



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

JUL 02 2002

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Science Review in Support of a Petition for the Exemption From Tolerances for Citronellol and Geraniol, Two Active Ingredients in Biomite™ (EPA File Symbol. No. 070057-R), containing 0.17% Farnesol, 0.42% Nerolidol, 0.42% Geraniol, and 0.42% Citronellol (Chemical Nos. 128910, 128911, 167004, and 597501, respectively) As Its Active Ingredients. Review of Metabolism, Acute Toxicity, Chronic Toxicity, and Mutagenicity/Genotoxicity/Carcinogenicity Data/Information. Petition Nos. 0F6145 and 0F6073; No DP Barcodes; No Case No.; No Submission; No MRIDs.

FROM: Russell S. Jones, Ph.D., Biologist
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511 C)

TO: Raderrio Wilkins, Regulatory Action Leader
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511C)

ACTION REQUESTED

In response to a request for additional information (see Memorandum from R. S. Jones to R. Wilkins, dated 7/18/2001), Natural Plant Protection S. A. submitted additional data/information in support of the registration of Biomite™ (EPA File Symbol. No. 070057-R), containing 0.17% farnesol, 0.42% nerolidol, 0.42% geraniol, and 0.42% citronellol as its active ingredients. Biomite™ is intended for food and non-food use in the control of mites (*Eotetranychus* spp., *Tetranychus* spp., and *Panonychus* spp.) on agricultural crops, ornamentals plants, and in professional landscape settings. In support of the registration, the registrant has submitted data/information pertaining to the biochemistry, metabolism, and dietary intake/safety of geraniol and citronellol.

This review does not address any other deficiencies identified in the Memorandum from R. S. Jones to R. Wilkins (dated 7/18/2001).

RECOMMENDATIONS AND CONCLUSIONS

1. Based on the rationale presented by the registrant, it is highly unlikely that residues of geraniol and citronellol in/on food commodities resulting from applications of Biomite (EPA File Symbol No. 070057-R) will pose any human health and/or environmental concerns when the product is applied according to proposed label use directions. BPPD concurs with the risk assessment presented by the registrant for geraniol and citronellol.
2. The information/data presented by the registrant support the Petition for the Exemption of the Requirement of Tolerances (PP Nos. OF 6145 and OF6073) for citronellol and geraniol.
3. The deficiencies listed below were adequately resolved by the registrant.

SUMMARY OF BPPD DATA REQUIREMENTS AND THE REGISTRANT RESPONSES

Deficiency No. 1: No data were submitted to support an ADI of 5 mg/kg/day for both geraniol and citronellol.

BPPD Note: Registrant response demonstrates that an ADI of 5 mg/kg/day was promulgated by the World Health Organization (WHO, 1998)

Deficiency No. 2: BPPD concluded that the proposed label uses of Biomite™ (EPA File Symbol. No. 070057-R) may result in increased human dietary exposure, including infants and children.

BPPD Note: Registrant response indicates that the theoretical maximum dietary exposure to geraniol and citronellol will be well below the WHO ADI

Deficiency No. 3: No data were presented to support a conclusion that there would be no significant level of residues on treated crops.

BPPD Note: Registrant response demonstrates that residues will be low and indistinguishable from endogenous levels of geraniol and citronellol present in the edible portions of many food crops

Deficiency No. 4: Although the Petitions for Exemptions from the requirements of tolerances stated that these compounds were widespread in the environment and were considered GRAS, no specific concentrations were reported.

BPPD Note: Registrant response listed many crops that contain both geraniol and/or citronellol, and their concentrations, together with FDA GRAS citations and literature citations.

Summary of Registrant Response:

In response to the aforementioned deficiencies, the registrant submitted a compendium of literature citations organized in three appendices (see Response to Interim Letters Dated June 21, 2001 Regarding Petition No. OF6145/EPA File Symbol 70057-R; No MRID No., pp. 13-53).

