOXICITY AND CARCINOGENICITY, AND MUTAGENICITY STUDIES CONDUCTED WITH METHYL SALICYLATE** listed on page16 suggests that one could be determined. The lowest NOELs for systemic toxicity were established in the 2-year oral study in dogs and the 17-week feeding study in rats at 50 mg/kg/day. Application of uncertainty factors (UF) for interspecies extrapolation (UF = 10) to 50 mg/kg/day NOEL (i.e., NOEL/UF) would result in a reference dose of 0.5 mg/kg/day which is the same value as the acceptable daily intake (ADI) published by the Council of Europe and the Joint FAO/WHO Expert Committee on Food Additives in 1967.

Carcinogenicity Classification and Risk Quantification

The Agency found that only limited information was available for evaluation of methyl salicylate's carcinogenic potential. A 2-year feeding study in rats given diets containing 0, 1,000, 5,000, 10,000, and 20,000 ppm (MRID 44213014) reported no increased tumor incidences. An abstract reported a second 2-year study in which rats were fed diets containing 0, 0.07, and 0.21% natural oil of sweet birch (MRID 44213018) without an increased incidence of tumors. Three bacterial assay studies showed no mutagenic activity for methyl salicylate unless administered in very high doses were (>5,000 µg/plate) (MRID44213012 and 13). This limited information (carcinogenicity data from one species and genotoxicity studies from microorganisms) suggests no carcinogenic potential for methyl salicylate.

Ordinarily, such limited data would not adequately support a carcinogenicity risk assessment, but the following factors suggest that one is not necessary. Occupational exposure is likely to be significantly reduced by use of personal protective equipment such as rubber gloves, splash-proof goggles and/or face shield. Insect repellent packaging materials will only contain methyl salicylate in stable chemical matrices, thus minimizing release or migration into food contents. Also, the levels of methyl salicylate found in packaging materials is substantially less than levels found in ointments, liniments, lotions, oral mouth washes, and certain foods such as baked goods, candies, chewing gum and beverages. Finally mutagenicity and acute, subchronic, developmental, reproduction and chronic toxicity studies of methyl salicylate have not indicated significant effects on relaxant endpoints at low dose levels.

Other Toxicological Endpoints

Acute Dietary

A single dose oral developmental toxicity in hamster (MRID 44213015) indicated that methyl salicylate has the potential to reduce litter size and cause total litter loss at a very high single dose level (1.75 g/kg). Similar effects were observed in other species after repeated doses in rat multigenerational reproduction study (MRID 44213020) and a continuous breeding study in mice (MRID 44213019) at doses ≥250 mg/kg/day. The NOELs for reduced litter size indicated by the multigeneration and continuous breeding studies are 75 and 250 mg/kg/day in rats and mice, respectively, and respective LOELs are 150 and 250 mg/kg/day. Therefore, uncertainty factors applied to the 1750 mg/kg/day LOEL from the hamster single dose study should include 10 for interspecies extrapolation, 10 for intraspecies variability, 10, for the severity of the effect and 3 because a LOEL is used (total UF = 3,000). An acute dietary reference dose is calculated at ≈(1750 mg/kg/day ÷ 3,000) ≈0.5833 mg/kg/day which would equate to an MOE ≥3,000. As a reference note, MOE's <3,000 would be of concern as an acute dietary risk. It should be noted that the FAO/WHO's recommended acceptable daily intake of 0.5 mg/kg/day would result in an MOE = 1750 mg/kg/day ÷ 0.5 mg/kg/day = 3500, which is roughly equivalent to the previously calculated acute dietary reference dose.

