Exposure and Risk Assessment on Lower Risk Pesticide Chemicals

D-Limonene

Prepared by

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Background:

This document represents the Lower Risk Pesticide Chemical Focus Group's (LRPCFG) Tolerance Reassessment Eligibility Decision (TRED) on d-limonene. This assessment summarizes the available information on the use, physical/chemical properties, toxicological effects, exposure profiles, and environmental fate and ecotoxicity for d-limonene. In performing this assessment, EPA has utilized reviews previously performed by EPA and the World Health Organization (WHO). The Agency did not review any data in association with this assessment.

In September 1994, a Registration Eligibility Decision (RED) document was issued for d-limonene and a tolerance exemption has also been granted for its use as an inert ingredient as a solvent or a fragrance in pesticide formulations. The purpose of this TRED document is to reassess the exemptions from the requirement of a tolerance for residues of this chemical when used as an active ingredient and an inert ingredient in pesticide formulations. Because the original d-limonene RED was issued in September 1994, prior to the development of the Food Quality Protection Act (FQPA) in August 1996, tolerances also 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. The Agency was assisted in the preparation of parts of this document by its contractor Versar.

I. Executive Summary:

d-Limonene has a lemon-like flavor and smell, and occurs naturally in citrus and certain fruits, vegetables, meats and spices. d-Limonene is used as both an active and inert ingredient in pesticide products, and as an ingredient in food products, soaps, and perfumes. As an active ingredient, it is used as an insecticide, insect repellent, and animal (dog and cat) repellent. As a pesticide inert ingredient is used as a solvent or fragrance. It is also found in consumer products such as certain foods, soaps, and perfumes. FDA considers d-limonene to be GRAS as a food additive when used as a synthetic flavoring substance and adjuvant (21CFR 182.60). d-Limonene is not registered for food or feed crop uses as an active ingredient, but can be used on compost and manure.

In conducting risk assessments, an oral LOAEL of 400 mg/kg-bw/day was used for the short-term exposure scenarios, while an oral NOAEL of 150 mg/kg-bw/day was used for the long-term exposure scenarios. Since the short-term toxicity endpoint is based on an LOAEL, an additional safety factor of 3X was applied to the Margin of Exposure (MOE) of 100. Thus, an MOE of 300 is of concern for the short-term exposure scenarios. For long-term exposures, an additional safety factor was not necessary, so the MOE of concern is 100.

For products containing d-limonene as an active ingredient, exposure scenarios were chosen based on the anticipated use patterns and current labeling for d-limonene pesticide products. Application rates were also estimated based on information provided on the product labels. Calculated MOEs ranged from a low of 81 for the application of pet dips to a high of 7,300 for the application of liquid pesticides with a watering can. For products containing d-limonene as an inert ingredient, the Pesticide Inert Risk Assessment Tool (PIRAT, test version) was used to estimate handler dermal and inhalation exposure. It was assumed that exposure would be to pressurized liquid, ready-to-use liquid, and emulsifiable and soluble concentrate formulations, all of which may contain inert ingredients used as fragrances. Calculated MOEs ranged from a low of 420 for ready-to-use outdoor paints/stains that are applied by airless sprayer to a high of 3,300,000 for emulsifiable concentrates applied using a backpack sprayer. To

examine exposure to d-limonene through the use of products such as general purpose cleaners and aerosol spray cans, the Consumer Exposure Module (CEM) was used.

In this assessment, the only exposure scenario that exceeded the Agency's level of concern was the use of pet dips with d-limonene as an active ingredient (MOE of 81). However, several factors need to be considered when interpreting this MOE, including: (1) the uncertainties associated with the assessment as outlined in the OPP Health Effects Division's Standard Operating Procedures (SOP) for Residential Exposure Assessments, (2) a multi-day continuously dosing endpoint was compared to a pet dip scenario for which the Agency believes that it is most likely that there will only be a single event exposure for less than an hour's duration, (3) the dermal absorption rate for this assessment is assumed to be 100% of the oral , which may be conservative for this particular chemical, and (4) on the label in question, there is a specific recommendation that users wear rubber gloves while performing the pet dip activity. The Agency does not require personal protective equipment for residential use labels, but the Agency also does not typically request that registrants remove PPE from their existing labels, when the use of such PPE is health protective for users. Taken together, these factors make a strong case that the resulting estimate significantly overestimate exposures and risks for this pet dip scenario.

