United States Environmental Protection Agency | Prevention, Pesticides and Toxic Substances (7508C) | September 28, 2004

EPA

# Report of the Food Quality Protection Act (FQPA) Tolerance Reassessment Progress and Risk Management Decision (TRED) for Menthol

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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

**CERTIFIED MAIL**

Dear Registrant:

This is the Environmental Protection Agency's (hereafter referred to as EPA or the Agency) "Report of the Food Quality Protection Act (FQPA) Tolerance Reassessment Progress and Risk Management Decision for Menthol," which was approved on September 28, 2004. This document is also known as a Tolerance Reassessment Decision, or TRED.

The Federal Food, Drug and Cosmetic Act (FFDCA), as amended by FQPA, requires EPA to reassess all the tolerances for registered chemicals in effect on or before the enactment of the FQPA on August 3, 1996. In reassessing these tolerances, the Agency must consider, among other things, aggregate risks from non-occupational sources of pesticide exposure, whether there is increased susceptibility to infants and children, and the cumulative effects of pesticides with a common mechanism of toxicity. Once a safety finding has been made, the tolerances or exemptions from the requirement of a tolerance are considered reassessed.

Menthol, as an active ingredient, is used in over-wintering beehives to control tracheal mites in honey bees. Menthol has a peppermint flavor and smell and occurs naturally in many plants, especially mint. It is also found in foods derived from those plants, including honey made from pollen that naturally contains menthol. The Agency has evaluated all current registered uses of menthol and has determined that there is a reasonable certainty that no harm to any population subgroup will result from exposure to menthol when considering dietary exposure and all other non-occupational sources of pesticide exposure for which there is reliable information. Therefore, no mitigation measures are needed, and the current exemption from the requirement of a tolerance at 40 CFR 180.1092 is now considered reassessed under section 408(q) of the FFDCA.

FQPA requires that EPA 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 considers other substances because low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect, as would a higher level of exposure to any of the other substances individually. The Agency has not yet determined whether the chemical class which includes menthol exhibits a common mechanism of toxicity. Therefore, the Agency defers any cumulative risk assessment to a later date. For the purposes of the tolerance exemption reassessment of menthol, EPA is assuming no common mechanism with other compounds. Therefore, a cumulative assessment was not conducted for this TRED.

The current tolerance exemption for menthol at 40 CFR 180.1092 is now considered reassessed under section 408(q) of the FFDCA. This document summarizes the Agency's decision on the tolerance reassessment for menthol. Please contact Mark Perry of my staff with any questions regarding this decision. He may be reached by phone at (703)308-8024 or by e-mail at perry.mark@epa.gov.

Sincerely,

Debra Edwards, Ph.D.
Director
Special Review and Reregistration Division

Enclosures: *FQPA Risk Assessment for Tolerance Reassessment of Menthol* (9/28/2004, OPP Lower Toxicity Pesticide Chemical Focus Group)

# Tolerance Reassessment Eligibility Decision

# Menthol

# CASE 4063

**Special Review and Reregistration Division**
**Office of Pesticide Programs**
**U.S. Environmental Protection Agency**
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## Background:

This document represents the Lower Risk Pesticide Chemical Focus Group's (LRPCFG) Tolerance Reassessment Eligibility Decision (TRED) on menthol. This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, exposure profile, and environmental fate and ecotoxicity for menthol. In performing this assessment, EPA has utilized reviews previously performed by EPA, the World Health Organization (WHO) and the Organisation for Economic Co-operation and Development (OECD). Information from the Hazardous Substance Data Bank (HSDB) has also been used in this assessment.

In January 1993, a Reregistration Eligibility Decision (RED) was made for menthol, although the Agency determined that the need for full documentation was waived (i.e., an actual RED document was not issued). The purpose of this TRED document is to reassess the exemption from the requirement of a tolerance for residues of this chemical when used as an active ingredient (40 CFR 180.1092) and as an inert ingredient in pesticide formulations. Because the menthol RED was prior to the development of the Food Quality Protection Act (FQPA) in August 1996, tolerances need to be reassessed to meet the FQPA standard. The Agency has considered any new data generated after the tolerance exemption was issued, new Agency guidance or other federal regulations, as well as previously available information in this assessment.

## I. Executive Summary:

Menthol, as an active ingredient, is used in over-wintering beehives to control tracheal mites in honey bees. As an inert ingredient, menthol is in pesticides products used to control worms and caterpillars on fruits, vegetables, ornamental and shade trees. Toxicity information was collected on menthol and an endpoint for assessing short-term residential dermal exposure to menthol was chosen. The endpoint selected was a No Observed Effect Level (NOEL) of 560 mg/kg/day, based on increased incidence of perivascular lymphoid hyperplasia and interstitial nephritis observed in female mice in the 1100 and 2300 mg/kg-bw dose groups in a 13-week rat oral study. The dermal dose was conservatively converted to an oral equivalent dose using a 100% dermal absorption factor. An uncertainty factor of 100 (10 for interspecies extrapolation and 10 for intraspecies variation) was used in this assessment. EPA had earlier concluded in the RED for menthol that exposure from reasonable pesticide usage is not expected to present an increased dietary risk or residential risk beyond that from ordinary exposure.