In Appendix 1 (see citation above, pp. 13-38), the registrant presented information demonstrating that the terpenoid esters, geranyl acetate and citronellyl acetate (used as flavoring agents) are readily hydrolyzed to their corresponding alcohols (geraniol and citronellol). This hydrolysis may occur in the intestines of mammals via a number of common esterases (carboxylesterases and β -esterases). Therefore, according to the World Health Organization [WHO Food Additives Series 40; 49th Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JEFCA), dated 1998], dietary intake of geraniol and citronellol are estimated based on the quantity of geranyl acetate and citronellyl acetate consumed in the diet. Geraniol and citronellol were shown to undergo further metabolism (alcohol oxidation, hydration, and hydrogenation) to non-toxic, polar compounds (subsequently metabolized by glucuronidation). The resulting glucuronide conjugates are subsequently excreted in the urine. A diagram of the metabolism of geraniol in rats was presented as an example (see registrant's Response, p. 14). According to WHO (1998), total dietary intake of geraniol, citronellol, and their corresponding terpenoid esters was 12.1 $\mu\text{g}/\text{kg}$ body weight/day (U. S.) and 43.2 $\mu\text{g}/\text{kg}$ body weight/day (Europe).

In the same WHO (1998) report cited above, and from the National Toxicology Program (NTP, 1987), toxicity data were presented for geraniol, citronellol and their esters. These data are summarized in Table 1 below.

Table 1. Selected Toxicological Data for Geraniol, Citronellol, & and their esters

Study Type	Data	Other Observations	US EPA Toxicity Category (if applicable)
Acute Oral Toxicity (rat)	geranyl acetate (GA) LD50 = 6330 mg/kg citronellyl acetate (CA) LD50 = 6800 mg/kg citronellyl formate LD50 = 8400 mg/kg geranyl formate LD50 = 5460 mg/kg citronellyl propionate LD50 = 5000 mg/kg geranyl propionate LD50 = 5000 mg/kg citronellyl butyrate LD50 = 5000 mg/kg geranyl butyrate LD50 = 10600 mg/kg citronellyl isobutyrate LD50 = 5000 mg/kg geranyl isobutyrate LD50 = 5000 mg/kg geranyl hexanoate LD50 = 5000 mg/kg geranyl isovalerate LD50 = 5000 mg/kg geranyl ethylbutanoate LD50 = >8000 mg/kg	-	IV
14-day daily oral gavage (mice)	Dose = 71% GA/29% CA NOAEL = 1000 mg/kg/day	Thickening of cardiac stomach & duodenal wall at 2000 mg/kg/day	-
13-week daily oral gavage (mice)	Dose = 71% GA/29% CA NOAEL = 1000 mg/kg/day	Vacuolization of liver, kidney, and myocardium at 2000 mg/kg/day	-
103-week chronic exposure/carcinogenicity (rat)	Dose = 71% GA/29% CA NOAEL = 1000 mg/kg/day	Reduced body weight in males throughout study and decreased survival at 2000 mg/kg; and in females at 1000 & 2000 mg/kg at 40 weeks.	-
Genotoxicity	No positive results were observed in a number of studies (Ames Assay, HGPRT gene mutation assay, Chromosomal aberration study, etc.) in studies using geranyl acetate.	Positive results were observed in one unspecified study at which the test substance dose was cytotoxic	-

In Appendix 2, the registrant presented a "Estimated Dietary Exposure to Geraniol and Citronellol" (see Response to Interim Letters Dated June 21, 2001 Regarding Petition No. OF6145/EPA File Symbol 70057-R; No MRID No., pp. 40-48). The dietary exposure estimation was based on the following information: (i) the amount of geraniol and citronellol on agricultural commodities treated with Biomite during the growing season; and (ii) the yield of each treated crop/acre during the 1998-2000 growing years. It was assumed that Biomite was applied at the maximum proposed label use rate (equivalent to 9 g geraniol and 9 g citronellol per acre per application). The number of applications of Biomite a on each crop was based on

