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

MEMORANDUM

NOV 17 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: SAB Review of the Product Chemistry Data, Toxicology Summary Information, and Toxicology and Residue Chemistry Waivers Submitted for the Registration of Technical Methyl Anthranilate and an End-Use Product, "Bird Shield Repellent". Product Chemistry (Case # 008125; Chemical # 128725; Submission # S455617; DP Barcode # D197915)

TO: Robert Forrest, Product Manager (PM-14)
Daniel Peacock, Reviewer (PM-14)
Insecticide-Rodenticide Branch
Registration Division (7505C)

FROM: Sheryl K. Reilly, Ph.D., Biological Section
Science Analysis Branch
Health Effects Division (7509C)

THROUGH: Roy D. Sjoblad, Ph.D., Section Head
Biological Section, Science Analysis Branch
Health Effects Division (7509C)

ACTION REQUESTED: Dolphin Trust has submitted a registration application for methyl anthranilate (MA) and Bird Shield Repellant for use in repelling birds (robins, Starlings, Cedar waxwings and sparrows) from ripening cherries, blueberries, and grapes; and from structures, roost and nest sites, water impoundments, and chemigation systems. The active ingredient (methyl anthranilate) is considered GRAS under 21 CFR 182.60, and is used as a flavoring agent in foods (alcoholic and nonalcoholic beverages, ice cream, candy, baked goods, gelatins and puddings, chewing gum), and is also a component of perfumes.

CONCLUSIONS:

Product Chemistry: The registrant did not submit a list of impurities, their percentages, or reasons for occurrence because MA is a GRAS substance of not less than 99% purity and is used as a flavoring agent; however, this data requirement cannot be waived unless it can be shown that the active ingredient is of food grade quality or is obtained from a supplier of food grade quality MA. No data were submitted to indicate the efficacy of the methods used to detect or quantitate impurities; analytical methods were submitted for certification of limits and a five-batch analysis.

Mammalian Toxicology: The registrant submitted a review of the scientific literature concerning the known toxicity of methyl anthranilate. The acute toxicity of methyl anthranilate is indicated as low by the oral and intraperitoneal (i.p.) routes, in rats, mice and guinea pigs. Limited data are available on the acute toxicity of anthranilic acid; however, an oral LD_{50} of 4549 mg/kg in rats has been reported, which indicates low toxicity. The subchronic oral toxicity of methyl anthranilate appears to be low in rats fed 1000 and 10000 ppm for 13 weeks (approx. 50 and 500 mg/kg/day in adult rats, with no adverse effects). Methyl anthranilate is a natural constituent of food, and has been found in grape juice (17.5 ppm), Concord grapes (33 ppm), and cocoa, grape musts, lemon, lime, mandarin, and tangerine oils, orange juice, black tea, and wine. The estimated *per capita* daily intake of methyl anthranilate in the diet is 0.01 mg/kg for a 60 kg person. In humans, anthranilic acid is a normal metabolite, excreted in the urine primarily as o-aminohippuric acid and anthranilic acid glucuronide.

DATA WAIVER

A data waiver was submitted for all mammalian toxicology studies, based upon the low toxicity reported in the literature, the history of safe use of methyl anthranilate in foods and as flavorings, and its GRAS status. In the absence of eye irritation data, SAB will assume that the end use product is toxicity category I (pH 9.7 and inerts are [redacted] The label should reflect this in the precautionary statement, or the registrant may perform a study to establish a different toxicity category. No information on dermal irritation for the end-use product was submitted, and a rationale is needed for waiver of this data requirement.

Tolerance Exemption for use of Methyl Anthranilate on Cherries, Grapes and Blueberries:

The submitted information on the toxicity of MA would support an exemption from the requirement for a tolerance on cherries, blueberries and grapes under the stated conditions of use if data on residues support the conclusion that exposure is not significantly greater than that which already occurs naturally in the diet. However, SAB was not able to interpret the residue data provided so as to make a conclusion on the validity of the method used and conversion of the data to actual residue values. SAB recommends that the appropriate chemistry branch review the data submitted in volume 8 and determine if the information is adequate for actual residue determinations, or if additional information is required.