Dietary (food) exposures have been assessed for menthol uses as an inert ingredient. Menthol is 7% of the cPAD for the general population and 24% of the cPAD for Children (1-2 years), indicating that the dietary exposures are not of concern to the Agency. Drinking water concentrations were not estimated for menthol due to its limited usage as an active ingredient and an inert ingredient, as well as its various physical and chemical properties (sorption to soil and sediment and volatilization).

Residential exposure to menthol is expected to occur through its use as an inert ingredient in pesticide formulations used in gardens, and through its use in disinfectants. To estimate residential handler and postapplication exposures to the inert uses of menthol, the Pesticide Inert Risk Assessment Tool (PIRAT, test version) was used. It was assumed that exposure would be to soluble and emulsifiable concentrate formulations. For residential handler exposure scenarios for the use of menthol as an inert ingredient, the calculated MOEs ranged from 310,000 for applications of soluble concentrate formulations using a low-pressure handwand to 1,400,000 for applications of emulsifiable concentrate formulations using a hose-

end sprayer in gardens and trees. For residential postapplication exposures, it was assumed that the transfer coefficient for adults would be 1000 $cm^2$/hr based on data from the Agriculture Reentry Task Force (ARTF) for adults performing postapplication tasks on tomatoes. The transfer coefficient for youths is assumed to be 500 $cm^2$/hr. No postapplication calculations were performed for toddlers' incidental oral ingestion, since toddlers are not expected to spend significant time contacting gardens or ornamental trees. For residential postapplication exposures, calculated MOEs ranged from a low of 460,000 for dermal contact with residue in foliage by adults following application of soluble concentrate formulations to a high of 1,400,000 for dermal contact with residue in foliage by youths following application of emulsifiable concentrate formulations. To examine exposure to menthol through the use of products such as general purpose cleaners, the Consumer Exposure Module (CEM) was used and a MOE of 121,000 was estimated. In this assessment, calculated MOEs did not exceed the Agency's level of concern (MOE<100) for any handler or postapplication scenarios. Considering aggregate exposure, it has been qualitatively determined that aggregate exposures due to the pesticidal uses of menthol would not be of concern to the Agency. This conclusion is based on the extremely low residential exposure, low dietary exposure and the absence of concern for drinking water exposures.

## II. Use Information:

Menthol has a peppermint flavor and smell and occurs naturally in many plants, especially mint. It is also found in foods derived from those plants, including honey made from pollen that naturally contains menthol. There are various isomers of menthol; the four most commonly used compounds are L-menthol (CAS No. 2216-51-5), D-menthol (CAS No. 15356-60-2), the racemic mixture D/L-menthol (CAS No. 89-78-1) and menthol, unspecified isomers, (CAS No.1490-04-6). Menthol is used as both an active (PC Code: 051601) and inert ingredient (PC Code: 851601) in various products. There is one product currently registered with menthol as an active ingredient, and it is listed in OPPIN as containing the unspecified isomers of menthol (CAS No. 1490-04-6). This product with menthol as an active ingredient is registered for use as a nearly pure crystalline solid in over-wintering beehives for the treatment of tracheal mites in honey bees.

FDA lists menthol in 21CFR 172.515 as a synthetic flavoring substance that may be safely used as a food additive. It is also considered by FDA to be Generally Recognized as Safe (GRAS) for use in food as an essential oil or natural extractive, with no limitations other than complying with good manufacturing practices (21 CFR 182.20). Menthol is also used extensively in drugs, cigarettes, cosmetics, and liqueurs to produce a mint flavor or odor, as well as in toothpastes. It is also used in medications for humans, as a topical antipruritic, and in inhalers for treatment of upper respiratory disorders or added to water for inhalation in acute bronchitis.

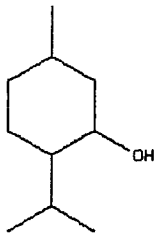
The exemption from the requirement for a tolerance being reassessed in this document, with the respective citation in the Code of Federal Regulations (CFR), and the use patterns as an active and inert ingredient are listed in Table 1. There are no exemptions for the requirement for a tolerance for the use of menthol as an inert ingredient.

| Table 1. Tolerance Exemptions Being Reassessed in this Document | | | | | |
|---|---|---|---|---|---|
| Tolerance Exemption Expression | CAS No. | 40 CFR | PC Code | Use Pattern | List Classification |
| Menthol | **Active Ingredient** | | | | |
| | 1490-04-6 | 180.1092 | 051601 | Used in over-wintering bee hives | N/A |
| | **Inert Ingredient** | | | | |
| | 89-78-1 | N/A | 851601 | Pesticide | 3[a] |

a. Inert ingredients are categorized into four lists as described in the 1987 and 1989 Policy Statements. List 3 inert ingredients are those inerts for which there was no basis for listing the chemical on any of the other lists.