geographic location of each crop type. All data was analyzed via a proprietary diet exposure model (TSG's Diet Risk™ and the US EPA Dietary Risk Evaluation System (DRES). Each model uses dietary consumption for raw agricultural commodities and their associated food types from the USDA Nationwide Food Consumption Survey (dated 1977-1978). Based on the data, estimated daily geraniol dietary intake was 0.000997 mg/kg/day. Non-nursing infants were estimated to have the highest consumption of geraniol at 0.0066 mg/kg/day. A table showing the amounts of geraniol contributed to the diet for selected commodities is attached. Dietary contributions of citronellol are expected to be similar to geraniol. The largest exposures are via fresh apples, applesauce, apple juice, peaches, and pears. The potential exposure of the general US population to geraniol is estimated to be 0.20% of the WHO (1998) Acceptable Daily Intake (ADI) of 0.5 mg/kg/day. Non-nursing infant exposure to geraniol was estimated to be 1.3% of the ADI.

Based on a conservative model (Diet Risk™) that calculates the maximum potential exposure to geraniol, based on the assumption that 100% of each crop is treated with Biomite, a Theoretical Maximum Residue Concentration (TMRC) for non-nursing infants is estimated to be 13.26% of the ADI, and the TMRC for the general population is estimated to be 1.99% of the ADI. Printouts of the model calculations were submitted by the registrant. A copy of a table showing estimated geraniol residues on representative crops is attached.

Appendix B (see Response to Interim Letters Dated June 21, 2001 Regarding Petition No. OF6145/EPA File Symbol 70057-R; No MRID No., pp. 50-53), the registrant presents two tables showing edible plants and the content of geraniol and citronellol contained in various edible plant parts, together with FDA citations from 21 CFR §145.135, 21 CFR 172.510, 21 CFR §182.10, and 21 CFR §182.10; as well as technical literature citations. These tables demonstrate that geraniol and citronellol are present in the edible portions of a diverse food plants and range in concentration from 10-145,200 ppm (see attached tables).

BPPD Conclusions: Based on the rationale presented above, it is highly unlikely that residues of geraniol and citronellol in/on food commodities resulting from applications of Biomite (EPA File Symbol No. 070057-R) will pose any human health and/or environmental concerns when the product is applied according to proposed label use directions. BPPD concurs with the risk assessment presented by the registrant for geraniol and citronellol.

cc: R. S. Jones, R. Wilkins, BPPD Subject File.
R. S. Jones: F.F. CM2, (703) 308-5071; 07/02/2002