Dermal absorption

According to the findings in a single dose developmental toxicity study with hamsters, plasma salicylate levels reached a peak of 125 mg/100ml at 2 hours after oral treatment with 1750 mg/kg and returned to control levels during the next 8-10 hours. Peak plasma concentrations of 50/mg/100ml were observed 5-6 hours following dermal application of 1750 mg of methyl salicylate/kg, and these plasma levels were similar to oral control values, several hours following dermal treatment. In a study increasing the dermal dose to approximately 8750 mg/kg, results in a peak plasma salicylate level of 120 mg/100ml (similar to that following oral treatment). However, the higher dose was difficult to apply and too stressful for the animals to continue being treated, and moreover, it is a dose that is well in excess of the limit dose for an acute dermal toxicity study (>5,000 mg/kg).

A rat dermal developmental toxicity study demonstrated development and maternal toxicity NOELs >6 g/kg/day (highest dose tested)(MRID 44213016) for methyl salicylate in petroleum based grease (PBG). In the same study, one group of rats received dermal applications of 2 g undiluted methyl salicylate per kg body weight for 4 consecutive days before the dose level was reduced to 1 g/kg/day because of excessive skin irritation and mortality. The report further noted that the urinary concentrations of salicylic acid in PBG treated animals were far below the toxic levels observed in the group receiving undiluted methyl salicylate. Although no data were included in the report, the results suggested that the vehicle containing methyl salicylate significantly decreases the biochemical's dermal absorption, but these results also indicated that the dermal absorption of undiluted methyl salicylate is significant at high doses.

A 96-day dermal toxicity study in rabbits established a NOEL for dermal toxicity at 2 ml/kg/day (~2.4 g/kg/day) (MRID 44213014). However, in this study a systemic toxicity NOEL could not be established because there was no concurrent control data reported, and the investigators noted kidney lesions at all dose levels tested (lowest dose was 0.5 ml.kg/day which is equivalent to ~0.585 g/kg/day). It should also be noted that the report on the 96-day dermal toxicity study suggested that dermal absorption was 100% when undiluted methyl salicylate was applied to the skin of rabbits.

The report on these three studies do not contain sufficient information from which to estimate a dermal absorption factor, but the rat study indicated that the vehicle (petroleum based grease) significantly inhibited the dermal absorption of methyl salicylate. The dermal route of exposure was shown in hamsters to increase time required to achieve peak plasma levels (from 2 hours following oral dosing to 5-6 hours after dermal application), the peak plasma level after dermal dosing was only 40% that following equivalent oral dosing, and a five-fold increase in the dermal dosage was required to achieve peak plasma levels equivalent to those following a given oral dose. These factors along with the chemical and physical barriers in methyl salicylate treated packaging materials indicate that significant dermal absorption of the biochemical is not very likely to occur outside an industrial setting.

Inhalation:

A 20-day inhalation toxicity study with rats exposed 7 hours per day at a saturation concentration ~700 mg/m^3) was mentioned in a review of methyl salicylate toxicity studies (MRID 44213006), and it was stated that the test atmosphere had no effect on the test animals. Therefore, a risk assessment for inhalation exposures is not required.

Occupation and residential short-term, intermediate and chronic endpoints:

In addition to the preceding evaluations of dermal and inhalation studies, the following factors do not indicate the need for an occupational risk assessment.

Methyl salicylate is used in consumer products as a counterirritant and analgesic in the treatment of painful muscles or joints. It is in ointment, liniment, or other preparations that are applied to human skin. These products contain from 10 to 40% methyl salicylate (U.S. Pharmacopeia). Other sources of human dermal exposure to methyl salicylate result from it use as a UV-absorber in suntan lotions and in perfumery as a modifier in blossom fragrances (HSDB 1996). Further, the biochemical, methyl salicylate, has a long history of safe use in these types of consumer products.

Methyl salicylate is currently registered as an insect repellent in food packaging. To mitigate and offset potential exposure to workers handling this manufacturing use product, explicit product labeling statements requiring personal protective equipment (e.g., rubber gloves, splash-proof goggles, and/or full face shield) are required.