## III. Physical/Chemical Properties:

The physical and chemical properties of menthol are provided in Table 2. The information was obtained from the Hazardous Substance Data Bank (HSDB) profile on L-menthol and the (SIDS) Initial Assessment Report for the menthols category. As indicated in the SIDS Initial Assessment Report, L-menthol, D-menthol, D/L-menthol and menthol (unspecified isomers) have similar physicochemical properties.

| Table 2. Physical/Chemical Properties of L-Menthol | | |
|---|---|---|
| Scientific name | 5-methyl-2-(1-methylethyl)-cyclohexanol | References: HSDB, 2003; OECD, 2003. |
| Structure for menthol (unspecified isomer) |   | |
| Molecular formula | $C_{10}H_{20}O$ | |
| Molecular weight | 156.27 g/mole | |
| Physical state | Colorless crystals or granules, peppermint odor and flavor | |
| Boiling point | 212 °C | |
| Melting point | 41-43 °C | |
| Solubility in water | 456 mg/L at 25°C | |
| Density/Specific Gravity | 0.890 | |

| Table 2. Physical/Chemical Properties of L-Menthol | | |
|---|---|---|
| Vapor Pressure | 0.0637 mm Hg (25 °C); 0.85 hPa (25 °C) | |
| Estimated Octanol/Water Coefficient | 3.4 | |
| Estimated Henry's Law constant | $1.5 \times 10^{-5}$ atm- $m^3$/mole | |
| Estimated Soil Sorption Coefficient | 1500 | |

## IV. Hazard Assessment:

In 1999, the World Health Organization published a document summarizing safety data on select food additives, including menthol, prepared by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). In this document, JECFA reviewed various studies conducted with L-menthol and D/L-menthol and concluded that there was no difference in the toxicity of the two isomers. As a result, the JECFA established an acceptable daily intake (ADI) not to exceed 4 mg/kg body weight for the two isomers of menthol, based on a NOEL of 380 mg/kg-bw per day in a long-term study in rats (WHO, 1999).

In 2003, a Screening Information Data Set (SIDS) Initial Assessment Report for the menthols category was published by the Organisation for Economic Cooperation and Development (OECD) under the HPV Chemicals Programme. In the SIDS Initial Assessment Report, the menthols category includes the isomers D-menthol (CAS No. 15356-60-2) and L-menthol (2216-51-5), the racemate D/L-menthol (CAS No. 89-78-1) and menthol, unspecified isomers, (CAS No. 1490-04-9). The SIDS Initial Assessment Report noted that all of these chemicals have similar physicochemical, toxicological, ecotoxicological and environmental fate properties. The SIDS Initial Assessment Report concluded that the chemicals in the menthols category are of low priority for further work due to their low hazard potential to human health. It was noted that although these chemicals may possess a hazard to the environment, no further work was needed, because acute toxicity is only evident at very high dose levels (OECD, 2003).

Key toxicological data for menthol are provided in Table 3. These data were obtained from published studies in peer reviewed journals summarized in the WHO JECFA document (WHO, 1999) and the SIDS Initial Assessment Report (OECD, 2003). Data cited in the initial proposed rules for tolerance exemption were previously reviewed by the Agency in the 1993 Reregistration Eligibility Document.

Menthol is relatively non-toxic in acute testing by the oral and dermal route. It is not a dermal sensitizer. There are no acute inhalation toxicity data for menthol (Table 3). The only long-term toxicity data showed limited toxicity concerns. When rats were exposed to L-menthol vapors (0.087, 0.15, or 0.26 ppm; equivalent to 0.57, 0.96, and 1.68 mg/$m^3$) in whole body exposures for 71-79 days, there were no systemic effects at any dose; however, histological examination revealed irritant effects on lungs and trachea, but only at highest dose, 0.26 ppm = 1.68 mg/$m^3$.