DETAILED CONSIDERATIONS:

A. Product Characterization

The following product data are required under 40 CFR § 158

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Subpart C, in accordance with Subdivision M § 151-10 to -18 of the Pesticide Assessment Guidelines:

1. Guideline 151-10: Identity of the Active Ingredient

Product Identity (MRID 421519-01)

Bird Shield Repellant (end-use product, 26.4% a.i.)

Confidential Statement of Formula (CSF)

The registrant has provided a CSF.

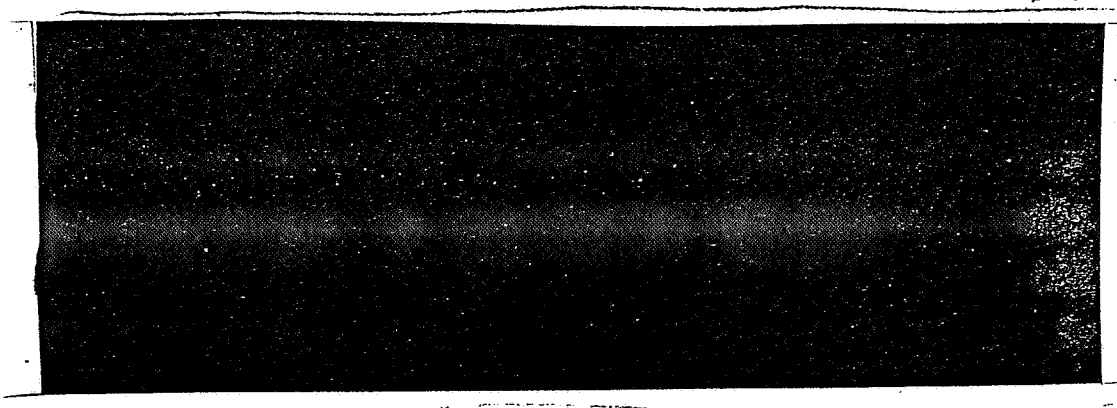
Information on Active Ingredient

The following table summarizes information submitted regarding the active ingredient:

Chemical Name	methyl 2-aminobenzoate
CAS Registry No.	134-20-3
Common Name	Methyl Anthranilate (MA)
Empirical Formula	$C_8H_9NO_2$
Molecular Formula	$COOCH_3-C_6H_4-NH_2$
Molecular Weight	151.17
Source of biochemical	synthetic process (see below)
Mode of Action	Bird repellant; presumably by taste or irritation owing to the aromatic nature of MA

2. Guideline 151-11: Manufacturing Process (MRID 421519-01)

The manufacturing process for Bird Shield is as follows:



MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

3. Guideline 151-12: Discussion of the Formation of Unintentional Ingredients (MRID 421519-01)

No data were submitted to indicate the method for determining

impurities; instead, the petitioner stated that since the active ingredient is a GRAS substance of ≥ 99% purity, and is used as a flavoring agent, the formation of unintentional ingredients was not considered to be significant. This data requirement cannot be waived for the reasons specified by the petitioner, unless the active ingredient used in the studies is food-grade and is produced to meet or exceed U.S. Food Chemical Codex and U.S. Pharmacopia specifications. The end-use product must also be made from this food-grade technical material, and the label precautionary statements must so indicate.

need food grade MA to waive data

4. Guideline 151-13: Analysis of Samples (MRID 421519-02)

Method Validation: Not provided.

5. Guideline 151-15: Certification of Ingredient Limits (MRID 421519-02)

The Certification of Ingredient Limits for technical MA and Bird Shield Repellant are reportedly attached in a Confidential Appendix, cross-reference 1 (not provided to reviewer). The certified limits (upper and lower) are found in column 14 of the CSF (form 8570-4), attached.

6. Guideline 151-16: Analytical Methods for Certified Limits (MRID 421519-02)

need

A GLC method of analysis of flavor aromatic chemicals and isolates was provided, but the specific methodology for determining methyl anthranilate was not included in the submission.