Dietary Exposure:

Residue in plants and animals:

Synthetic methyl salicylate is considered to be structurally and functionally equivalent to the naturally occurring oil of wintergreen derived from plants through maceration and steam distillation of leaves from *Gualtheria procumbens and Betula lenta* (MRID 44213004). The natural form of methyl salicylate, oil of wintergreen, is exempt from the requirement of a tolerance when used in accordance with good agricultural practices as an inert or an occasional active ingredient in pesticide formulations applied to growing crops or agricultural commodities after harvest, refer to 40 CFR §180.1001(c). Oil of wintergreen is also considered a minimal risk inert ingredient (List 4A), and as such, it is recognized as safe for use in pesticide products based on its know properties (59 FR 49400), (09/28/1994).

Magnitude of the resides:

The Flavor and Extract manufacturers Association (FEMA) includes both methyl salicylate and oil of wintergreen in its list of substances that are generally recognized as safe (GRAS). Refer to table below. The FFDCA §408(k) as amended by the Food Quality Protection Act of 1996 (FQPA) permits the Agency to recognize GRAS determinations in the context of an exemption from the requirements of a tolerance.

FEMA GRAS Levels in Food (ppm)

Food	Methyl salicylate	Oil of Wintergreen
Baked goods	54	1,500
Beverages	59	56
Candy	840	260
Chewing gum	8,400	3,900
Ice cream	27	44
Syrups	200	----

An exemption from the requirements of a tolerance for residues of the insecticide Methyl salicylate in or on food, when used as an insect repellent in food packaging and animal feed packaging at an application rate that does not exceed 0.2 mg of methyl salicylate per square inch of packing material was established at 40 CFR §180.1189.

Dietary Risk Characterization:

Comparison of the estimated residue level from methyl salicylate's use in food packaging materials with those listed in the previously listed table show the worst case scenario results in levels that vary from 0.2% (chewing gum) to 59% (ice cream) of the FEMA levels that are generally recognized as safe. Given the potential for acute dietary concern indicated by this worst case comparison, a maximum application rate of 0.2 mg/in^2 is recommended (74% of GRAS value for ice cream) as a condition of the exemption from the requirement for a tolerance for the insect repellent use of methyl salicylate in food packaging materials.

Occupational and Residential Exposure and Risk Characterization:

The insecticide active ingredient, methyl salicylate, is incorporated into food packaging during the manufacturing process and is not expected to be present in appreciable quantities under normal conditions of use. Therefore there were no exposure estimates provided for the dermal exposure route. It is the Agency's opinion that low level exposures and risks during formulation process of this biochemical are more than adequately mitigated by the use of personal protective equipment (i.e., rubber gloves, splash proof goggles and/or full face shield). The inhalation exposure risks from methyl salicylate were deemed to be minimal because inhalation exposures will be less than those conducted in a saturated (more concentrated) atmosphere which had no toxic effect in laboratory animals.

Aggregate Exposure:

An exemption from the requirements of a tolerance for residues of the insecticide methyl salicylate in or on food, when used as an insect repellent in food packaging and animal feed packaging at an application rate that does not exceed 0.2 mg of methyl salicylate per square inch of packing material was established at 40 CFR §180.1189. Oil of wintergreen is exempt from the requirement of a tolerance when used in accordance with good agricultural practices an inert or occasionally active ingredient in pesticide products applied to growing or raw agricultural commodities (40 CFR §180.100(c)). No maximum residue limits have been established for methyl salicylate by Codex Alimentarius Commission, and there is no Maximum Contaminant Level (MCL) for residues of methyl salicylate in drinking water under the Safe Drinking Water Act. Methyl salicylate is generally recognized as safe (GRAS) for use as a flavoring agent in foods. There are two registered pesticidal uses for methyl salicylate as cat and dog repellents on ornamental shrubs and bushes. The exposure to humans from the pesticidal use of methyl salicylate is expected to be minimal, compared with the widespread use of methyl salicylate as a flavoring ingredient in foods. Based on these considerations and those listed in the previously described hazard assessments, an assessment of an aggregate exposure for all pesticidal uses of methyl salicylate would result in minimal additional exposure; expected exposure levels from these uses would be well below defined acceptable levels, even considering the extra sensitivity of infants and children.