**Table 3. Summary of Toxicity Data for Menthol**

**Acute Toxicity**

| Test (Primary Reference) | Route of Administration | Form of Menthol | Dose | Species | Results | Source of Reference |
|---|---|---|---|---|---|---|
| Oral $LD_{50}$ (mg/kg-body weight (bw)) | Oral | L-menthol | various | Mouse | 3400; 4380 mg/kg-bw | WHO, 1999; OECD, 2003 |
| | | | | Rat | 940; 2615; 3300 | |
| | | D/L - menthol | | Mouse | 3100 | WHO, 1999; OECD, 2003 |
| | | | | Rat | 2602; 2900; 3180 | |
| Dermal $LD_{50}$ | Dermal | D/L-menthol | various | Rabbit | > 5000 | OECD, 2003 |
| Inhalation $LC_{50}$ | Studies on the acute inhalation toxicity of menthol have not been identified. When rats exposed to L-menthol vapors (whole body exposures) for 71-79 days, no systemic effects at any dose, but histological examination revealed irritant effects on lungs and trachea, but only at highest dose. | | | | | WHO, 1999; OECD, 2003 |
| Eye Irritation | | Not specified | N/A | Rabbit | Severe eye irritation | EPA, 1993 |
| | | all | | | Slightly irritating in testing with all four isomers | OECD, 2003 |
| Dermal Irritation | | D/L-menthol | N/A | Rabbit | Mild irritation | EPA, 1993 |
| | | all | | | Moderately irritating in testing with all four isomers | OECD, 2003 |
| Dermal sensitization | Buehler method | L-menthol | | Rabbit | negative | OECD, 2003 |
| | Local lymph node assay | L-menthol | | Mouse | negative | OECD, 2003 |
| | Modified Draize | L-menthol | | Guinea pig | "Ambiguous (positive after rechallenge)" | OECD, 2003 |

| Test (Primary Reference) | Route of Administration | Form of Menthol | Dose | Species | Results | Source of Reference |
|---|---|---|---|---|---|---|
| | skin sensitization and dermal challenge testing | various | | humans | "skin sensitization potency is low " | OECD, 2003 |
| **Subchronic and Chronic Toxicity** | | | | | | |
| 5-day oral (Litton Bionetics, Inc., 1975) | Oral-gavage | L-menthol | 2000, 25000, 32000, 4000, or 5000 mg/kg | Mice | $LD_{50}$ = 2600 mg/kg-bw | WHO, 1999; OECD, 2003 |
| 13-week oral (NCI, 1979) | Oral-diet | D/L-menthol | 0, 140, 280, 560, 1100, or 2300 mg/kg-bw/day | $B6C3F_1$ Mice | NOEL: 560 mg/kg-bw/day [d]<br>LOEL: 1100 mg/kg-bw/d,<br>based on increased incidence of perivascular lymphoid hyperplasia and interstitial nephritis in female mice only. | WHO, 1999 |
| | | | Males:<br>243, 488, 978, 1956, or 3913 mg/kg-bw/d<br>Females:<br>290, 595, 1193, 2386, or 4773 mg/kg-bw/d | | NOAEL: 1956 mg/kg-bw/d in males;<br>2386 mg/kg-bw/d in females;<br>LOAEL: 4773 mg/kg-bw/d in males;<br>3913 mg/kg-bw/d in females,<br>based on reduction in body weight gain only in highest dose group | OECD, 2003 |
| 13-week oral (NCI, 1979) | Oral-diet | D/L-menthol | 0, 93, 190, 380, 750, or 1500 mg/kg-bw/day | Fischer Rat | NOEL: 750 mg/kg-bw/d<br>LOEL: 1500 mg/kg-bw/d,<br>based on increased incidence of interstitial nephritis in male rats only. | WHO, 1999 |
| | | | Males:<br>59, 114, 231, 472, or 937 mg/kg-bw/d<br>Females:<br>67, 142, 285, 521, or 998 mg/kg-bw/d | | NOAEL: 937 mg/kg-bw/d in males;<br>998 mg/kg-bw/d in females.<br>LOAEL values were identified, since there were no effects on organ weights and no other adverse noted at highest dose tested; however, slight increase in the severity of spontaneous interstitial nephritis in males (which OECD stated was not an adverse effect). | OECD, 2003 |

| Test (Primary Reference) | Route of Administration | Form of Menthol | Dose | Species | Results | Source of Reference |
|---|---|---|---|---|---|---|
| 103-week oral (NCI, 1979) | Oral-diet | D/L-menthol | 0, 300, or 600 mg/kg-bw/day | $B6C3F_1$ Mice | NOEL: 600 mg/kg-bw<br>No significant carcinogenic nor organ-specific adverse effects at the highest dose tested. | WHO, 1999 |
| | | | 0, 334, or 667 mg/kg-bw/day | | NOAEL: 667 mg/kg-bw/d,<br>based on no adverse effects at highest dose tested | OECD, 2003 |
| 103-week oral (NCI, 1979) | Oral-diet | D/L-menthol | 0, 190, or 380 mg/kg-bw/day | Fischer Rat | NOEL: 380 mg/kg-bw,<br>based on no significant carcinogenic nor any other organ-specific adverse effects at the highest dose tested. | WHO, 1999 |
| | | | 0, 188, or 375 mg/kg-bw/day | | NOAEL: 375 mg/kg-bw/d in males (highest dose tested);<br>188 mg/kg-bw/d in females;<br>LOAEL: 375 mg/kg-bw/d in females, based on slightly reduced body weight in females. There was a slight increase in spontaneous, chronic inflamation of kidney in male rats in both dose groups (which study determined to be not an adverse effect). | OECD, 2003 |
| Pre-natal Developmental (Food and Drug Research Labs, Inc., 1973) | Oral-gavage | L-menthol | 0, 1.9, 8.6, 40, or 190 mg/kg-bw/day | CD-1 Mice | no teratogenic effects observed. | WHO, 1999; OECD, 2003 |
| Pre-natal Developmental (Food and Drug Research Labs, Inc., 1973) | Oral-gavage | L-menthol | 0, 2.2, 10, 47, or 220 mg/kg-bw/day | Wistar Rat | no teratogenic effects observed. | WHO, 1999; OECD, 2003 |
| Pre-natal Developmental (Food and Drug Research Labs, Inc., 1973) | Oral-gavage | L-menthol | 0, 4.1, 21, 98, or 400 mg/kg-bw/day | Golden hamsters | no teratogenic effects observed. | WHO, 1999; OECD, 2003 |
| Pre-natal Developmental (Food and Drug Research Labs, Inc., 1973) | Oral-gavage | L-menthol | 0, 4.3, 20, 92, or 430 mg/kg-bw/day | Dutch-belt rabbit | no teratogenic effects observed. | WHO, 1999; OECD, 2003 |