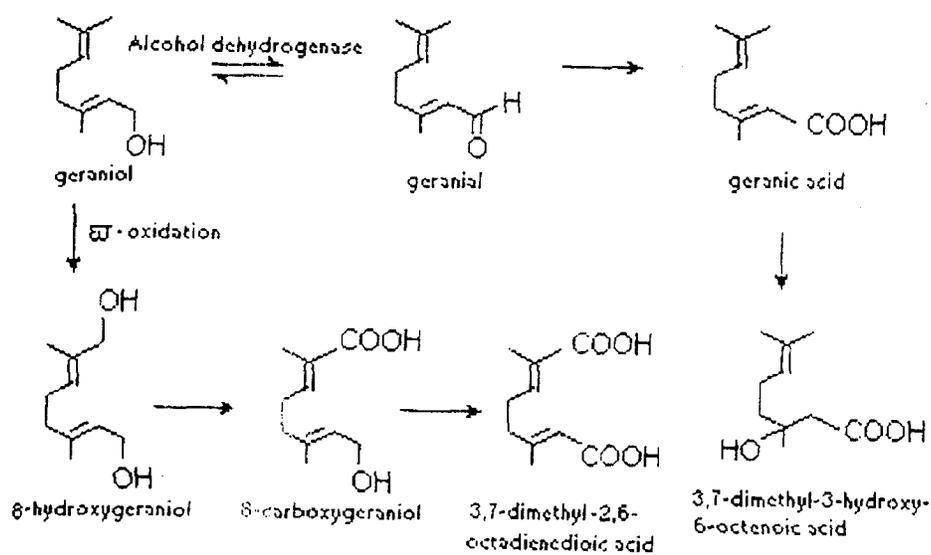


Figure 3. Metabolism of geraniol in rats

Table 3. Genotoxicity Test Results for Genotoxicity Assays

Test system	Substance name	Test object	Test concentration
In vivo			
Ames test	Benzenyl acetate	<i>S. typhimurium</i> TA98, TA100, TA1038, TA1537, TA1538	2000 nl/pla
Ames test	Benzenyl acetate	<i>S. typhimurium</i> TA98, TA100, TA1038, TA1537, TA1538	3333 µg/pla
Rec assay	Benzenyl acetate	<i>B. subtilis</i>	17 µg/disk ⁴
Rec assay	Benzenyl acetate	<i>B. subtilis</i>	20 µg/disk
Rec assay	Benzenyl formate	<i>B. subtilis</i>	18 µg/disk ⁴
HGPRT gene mutation assay	Benzenyl acetate	CHO cells	no details
Gene mutation assay	Benzenyl acetate	Human lymphoblast TK6	320 µg/ml 500 µg/ml
Chromosomal aberrations	Benzenyl acetate	Chinese hamster ovary cells	100 µg/ml 150 µg/ml
Sister chromatid exchange	Benzenyl acetate	Chinese hamster ovary cells	70 µg/ml 299 µg/ml
Unscheduled DNA synthesis	Benzenyl acetate	Rat primary hepatocytes	no details
Unscheduled DNA synthesis	Benzenyl acetate	Rat primary hepatocytes	100 nl/ml
Alkaline elution	Benzenyl acetate	Rat primary hepatocytes	0.30 mM
PAGE/PFGE ⁸	Benzenyl acetate	Rat primary hepatocytes	0.25 mM

Table 3. Continued.

Test system	Substance name	Test object	Test concentration
In vivo			
Sex-linked recessive lethal assay	Benzenyl acetate	<i>Drosophila melanogaster</i>	feeding 250 p injection 50
Micronucleus assay	Benzenyl acetate	Marrow B6C3F ¹ mouse bone cells	1800 mg/kg bw for 3 days, 1
Chromosomal aberrations	Benzenyl acetate	Marrow B6C3F ¹ mouse bone cells	no details, 1
Unscheduled DNA synthesis	Benzenyl acetate	Fisher F344 male rats	no details

¹ Highest ineffective dose (negative) or lowest affective dose (positive).

² Units based on information in Table 3.

³ Both with and without metabolic activation.

⁴ Single dose.

⁵ Without metabolic activation.

⁶ With metabolic activation.

⁷ Positive results were obtained at concentrations that were cytotoxic.

⁸ Programmed, autonomously-controlled electrode/pulsed-field gel electrophoresis

⁹ DNA fragmentation greater than that seen for 40 Gy of gamma radiation.

Table 1. Geraniol Residues Estimated for Representative Crops Used in the Dietary Exposure Assessment

Crop	1998-2000 Avg. Yield Per Acre in Tons	1998-2000 Avg. Yield Per Acre in kg	Number of Applications	Residue of Geraniol (ppm)
Grapes	7.1	6446.8	2	2,792
Almonds	1.19	1080.52	3	24,988
Macadamia	1.46	1325.68	2	13,578
Walnuts	1.3	1180.4	5	33,122
Hops	0.89	808.12	3	33,411
Pumpkin	14.39	13066.12	2	1,378
Watermelon	12.67	11504.36	2	1,565
Apricot	4.96	4503.68	2	3,997
Cherry-Sweet	3.78	3432.24	2	5,244
Cherry-Tart	3.69	3350.52	2	5,372
Nectarine	7.17	6510.36	3	4,147
Peach	7.96	7227.68	3	3,736
Plum	4.84	4394.72	3	6,144
Prune	6.13	5566.04	2	3,234
Apple	11.9	10805.2	3	2,499
Pear	14.96	13583.68	3	1,988