7. Guideline 151-17: Physical and Chemical Characteristics (MRID 421519-03)

The following table summarizes the data that satisfy the requirements of 40 CFR § 158.190:

Guideline No.	Characteristics	Technical	Bird Shield
63-2	Color	Colorless to Pale yellow	milky white
63-3	Physical State	liquid or crystals	liquid
63-4	Odor	grapes, oranges	grapes
63-5	Melting Point	24°C	NR
63-6	Boiling Point (760 mm Hg)	256°C	
63-7	Density (specific gravity for EUP)	1.1682	1.04 g/ml
63-8	Water Solubility	slight	soluble
63-9	Vapor Pressure @ 20 °in mm Hg)	0.012	NR
63-10	Dissociation Constant	NR	NR
63-11	Octanol/Water Partition Coefficient	unknown	NR
63-12	pH	11.15	9.7
63-13	Stability	stable under normal conditions	NR
63-15	Flammability: Flash point	>110°C	NR
63-16	Explodability	NR	NR
63-17	Storage Stability	NR	NR
63-18	Viscosity	NR	NR
63-19	Miscibility in H20	NR	Miscible
63-20	Corrosion Characteristics	None	None

NR = Not required

8. Data Gaps: The following product chemistry data gap exists for this petition:

Guideline

151-12 Discussion of the Formation of Unintentional Ingredients for the technical and both end-use products

151-13 Analysis of Samples

9. Data Waivers

The registrant has requested a waiver from residue data requirements based on the biochemical classification of MA, its GRAS status and use as a flavoring agent in foods, the extensive body of knowledge of the safety of MA. In addition, they indicate that the maximum amount of MA that can be applied to whole fruit

dipped in the repellent solution as formulated on the label is approximately 34.53 mg/kg for cherries, and 11.64 mg/kg for grapes, which is low in comparison with the established oral LD50s for rats, mice and guinea pigs (2910, 3900 and 2780 mg/kg respectively). MA also decomposes in the uv spectrum of sunlight and dissipates from the treated area depending on ambient air temperatures and air movements. Preliminary residue studies suggested that little retention of the active ingredient remains on cherries and blueberries when applied at 7 day intervals.

The submitted information on the toxicity of MA would support an exemption from the requirement for a tolerance on cherries, blueberries and grapes under the stated conditions of use <u>if</u> data on residues support the conclusion that exposure is not significantly greater than that which already occurs naturally in the diet. However, SAB was not able to interpret the residue data provided so as to make a conclusion on the validity of the method used and conversion of the data to actual residue values. SAB recommends that the appropriate chemistry branch review the data submitted in volume 8 and determine if the information is adequate for actual residue determinations, or if additional information is required.

B. <u>Human Health Assessment</u>

1. <u>Mammalian Toxicology Data Base: active ingredient</u>

Acute and Subchronic Toxicity Studies: The registrant submitted safety data to support a petition for exemption from tolerance when used on cherries, blueberries and grapes (**see attached scientific literature review; MRID 421519-04**). The acute toxicity of methyl anthranilate appears to be low by the oral and intraperitoneal (i.p.) routes. The subchronic toxicity of methyl anthranilate also appears to be low. In a subchronic oral toxicity study, adult rats were administered 1000 and 10,000 ppm (approximately 50 and 500 mg/kg) anthranilate in the diet for 13 weeks. No treatment-related effects on growth, hematology, gross pathology, or histopathology were observed (Hagen et al., 1967). In another study, mice were injected intraperitoneally with methyl anthranilate in tricaprylin solution three times per week for 8 weeks (24 doses), and were observed for an additional 16 weeks. Dose levels were 0.47 g/kg (the maximum tolerated dose, MTD) or 0.09 g/kg (20% of the MTD), for a total dose of 2.25 or 11.2 g/kg, respectively. Survival was 90% (18/20) at 0.09 g/kg, and 95% (19/20) at 0.47 g/kg. At 24 weeks, lung tumors were found in 17% (3/18) of the 0.09-g/kg rats, and 26% (5/19) of the 0.47-g/kg rats, but this did not appear to be greater than controls, in which the incidence of lung tumors was 28% for males and 20% for females (Stoner et al., 1973).

Metabolism: methyl anthranilate is hydrolyzed in the small intestine to an alcohol, and either anthranilic acid or an N-alkyl

anthranilic acid. In humans, anthranilic acid is a normal metabolite, and is excreted in the urine primarily as o-aminohippuric acid (27 μmoles/day) and anthranilic acid glucuronide (6 μmoles/day); therefore, the total average daily excretion is about 5 mg anthranilic acid. Limited data are available on the acute toxicity of anthranilic acid; however, an oral LD_{50} of 4549 mg/kg in rats has been reported, which indicates low toxicity.