In rats, most of the orally administered menthol is rapidly eliminated in the urine or feces as the glucuronic acid conjugate or various oxidation products. In rabbits, orally administered menthol is similarly conjugated with glucuronic acid and eliminated in the urine, with about 86% elimination by glucuronidation within 10 hours. Similarly, humans also rapidly metabolize menthol primarily by conjugation with glucuronic acid and elimination in the urine. WHO (1999) postulated that cytochrome P450-mediated oxidation occurs in humans, yielding various alcohol and hydroxy acid derivatives, which would also be eliminated in the urine unchanged or conjugated with glucuronic acid.

In feeding studies with D/L-menthol, no evidence of carcinogenicity was found in mice and rats at the doses tested. According to WHO (1999), the highest doses tested were 380 mg/kg-bw/day in rats, and 600 mg/kg-bw/day in mice, while OECD (2003) reported these maximum doses as 375 and 667 mg/kg-bw/day, respectively for the rats and mice. Note that these data indicate that there was a slight recalculation of the doses between the WHO and OECD documents; however, in addition, the OECD document assessed the data to determine the actual severity of the adverse effects, and reported NOAELs, while the WHO document only reported the levels at which effects were noted, without assessing whether the effects were truly "adverse." Thus, the information listed in Table 3 for the NCI 1979 study is as reported in the respective WHO (1999) and OECD (2003) documents. Note that regardless of whether NOEL or NOAEL values are reported, menthol has a very low degree of subchronic and chronic toxicity to rats and mice.

While no studies of reproductive toxicity were available with menthol, in repeated dose studies with gavage-administered L- menthol to test developmental effects, no effects on reproduction were observed in mice, rats, hamsters, or rabbits. There were no effects on maternal body weights, appearance, behavior, or food consumption. In examinations of the fetuses of each species, there were no effects on nidation (nest building), maternal survival, fetal survival, or fetal abnormalities. The numbers of abnormalities seen in soft or skeletal tissues of treated animals did not differ from those occurring spontaneously in the controls. In addition, OECD (2003) concluded that although no fertility studies were available, histopathological examinations of the reproductive organs of rats and mice showed no changes following repeated dose 90-day and 2-year duration toxicity studies with D/L-menthol and also in carcinogenicity studies with D/L-menthol, and concluded "there is no indication of a potential of D/L-menthol to interfere adversely with reproduction." In addition, OECD (2003) specifically concluded that "L-menthol was not embryo- or fetotoxic and had no teratogenic properties in well performed gavage studies in various species (rat, mouse, rabbit, hamster) at not maternally toxic doses (185-425 mg/kg bw/d). No maternally toxic levels were used in these studies."

Available data indicate that menthol is generally not genotoxic, based on studies conducted *in vitro* with bacterial and mammalian test systems with L-menthol and D/L-menthol (WHO, 1999; OECD, 2003). In 29 studies, the results were negative. When menthol was administered at the maximum tolerated dose to rats and mice, and hepatocytes were removed after 1 to 2 days and replicative DNA synthesis measured, there was a 6% increase in rats and 1.7% in mice; however, WHO (1999) concluded that these results indicate cell replication (i.e., mitogenesis), but not genotoxicity, and OECD (2003) concluded that these results "demonstrated no mutagenic potential."

**Special Considerations for Infants and Children**

At this time, there is no concern for potential sensitivity to infants and children. Therefore, the additional tenfold FQPA safety factor (SF 10X) is unnecessary, and has been removed (equivalent to 1x). In developmental toxicity studies in which L-menthol was fed to mice, rats, hamsters, and rabbits, no teratogenic effects were observed at doses ranging from maximum doses of 190 to 430 mg/kg-bw,

depending on the species (WHO, 1999; OECD, 2003).