EDIBLE PLANTS CONTAINING GERANIOL

Species	Part	Quantity	FDA Citation	Reference
<i>Vitis vinifera</i> L. -- European Grape, Grape. Grapevine, Parra (Sp.), Vid (Sp.), Vigne Vinifere (Fr.), Weinrebe (Ger.), Wine Grape	Leaf Essent Oil	145,200 ppm	21 CFR 145.135	1
<i>Thymus vulgaris</i> L. -- Common Thyme, Garden Thyme, Thyme	Plant	10,660 ppm	21 CFR 182.10	2,3.
<i>Daucus carota</i> L. -- Carrot	Root Seed	8,120 ppm 8,120 ppm	21 CFR 182.20	1
<i>Cymbopogon martinii</i> (ROXB.) J. F. WATSON -- Palmarosa, Roshā	Plant	4,794 ppm	21 CFR 182.20	3
<i>Cymbopogon flexuosus</i> (NEES ex AUDEL) J. F. WATSON -- East Indian Lemongrass	Plant	2,500 ppm	21 CFR 182.20	4
<i>Pelargonium graveolens</i> (L.) L'HER ex AIT. -- Rose Geranium, Scented Geranium	Plant	1,400 ppm	21 CFR 182.20	1
<i>Bursera delpechiana</i> POISS. -- Linaloe, Linaloe	Wood	1,200 ppm	21 CFR 172.510	1
<i>Thymus zygis</i> subsp. <i>sylvestris</i> -- 'Portuguese' Thyme	Shoot	0-2,350 ppm	21 CFR 182.20	5
<i>Ocimum basilicum</i> L. -- Basil, Cuban Basil, Sweet Basil	Plant	1,000 ppm	21 CFR 182.10	6
<i>Salvia sclarea</i> L. -- Clary Sage	Plant	735 ppm	21 CFR 182.10	7
<i>Coriandrum sativum</i> L. -- Chinese Parsley,antro, Coriander	Fruit	442 ppm	21 CFR 182.10	1
<i>Jasminum officinale</i> L. -- Jasmine, Poet's Jessamine	Flower	380 ppm	21 CFR 182.20	1
<i>Citrus aurantium</i> L. -- Bitter Orange, Petitgrain	Leaf	350 ppm	21 CFR 182.20	1
<i>Zingiber officinale</i> ROSCOE -- Ginger	Rhizome	345 ppm	21 CFR 182.10	1
<i>Rosa gallica</i> L. -- French Rose	Flower	275 ppm	21 CFR 182.20	1
<i>Rosmarinus officinalis</i> L. -- Rosemary	Plant	50-370 ppm	21 CFR 182.10	8
<i>Anethum graveolens</i> L. -- Dill, Garden Dill	Fruit	154 ppm	21 CFR 182.10 and 182.20	1
<i>Elettaria cardamomum</i> (L.) MATON -- Cardamom	Plant	140 ppm	21 CFR 182.10	1

EDIBLE PLANTS CONTAINING GERANIOL

Species	Part	Quantity	FDA Citation	Reference
Citrus sinensis (L.) OSBECK -- Orange	Fruit	50 ppm		1
Thymus capitatus (L.) HOFFM. -- 'Sicilian' Thyme, Spanish Origanum, Spanish Thyme	Plant	40 ppm	21 CFR 172.510	2
Cymbopogon citratus (DC. ex NEES) STAPP -- Lemongrass, West Indian, Lemongrass	Plant	36 ppm	21 CFR 182.20	9

References

- 1 Duke, James A. 1992. Handbook of phytochemical constituents of GRAS herbs and other economic plants. Boca Raton, FL. CRC Press.
- 2 Lawrence, B.M., Essential Oils 1976-1977, Essential Oils 1978, Essential Oils 1979-1980. Note: Three annual compilations on essential oils. Percentages multiplied by 250-10,000 ppm and rounded to get fresh and dry weights.
- 3 List, P.H. and Horhammer, L., Hager's Handbuch der Pharmazeutischen Praxis, Vols. 2-6, Springer-Verlag, Berlin, 1969-1979.
- 4 Leung, A.Y., Encyclopedia of Common Natural Ingredients Used in Food, Drugs, and Cosmetics, John Wiley & Sons, New York, 1980.
- 5 De Cunha, A.P. and Salguiero, L.R. 1991. The Chemical Polymorphism of Thymus zygis ssp. sylvestris from Central Portugal. J. Ess. Oil Res. 3: 409-12.
- 6 Duke, J. A. Writeups or information summaries on approximately 2,000 economic plants, USDA, ARS, Beltsville, MD 20705
- 7 Flavour and Fragrance Journal, 6: 154.
- 8 J. Ethnopharmacology, 39: 167.
- 9 ANON. 1948-1976. The Wealth of India raw materials. Publications and Information Directorate, CSIR, New Delhi. 11 volumes.