INERT INGREDIENT INFORMATION IS NOT INCLUDED

2. Mammalian Toxicology Database: inerts

[redacted]

3. Data Waivers:

A data waiver was submitted for all mammalian toxicology studies on the active ingredient, based upon the low toxicity reported in the literature, the history of safe use of methyl anthranilate in foods and as flavorings, and its GRAS status. No information on dermal irritation for the end-use product was submitted, and a rationale is required for waiver of this data requirement. In addition, eye irritation data were not provided; however, SAB will assign the end-use product toxicity category I based on its pH (9.7) and the inert ingredients [redacted] The label precautionary statement should reflect this. The registrant may submit a study to change the toxicity category.

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eye irr.

EPA Reviewer: Sherl Reilly, Ph.D. 10/31/94
Biological Section, Science Analysis Branch
Health Effects Division (7509C)

EPA Section Head: Roy Sjoblad, Ph.D. 11/17/94
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SCIENTIFIC LITERATURE REVIEW

MATERIAL:	Methyl anthranilate
CAS NUMBER:	134-20-3
TOX CHEM. NUMBER:	128725
MRID NUMBER:	421519-04
TITLE OF REPORT:	Methyl Anthranilate Safety Data — In Support of Petition Proposing an Exemption from the Requirements of a Tolerance for Methyl Anthranilate for Use in Cherry, Blueberry, and Grape Production
DATA REQUIREMENT:	Subdivision M, Guidelines 152-10, 152-14
PROJECT NUMBER:	IR-4 PR No. 5026, 5028, 5029
AUTHOR:	W.L. Biehn IR-4 Project, Cook College, Rutgers University New Brunswick, NJ
STUDY COMPLETED:	November 11, 1991

A. TEST MATERIAL

Name/formula: Methyl anthranilate, $C_8H_9NO_2$

Synonyms: Methyl o-methylaminobenzoate; methyl 2-methylaminobenzoate; o-amino methyl benzoate; methyl-o-aminobenzoate; methyl 2-aminobenzoate

Molecular weight: 151.18

Physical properties:

Appearance:	Colorless to pale yellow liquid, with a bluish fluorescence and grape-like or orange-flower odor
Melting/boiling points:	m.p., 23.8°C; b.p., 237°C
Solubility:	Soluble in oils; slightly soluble in water
Specific gravity:	1.161-1.169 at 25°C

B. TOXICOLOGY/METABOLISM

Acute toxicity

The acute toxicity of methyl anthranilate appears to be low by the oral and intraperitoneal (i.p.) routes. Table 1 presents selected acute toxicity data.

Subchronic/chronic toxicity

The subchronic toxicity of methyl anthranilate appears to be low. Adult rats were administered 1000 and 10,000 ppm (approximately 50 and 500 mg/kg) anthranilate in the diet for 13 weeks. No treatment-related effects on growth, hematology, gross pathology, or histopathology were observed (Hagen et al., 1967).

Mice were injected intraperitoneally with methyl anthranilate in tricaprylin solution three times per week for 8 weeks (24 doses), and were observed for an additional 16 weeks. Dose levels were 0.47 g/kg (the maximum tolerated dose, MTD) or 0.09 g/kg (20% of the MTD), for a total dose of 2.25 or 11.2 g/kg, respectively. Survival was 90% (18/20) at 0.09 g/kg, and 95% (19/20) at 0.47 g/kg. At 24 weeks, lung tumors were found in 17% (3/18) of the 0.09-g/kg rats, and 26% (5/19) of the 0.47-g/kg rats. It was of note that the incidence of lung tumors for vehicle control animals was 28% for males and 20% for females (Stoner et al., 1973).

Metabolism

As summarized in FEMA (1974), methyl anthranilate is hydrolyzed in the small intestine to an alcohol, and either anthranilic acid or an N-alkyl anthranilic acid. In humans, anthranilic acid is a normal metabolite and is excreted in the urine, primarily as o-aminohippuric acid (27 μmoles/day) and anthranilic acid glucuronide (6 μmoles/day); therefore, the total average daily excretion is about 5 mg anthranilic acid. Limited data are available on the acute toxicity of anthranilic acid; however, an oral LD_{50} of 4549 mg/kg in rats has been reported, which indicates low toxicity.