Other Food Quality Protection Act Considerations:

(A) Cumulative risk from exposure to substances with a common mechanism of toxicity.

Section 408(b)(2)(D)(v) of the Food Quality Protection Act 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". The Agency believes that "available information" in th this context might include not only toxicity, chemistry, and exposure data, but also scientific polices and methodologies for understanding common mechanisms of toxicity and conducting cumulative risk assessments. For most pesticides, although the Agency has some information in its files that may turn out to be helpful in eventually determining whether a pesticide shares a common mechanism of toxicity with any other substances, EPA does not at this time have methodologies to resolve the complex scientific issues concerning common mechanisms of toxicity in a meaningful way. EPA has begun a pilot process to study this issue further through the examination of particular classes of pesticides. The Agency hopes that the results of this pilot process will increase the Agency's scientific understanding of this question such that EPA will be able to develop and apply scientific principles for better determining which chemicals have common mechanisms of toxicity and evaluating the cumulative effects of such chemicals. The Agency anticipates, however, that even as its understanding of the science of common mechanisms increases, decisions on specific classes of chemicals will be heavily dependent on chemical specific data, much of which may not be presently available.

Although at present the Agency does not know how to apply the information in its files concerning common mechanism issues to most risk assessments, there are pesticides in which the common mechanisms issue can be resolved. These substances include pesticides that are toxicologically dissimilar to existing chemicals (in which case the Agency can conclude that it is unlikely that a pesticide shares a common mechanism of activity with other substances) and pesticides that produce a common toxic metabolite (in which case common mechanism of activity will be assumed).

Methyl salicylate is used in packaging materials as an insect repellent and subsequent human exposure from this pesticide use is expected to be minimal, since it is applied at rates much lower that those used as flavoring ingredients in foods. The Flavor and Extract manufacturer 's Association has designated methyl salicylate as generally recognized as safe (GRAS) for use as a flavor ingredient. It is also used in the perfume and food flavoring industries, and in medicine as a counterirritant and analgesic. Based on these widespread uses of methyl salicylate and the expectation of extremely low human exposures from insect and animal repellent uses, a cumulative risk assessment indicates that the risks were well below the level of concern, even though the extra sensitivity of infants and children have been considered.

(b) Effects on Endocrine System

EPA is required under FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active ingredients_ "may have a effect in humans that is similar to an effect produced by naturally-occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific basis for including, as part of the program, the androgen-and thyroid hormone systems, in addition to estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require wildlife evaluations. As science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

(C) Determination of safety (U.S. Population, infants and children)

The toxicity data reviewed in the previous toxicology sections of this document indicated that acute dietary exposures >0.583 (1750 mg/kg LOEL divided by a 3,000-fold uncertainty factor) are of concern, particularly for females 13+ years of age since the toxicity endpoints were maternal and developmental toxicity. An average daily dietary intake >0.5 mg/kg/day (50 mg/kg/day NOEL divided by a 100-fold uncertainty factor) is the same as the Acceptable Daily Intake (ADI) recommended by WHO, and both of these references levels were based on uncertainty factors that adequately consider in this risk assessment are also less than levels recommended by FEMA for its GRAS list. The application rate for repellant and insecticide Methyl salicylate products in combination from the consumption of methyl salicylate as a favoring in foods is not expected to reach the ADI (0.5 mg/kg/day). Consequently the Agency assumes that there is a degree of reasonable certainty of no harm to the U.S. population or subpopulations including infants and children

Environmental Assessment

Since the uses of methyl salicylate to manufacture vertebrate and insect repellants is an indoor use pattern, the acute toxicity data from the environmental guideline studies (Avian Acute Oral Toxicity 154-6; Avian Dietary 154-7; Freshwater Fish LC_{50} 154-8; and Freshwater Invertebrate LC_{50} 158-154-9) are conditionally required on a case-by-case basis, depending on use pattern, production volume, and other factors. These data requirements are waived based on the following discussion.