**Toxic Endpoint Selection:**

The WHO (1999) report stated that the limited data which allow comparisons of metabolism and toxicity between the various forms provide no indication of any differences in the toxicity between L-menthol and D/L-menthol. And OECD (2003) also concluded the available toxicity data indicate very similar toxicity profiles for all of the menthol isomers investigated. Thus, toxicity endpoint selection was made without regard to the specific menthol isomer which had been tested.

For conducting dietary exposures for menthol, there was no single dose (i.e., acute) effect endpoint identified. For chronic dietary exposures, the toxicological endpoint of concern selected was the lowest long-term NOAEL observed, 188 mg/kg/day, for the female rats from the 103-week oral feeding study (Table 3). The selection of this endpoint is very "conservative" (i.e., health-protective), because it represents the maximum dose tested in the study, and there were no effects observed at this dose; thus, if a higher dose had been tested, there may have been an even higher NOAEL.

For the residential exposure assessment of menthol, there are no dermal toxicological studies and no dermal absorption studies available in the existing literature. Therefore, an oral endpoint was used to assess short-term dermal exposure. The dermal dose was conservatively converted to an equivalent oral dose using a 100% dermal absorption factor. The oral toxicological endpoint that was selected was 560 mg/kg-bw/day, which was actually a NOEL. This NOEL was based on increased incidence of perivascular lymphoid hyperplasia and interstitial nephritis in female mice in the 1100 and 2300 mg/kg-bw dose groups in a 13-week oral study in mice (WHO, 1999). This endpoint is similar to the endpoint observed in a 13-week oral study in rats (WHO, 1999) where similar adverse toxicological effects are observed in male rats. Therefore, the adverse effects are not considered sex-specific and a body weight of 70 kg, representing the body weight of an average adult, is used in the assessment. An uncertainty factor of 100 (10 for interspecies extrapolation and 10 for intraspecies variation) was used for this assessment.

There are no acute inhalation toxicity data for menthol, and the only long-term toxicity data showed limited toxicity concerns (Table 3). Therefore, in the absence of adverse toxic effects, and no inhalation toxicity endpoint identified, a residential inhalation exposure assessment of menthol was not completed.

## V. Dietary (Food) Assessment

The chronic dietary (food) exposure assessments were conducted for menthol using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.03), which incorporates consumption data from US Department of Agriculture (USDA) Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The 1994-96 and 1998 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. For the chronic exposure assessment, consumption data are averaged for the entire U.S. population and within population subgroups.

For chronic dietary exposure assessment, an estimate of the residue level in each food or food-form (e.g., cucumbers or pickles) on the food commodity residue list is multiplied by the average daily consumption estimate for that food/food form. The resulting residue consumption estimate for each food/food form is summed with the residue consumption estimates for all other food/food forms on the commodity residue

list to arrive at the total average estimated exposure. The exposure is expressed in mg/kg body weight/day, and as a percent of the chronic Population Adjusted Dose (cPAD). The value for the PAD was taken as equal to the Reference Dose (RfD) of 1.88 mg/kg/day, derived from the oral NOAEL of 188 mg/kg/day from the two-year feeding study in the rat, with a Safety Factor of 100 applied to determine the RfD. This exposure estimation procedure for dietary exposures is performed for each population subgroup.

Since there were no available residue data for menthol in the respective food commodities, in conducting this assessment, the Agency has utilized a screening model, the inert screening level assessment, to estimate the residue levels and applied them to the various crops treated with products containing menthol as an inert ingredient. The screening level assessment uses the following generic assumptions and criteria in selecting and assigning residue values:

- Actual crop-specific residue data for various active ingredients can be utilized as surrogate data for menthol residue levels associated with its use as an inert ingredient (including secondary residues in meat, milk, poultry and eggs);
- Menthol is used on all crops and 100% of all crops are "treated";
- No adjustments are made for % of menthol used as an inert ingredient in formulation, the application rate, or multiple applications of the different active ingredient formulations in which menthol is an inert ingredient; and
- The model only considers preharvest applications.

Dietary modeling (Table 4) was performed utilizing the highest established tolerance level residue for each commodity. The results estimated for menthol indicate that chronic dietary exposures are not of concern to the Agency.

| Population Subgroup[2] | Chronic Dietary | |
|---|---|---|
| | Estimated Exposure (mg/kg/day) | % cPAD |
| General U.S. Population | 0.120 | 7 |
| All Infants (< 1 year old) | 0.245 | 14 |
| Children 1-2 years old | 0.422 | 24 |
| Children 3-5 years old | 0.310 | 18 |
| Children 6-12 years old | 0.174 | 10 |
| Youth 13-19 years old | 0.100 | 6 |
| Adults 20-49 years old | 0.087 | 5 |
| Adults 50+ years old | 0.086 | 5 |
| Females 13-49 years old | 0.087 | 5 |

[1]Exposure estimates are based on highest-tolerance-level residues of high-use active ingredients for all food forms, including meat, milk, poultry, and eggs.
[2] Only representative population subgroups are shown.