EDIBLE PLANTS CONTAINING CITRONELLOL

Species	Part	Quantity	FDA Citation	Reference
<i>Zea mays</i> L. - Corn	Corn Leaf	19,000 ppm		1
<i>Zingiber officinale</i> ROSCOE -- Ginger	Rhizome	6,500 ppm	21 CFR 182.10	2
<i>Ocimum basilicum</i> L. -- Basil, Cuban Basil, Sweet Basil	Plant	2,419 ppm	21 CFR 182.10	3,1
<i>Rosa centifolia</i> L. -- Cabbage Rose	Essential Oil	1,200 ppm	21 CFR 182.20	2
<i>Pelargonium graveolens</i> (L.) L'HER ex AIT. -- Rose Geranium, Scented Geranium	Plant	1,176 ppm	21 CFR 182.20	2
<i>Cymbopogon nardus</i> (L.) RENDLE -- Ceylon Citronella, Citronella	Plant	1,008 ppm	21 CFR 182.20	4
<i>Mentha pulegium</i> L. -- European Pennyroyal	Plant	180 ppm	21 CFR 172.510	1
<i>Satureja montana</i> L. -- Savory, Winter Savory	Plant	0-325 ppm	21 CFR 182.10	5
<i>Citrus reticulata</i> BLANCO -- Mandarin, Tangerine	Fruit	50 ppm	21 CFR 182.20	2
<i>Elettaria cardamomum</i> (L.) MATON -- Cardamom	Fruit	40 ppm	21 CFR 182.10	2
<i>Melissa officinalis</i> L. -- Balm, Bee Balm, Lemonbalm, Melissa	Shoot	10-80 ppm	21 CFR 182.10	6
<i>Citrus limon</i> (L.) BURMAN f. -- Lemon	Leaf Essent. Oil	20 ppm	21 CFR 182.20	2
<i>Coriandrum sativum</i> L. -- Chinese Parsley, Cilantro, Coriander	Fruit	8 ppm	21 CFR 182.10	2
<i>Ocimum basilicum</i> L. -- Basil, Cuban Basil, Sweet Basil	Plant		21 CFR 182.10	
<i>Vaccinium corymbosum</i> L. -- Blueberry	Fruit			

References

- 1 Duke, J. A. Writeups or information summaries on approximately 2,000 economic plants, USDA, ARS, Beltsville, MD 20705
- 2 Duke, James A. 1992. Handbook of phytochemical constituents of GRAS herbs and other economic plants. Boca Raton, FL: CRC Press.

EDIBLE PLANTS CONTAINING CITRONELLOL

- 3 Die Nahrung. Pino, J., Rosado, A., Goire, J., Roncal, E., and Garcia, I. 1993. Analysis of the Essential Oil from Cuban Basil. *Die Nahrung* 37:(5): 501-504. Note: Also published in *JEO6:89*, 1994.
- 4 Lawrence, B.M., *Essential Oils 1976-1977*, *Essential Oils 1978*, *Essential Oils 1979-1980*. Note: Three annual compilations on essential oils. Percentages multiplied by 250-10,000 ppm and rounded to get fresh and dry weights.
- 5 Stanic, G., Petricic, J., and Blazevic, N. 1991. Gas Chromatographic Investigations of Essential Oils of *Satureja montana* and *Satureja subspicata* from Yugoslavia. *J. Ess. Oil Res.*, 3: 153-158.
- 6 *Deutsche Apot. Ztit.* 129(4):155-163. W. Schulze et al. *Die Melisse*.