The technical grade active ingredient, methyl salicylate, is registered for manufacturing use only and reformulation into other products. No significant exposure of nontarget organisms (i.e., wildlife and aquatic organisms) is likely as a direct result of this manufacturing use because these products are produced indoors in industrial facilities under controlled conditions which are expected to minimize release into the environment. Moreover, the very small release of methyl salicylate from the end-use products is also expected to be minimal and occur very slowly over time.

The biochemical is currently released to the environment in effluents and emissions as a result of it production, disposal and use as a flavoring in foods and beverages, as a fragrance agent in cosmetics and perfumes, as a pharmaceutical agent (counterirritant) in ointments and oral rinses, as a UV-absorber in suntan lotions, as a carrier for fabric dyes, and as a UV-stabilizer in acrylic resins (HSDB 1996). Release of methyl salicylate to the environment from its use in registered pesticide products is estimated to be very small when compared to releases from non-pesticide uses.

Exposure of nontarget organisms would be further minimized because any methyl salicylate released to the environment would be expected to degrade rapidly. The biochemical is readily biodegradable in screening tests and may be expected to degrade rapidly. The biochemical is readily biodegradable in screening tests and may be expected to biodegrade in soils and surface waters (HSDB 1996). Moreover, methyl salicylate is likely to hydrolyze in water, especially at alkaline pH (HSDB 1996). At pH 7.5, its hydrolysis half-life is estimated to be 14.1 days (HSDB1996). Methyl salicylate absorbs UV radiation >2990 nm and therefore may undergo direct photo lysis under environmental conditions ((HSDB 1996); the photo lysis half-life was reported to be 48 minutes in one study (HSDB 1996). In the atmosphere, methyl salicylate reacts with photochemically produced hydroxyl radicals with an estimated rate constant of 11.6×10^{-12} cm^3 /molecule. Assuming a hydroxyl radical concentration of 5×10^{-5} radicals/cm^3, the half-life of methyl salicylate in the atmosphere would be 1.4 days (HSDB 1996).

Efficacy Data :

Although efficacy data for all pesticide products is a requirement for federal registration, the Agency only requires this type of data to be submitted under certain specific circumstances. No efficacy data for methyl salicylate were required to be submitted to the Agency since no public health uses were involved.

Risk management Decision:

Determination of Eligibility for Registration:

Section 3(c)5) of FIFRA provides for the registration of new active ingredients if it is determined that (A) its composition is such as to warrant the proposed claims for it; (B) its labeling and other materials required to be submitted comply with the requirements of FIFRA; (C) it will perform its intended function without unreasonable adverse effects on the

environment; and (D) when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment.

To satisfy criteria "A" above, methyl salicylate products are not expected to cause no unreasonable adverse effects when used according to label instructions. Criteria "B" is satisfied by the current label and the data presented in this document. It is believed that this pesticidal active ingredient will not cause any unreasonable adverse effects, is an effective insect repellent, and does provide protection as claimed satisfying Criteria "C". Criteria "D" was satisfied by the data presented in the initial registration of this biochemical. Therefore, methyl salicylate is eligible for reregistration.

Regulatory Position:

Unconditional Registration/Reregistration

All of the data requirements are fulfilled and BPPD recommends the reregistration or the continued unconditional registration for the active ingredient, methyl salicylate.

Tolerance Reassessment:

An exemption from the requirements of a tolerance for residues of the insecticide methyl salicylate in or on food, when used as an insect repellent in food packaging and animal feed packaging at an application rate that does not exceed 0.2 mg of methyl salicylate per square inch of packing material was established at 40 CFR §180.1189. Safety factors from the Food Quality Protection Act of 1996 were considered in the initial establishment of this tolerance exemption. This tolerance exemption was established after the implementation of FQPA and is not subject to a tolerance reassessment.

CODEX Harmonization

No maximum residue limits have been established for methyl salicylate by the Codex Alimentarius Commission.

Non-food Reregistration

There are no issues at this time.