## VI. Drinking Water Considerations

According to the Hazardous Substance Data Bank (HSDB) environmental fate profile, volatilization from water surfaces is expected to be an important fate process for L-menthol; estimated volatilization half-lives for a model river are 2 days, and for a model lake 18 days. In soils, L-menthol is expected to have low mobility and will volatilize rapidly under moist conditions.

In addition, there is only one product which contains menthol as an active ingredient, and it has an enclosed usage pattern (the product is used for over-wintering of beehives). The products containing menthol as an inert ingredient, similarly have limited usage. Based on the environmental fate properties (especially sorption to soils/aquatic sediments and the estimated volatilization half-lives) and the limited usage for menthol-containing products, detailed drinking water modeling was not required. Note also, that OECD (2003) had indicted that various forms of menthol exhibited a low (1) Class of danger for water pollution for menthol for all uses of the chemical, with 1 indicating a potential for "weakly water polluting."

## VII. Residential Exposure Assessment

Exposure to menthol can occur through the use of certain pesticide products. In addition, exposure can occur naturally through different foods, or through FDA-approved GRAS uses.

### Residential Exposure

Residential exposure to menthol could occur through its use as an inert ingredient in pesticide products used in and around the home. An inhalation exposure assessment was not performed due to absence of toxic endpoints for that route of exposure. In the 1993 RED for menthol, the Agency indicated that potential for inhalation exposure does exist; however, menthol is an ingredient added in liqueurs, candies, as well as inhalers and cough remedies to sooth respiratory congestion, and is of little concern from a toxicity perspective (EPA, 1993).

*Outdoor uses*

Residential handler dermal exposure to menthol during outdoor applications as an inert ingredient was examined in this risk assessment (Table 5). Postapplication dermal exposure to adults and youths (10-12 years) from contact with residues on foliage were also evaluated (Table 6).

The exposure scenarios chosen for this risk assessment were based on the anticipated use patterns and current labeling for pesticide products containing menthol as an inert ingredient. Exposure estimates for residential handler and postapplication scenarios were calculated using the Pesticide Inert Risk Assessment Tool (PIRAT, test version) (Versar, 2004). This tool is based on weight fractions of inert ingredients in pesticide products. For this risk assessment, it was assumed that exposure would be to pesticide products formulated as soluble and emulsifiable concentrates. Product uses evaluated include applications to trees and garden plants. The 90$^{th}$ percentile default weight fractions were assumed. An application rate of 0.00013 lb/ft$^2$ was used. In addition, a 100% dermal absorption factor was used to convert dermal doses to equivalent oral doses. The oral NOEL of 560 mg/kg/day was used to assess risks from short-term exposures. Intermediate-term exposures are not expected in the residential setting. The Agency does not have concern when MOE values are greater than 100.

For postapplication scenarios, the following assumptions are used:

- transfer coefficient of 1000 $cm^2$/hr for adults and 500 $cm^2$/hr for youths (from hand harvesting, hand pruning, staking, thinning, training, or tying tomatoes based on data from the Agriculture Reentry Task Force (ARTF) for adults performing postapplication tasks on tomatoes);
- time in treated area 0.67 hours/day for adults and 0.33 hours/day for youths; and
- body weight is 70 kilograms for adults and 39.1 kilograms for youths.

The scenarios, application rates, areas treated or amounts used and calculated MOEs for residential handler and postapplication exposure are provided in Tables 5 and 6, respectively. For residential handler exposure scenarios, calculated MOEs ranged from 310,000 for applications of soluble concentrate formulations using a low-pressure handwand to 1,400,000 for applications of emulsifiable concentrate formulations using a hose-end sprayer in gardens and trees. For residential postapplication exposures, calculated MOEs ranged from a low of 460,000 for dermal contact with residue in foliage by adults following application of soluble concentrate formulations to a high of 1,400,000 for dermal contact with residue in foliage by youths following application of emulsifiable concentrate formulations. Exposure outputs from the PIRAT model are provided in Appendix A.

**Table 5. Residential Handler Risks Due to Exposure to Menthol as an Inert Ingredient**

| Formulation Type | Product Use | Application Rate[a] | Application method | Area treated or Amount Used[a] | Dermal MOE[b] |
|---|---|---|---|---|---|
| Soluble Concentrate | vegetable garden, ornamental trees | 0.00013 lb/$ft^2$ | Low-pressure handwand | 1000 $ft^2$ | 310,000 |
| | | | Hose-end sprayer | 1000 $ft^2$ | 1 x $10^6$ |
| Emulsifiable Concentrate | vegetable garden, ornamental trees | 0.00013 lb/$ft^2$ | Low-pressure handwand | 1000 $ft^2$ | 410,000 |
| | | | Hose-end sprayer | 1000 $ft^2$ | 1.4 x $10^6$ |

a. Values for application rate and area treated are default values provided by PIRAT.
b. MOE = NOAEL (560 mg/kg)/Potential Dose Rate estimated by PIRAT.