C. NATURAL OCCURRENCE/FLAVOR USAGE

Methyl anthranilate is a natural constituent of food, and has been found in grape juice (17.5 ppm), Concord grapes (33 ppm), and cocoa, grape musts lemon, lime, mandarin, and tangerine oils, orange juice, black tea, and wine.

Use level (ppm):	Maximum, 2.41-1583.12 Usual, 2.04-387.36
Possible mean daily intake:	0.08 mg (from chewing gum)
Per capita intake:	0.7330 mg/day

Methyl anthranilate is listed by the Food and Drug Administration (FDA) in Title 21 of the Code of Federal Regulations as a flavoring compound, and is classified Generally Recognized as Safe (GRAS) by the Expert Panel of the Flavor and Extract Manufacturer's Association (FEMA). Table 2 presents the usage data for methyl anthranilate.

Table 1. Selected Acute Toxicity Data for Methyl Anthranilate

Species	Route/Study Type	Exposure	LD_{50}	Effect	Reference
Rabbit	Dermal irritation	500 mg for 24 hours		Moderate	RTECs, 1981-82
Mouse	Oral/reproductive		TD_{Lo}, 34,800 mg/kg		RTECs, 1980-82
Mouse	Ip/tumorigenic		TD_{Lo}, 2250 mg/kg		RTECS, 1980-82
Rat	Oral	Acute	2910 mg/kg		Jenner, 1964
Mouse	Oral	Acute	3900 mg/kg		
Mouse	Ip	Acute	1.04 ml/kg		FDA, 1977
Mouse	Gavage	Acute	3900 mg/kg	Depression, death within 4-18 hours	Jenner, 1964
Rat	Ip	Acute	1.39 ml/kg		FDA, 1977
Rat	Gavage	Acute	2910 mg/kg	Depression, coma, death within 1-2 days	Jenner, 1964
Guinea pig	Gavage	Acute	2780 mg/kg	Depression, gasping, rapid respiration, GI irritation, death within 4 hours-4 days	Jenner, 1964
Deer mouse	Food reduction(fr)	3-day feeding at 2% treatment rate	LD_{fr}, 1250 mg/kg/day		Schafer, 1985
Redwing blackbird			R_{50}*, 1.0		Schafer, 1985

ip = intraperitoneal

* Repellency toxicity index calculated by assuming that at the R_{50} level, a 65-gram male redwing would consume 50% of his approximate individual maximum food capacity of 1 gram. This value, when divided by the acute oral LD_{50}, provides an index that indicates how likely it would be for acute oral poisoning to occur in the wild. An index value >1 indicates well-accepted toxic agents that have definite potential for causing acute poisoning episodes.

Table 2. Usage Levels for Methyl Anthranilate*

Annual Poundage (1970) Used in Flavors	Food Category	Number of Firms Reporting Use	Weighted Mean Level of Use (ppm)		Possible Average Daily Intake (mg)			
			Usual	Maximum	0-5 months	6-11 months	12-23 months	2-65+ years
73,300 pounds	All categories	66	NR	NR	0.1493	1.2113	2.3615	5.3767
	Baked goods	4	27.067	38.146	0.0920	0.6875	1.4751	3.7135
	Frozen dairy	20	11.388	19.592	0.0114	0.1082	0.1640	0.2915
	Soft candy	21	20.293	37.199	0.0041	0.0446	0.0710	0.1177
	Gelatin, puddings	16	10.883	20.007	0.0218	0.1393	0.1502	0.2220
	Non-alcoholic beverages	39	8.366	15.764	0.0201	0.1899	0.4534	0.8701
	Alcoholic beverages	4	2.042	2.418	0.000	NR	NR	0.0664
	Hard candy	14	29.99	161.25	0.0000	0.0030	0.0090	0.0180
	Chewing gum	9	387.36	1583.12	NR	0.0387	0.0387	0.0775
	Miscellaneous unclassified	fewer than 3	20.5	59.0	NR	NR	NR	NR

NR = not reported

* Data were extracted from Table IV-2, pages 60-62 of the study report (MRID 421519-04).