Risk Mitigation

Since there are no identifiable risk issues, no risk mitigation measures are required at this time for: dietary risk; occupational and residential risks; risks to nontarget species (plants and wildlife); or ground and surface water contamination for methyl salicylate products. The product label of manufacturing use products will, however, be required to bear an Environmental Hazard precautionary text to mitigate potential risks to aquatic species from effluent discharges.

Endangered Species Statement.

No incremental risk hazard of methyl salicylate is anticipated for endangered species (fish, animals, or plants). This assumption is based on the very low anticipated exposure rates and low values for acute mammalian toxicity of methyl salicylate. As previously mentioned in the risk mitigation section, only the label of the manufacturing use product will contain an Environmental Hazard precautionary text pertaining to effluent discharge to further mitigate any potential risk to aquatic species. (See the Environmental Hazard Labeling section of this document).

Labeling Rationale

It is the Agency's position that the labeling for all methyl salicylate products complies with current pesticide labeling requirements imposed under FIFRA, 40 CFR §156.10 .

Human Health Hazard

Worker Protection Standard (WPS) Labeling

The manufacturing use methyl salicylate product is not subject to WPS labeling. The insect repellent products are indoor use products and not subject to WPS labeling. Also, the two animal repellent products are not subject to WPS labeling since they are clearly intended for for homeowner or residential use.

Non-Worker Protection Standard (WPS) Labeling:

There are no non-WPS human health hazard issues for all methyl salicylate products.

Precautionary Labeling:

The Agency has examined the toxicological data base for methyl salicylate products and has concluded that the current precautionary labeling (i.e., Signal word, First Aid statement and other label statements) adequately mitigates the risks associated with the currently registered uses. It should be noted here that the Agency has reserved the following stringent language for the most concentrated of all of the methyl salicylate formulations, a manufacturing use product ("WARNING" and "Causes substantial but temporary eye irritation. Causes skin irritation. Do not get in eyes, on skin or on clothing. Avoid breathing vapor. During use. Wear protective clothing, rubber gloves, splash-proof goggles and/or face shield. Wash throughly with soap and water after handling. Remove contaminated clothing, and wash before reuse".).

Additionally, it should be clearly understood that the Agency will continue reexamine the toxicological data base and the precautionary labeling for methyl salicylate as additional toxicological information becomes available, or when new data are submitted in connection with new uses patterns proposed for methyl salicylate products.

Environmental Hazard Labeling:

There is no specific environmental hazard product labeling for methyl salicylate animal and insect repellent products. However, the methyl salicylate manufacturing use product labeling is required to bear the following environmental hazard discharge statement:

> "Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans, or public waters unless this product is specifically addressed in a National Pollution Discharge Elimination System (NPDES) permit. Do not discharge effluent containing this product to sewer system without previously notifying the sewage treatment plant authority. For guidance contact your State Water Board or Regional Office of the Environmental Protection Agency."

What Registrants Need to Do:

The Agency has evaluated all of the data in its files that has been submitted in connection the initial registration of methyl salicylate products and determined that these data are sufficient to satisfy current registration guidelines. Therefore, all products that are currently registered are eligible for reregistration. No additional data are required to be submitted to the Agency at this time.

Not withstanding the information stated in the previous paragraph, it should be clearly understood by the registrants of all pesticide products containing the active ingredient methyl salicylate, that certain, specific, data are required to be reported to the Agency as a requirement for maintaining the federal registration for a pesticide product. A brief summary of these types of data is listed below.

1. Reporting of Adverse Effects:

Reports of all incidents of adverse effects to humans or domestic animals (including both suspected and confirmed incidents) must be submitted to the Agency under the provisions stated in FIFRA, Section 6(a)(2).

2. Reporting of Hypersensitivity Incidents:

Additionally, all incidents of hypersensitivity (including both suspected and confirmed incidents) must be reported to the Agency under the provisions of 40 CFR Part 158.690(c), guideline reference number 152-16.

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