| Table 6. Residential Post-Application Risks Due to Exposure to Menthol as an Inert Ingredient | | | | | | | |
|---|---|---|---|---|---|---|---|
| Formulation Type | Product Use | Application Rate[a] | Population | Exposure Time (hours) | Transfer Coefficient | PDR[a] (mg/kg/day) | Dermal MOE[b] |
| Soluble Concentrate | Garden/ Trees | 0.00013 lb/ft$^2$ | Adults | 0.67 | 1000 | 0.001206 | 460,000 |
| | | | Youth (10-12 years) | 0.33 | 500 | 0.000532 | 1.1 x 10$^6$ |
| Emulsifiable Concentrate | Garden/ Trees | 0.00013 lb/ft$^2$ | Adults | 0.67 | 1000 | 0.000896 | 630,000 |
| | | | Youth (10-12 years) | 0.33 | 500 | 0.000395 | 1.4 x 10$^6$ |

a. Potential Dose Rate estimated by PIRAT.
Potential Dose Rate = (AR*WF*F*4.54e5 mg/lb*1.08E-3 ft2/cm2*Tc*ET)/BW*ABS; where AR= application rate; WF= weight fraction; F = Fraction Exposed; Tc= Transfer coefficient; ET= Exposure time; BW= Body weight; and ABS= Absorption factor.
b. MOE = NOAEL (560 mg/kg)/Potential Dose Rate estimated by PIRAT.

*Indoor uses*

In terms of consumer use exposure to products containing menthol, the Consumer Exposure Module (CEM) (Versar, 1999) was used to determine the average daily dose (ADD) from exposure to menthol. The exposure scenario examined was the use of a general purpose cleaner assuming a weight fraction range of 1% to 5%. Table 7 provides the CEM dermal MOE estimates. Exposure output information from the CEM model is provided in Appendix B. Using the oral NOEL of 560 mg/kg-day and assuming 100% dermal absorption, the MOE was calculated to be 121,000.

Postapplication dermal and oral exposure to toddlers resulting from the use of menthol as an inert in general purpose cleaners was not estimated due to lack on information on application rates. However, postapplication exposure is not expected to be significant given the low concentration of menthol in disinfectants.

| Table 7. Summary of Consumer Exposure | | | | | | |
|---|---|---|---|---|---|---|
| Scenario | Weight Fractions[a] | Years of Use | Surface Area/Body Weight Ratio (cm$^2$/kg) | Frequency of Use (events/yr) | Average Daily Dose Rate (mg/kg-day) | Dermal MOE[b] |
| General Purpose Cleaner | 0.01-0.05 | 57 | 15.6 | 300 | 4.62e-03 | 121,000 |

a. Based on inert ingredient information provided for Comet disinfectant, a weight fraction range of 1% to 5% was assumed for menthol.
b. MOE = NOAEL (560 mg/kg-day)/Average Daily Dose Rate estimated by PIRAT.

## VIII. Aggregate Assessment

Based on the extremely low residential exposure, low dietary exposure and the absence of concern for drinking water exposures, it has been qualitatively determined that the aggregate exposures due to the pesticidal uses of menthol would not be of concern to the Agency.

## IX. Risk Characterization

Regarding use as an active ingredient, EPA concluded in the 1993 RED for menthol, and is reaffirming in this TRED, that exposure from reasonable pesticide usage is not expected to present an increased dietary risk or occupational risk beyond that from ordinary exposure (EPA, 1993). There were no concerns for dietary (food) exposures for menthol. In addition, none of the handler or postapplication risks were of concern for menthol resulting from its use as an inert ingredient.

## X. Cumulative Exposure

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." If chemicals are structurally related and all are low toxicity chemicals, then the risks either separately or combined should also be low.

EPA does not have, at this time, available data to determine whether menthol has a common mechanism of toxicity with other substances. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to menthol and any other substances, and menthol does not appear to produce a toxic metabolite produced by other substances.

For the purposes of this tolerance action, therefore, EPA has not assumed that menthol has a common mechanism of toxicity with other substances. For information regarding the Agency's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

## XI. Tolerance Reassessment

In 1993, a tolerance exemption was established for residues of menthol in or on beeswax and honey when used in accordance with good agricultural practices in over-wintering hives. The residue data submitted to the Agency in support of the tolerance exemption were adequate, and indicated that menthol residues in honey will not exceed 5 ppm as a result of the registered use. The Agency is concluding that the residue data continue to support the tolerance exemption for the active use of menthol. The technical justification for this finding is based partially on the negligible dietary exposure associated with this pesticide use when compared with confectionary, pharmaceutical and other uses for menthol. At this time the Agency considers the tolerance exemption for menthol to be reassesed.

## XII. References

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