For chronic dietary assessments, a NOAEL of 150 mg/kg-bw/d was selected, based on an 103-week oral gavage study in the male rat. For all populations addressed, the MOEs for d-limonene were greater than the MOE of concern of 100.

In terms of environmental exposures, studies have been performed on both the technical form of d-limonene and the formulated products and have been shown to be practically nontoxic or slightly toxic to birds, fish and invertebrates.

II. Use Information:

d-Limonene occurs naturally in citrus and certain fruits, vegetables, meats and spices. It has a lemon-like flavor and smell, and is used as both an active and inert ingredient in various products. As an active ingredient, it is used as an insecticide, insect repellent, and animal (dog and cat) repellent. As a pesticide inert ingredient is used as a solvent or fragrance. It is also found in consumer products such as certain foods, soaps, and perfumes. FDA considers d-limonene to be GRAS as a food additive when used as a synthetic flavoring substance and adjuvant (21CFR 182.60). d-Limonene is not registered for food or feed crop uses as an active ingredient, but can be used on compost and manure.

The tolerance exemptions 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.

Table 1. Tolerance Exemptions Being Reassessed in this Document					
Tolerance Exemption Expression	CAS No.	40 CFR	PC Code	Use Pattern	List Classification
d-Limonene	5989-27-5	**Active ingredient**			
		180.539	079701	Used in insect-repellent tablecloths and in insect-repellent strips used in food or feed-handling establishments	NA
		Inert Ingredient			
		180.910 and 180.930 (formerly 180.1001(c) and (e))[a, b]	879701	"Solvent, fragrance"	4B[c]

a Residues listed in 40 CFR 180.910 are exempt from a tolerance when used as inert ingredients in pesticide formulations applied to growing crops or to raw agricultural commodities after harvest and those listed in 40 CFR 180.930 are exempt from a tolerance when used as inert ingredients in pesticide formulations applied to animals.
b In both sections, the inert ingredient is listed as "d-Limonene (CAS Reg. No. 5989-27-5)".
c Inert ingredients are categorized into four lists as described in the 1987 and 1989 Policy Statements. List 4B inert ingredients are those inerts for which EPA has sufficient information to reasonably conclude that the current use pattern in pesticide products will not adversely affect public health or the environment.

III. Regulatory Background

The World Health Organization published a document in 1993 summarizing safety data on select food additives and naturally occurring toxicants (including d-limonene) reviewed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (WHO, 1993). Based on information from various studies, the JECFA utilized data on reduced body weights in male rats to establish an acceptable daily intake of 0-1.5 mg/kg body weight for d-limonene. The committee concluded, however, that only a small proportion of total intake would likely be from direct additive use and therefore restricted food additive intake to 0.075 mg/kg body weight/day. Note that in a subsequent report (WHO, 1998), a later panel "withdrew the existing acceptable daily intake ... and in its place allocated "not specified"."

In 1994, a Reregistration Eligibility Decision (RED) document was issued by EPA to ensure that as an active ingredient Limonene can be used without posing unreasonable risks to human health or the environment. (Note that the RED was written on "Limonene" and lists a CAS number of 138-86-3, which is actually the CAS number for α-limonene, although the RED indicates the "Trade and Other Names" is d-limonene. Thus, this TRED is intended to be for the CAS number 5989-27-5, which is the CAS Registry No. actually assigned for d-limonene.) Both human health and environmental risk assessments were performed. The RED reported that dietary exposure to limonene was not a concern, and that exposure through the use of insecticide sprays or animal repellent granules could result in skin irritation/sensitization or eye irritation. The RED also reported that there would be minimal risks to birds, mammals and aquatic species from exposure to limonene (EPA, 1994).

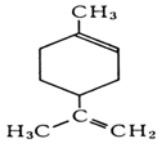
In 1998, a Concise International Chemical Assessment Document (CICAD) on limonene (d-limonene, l-limonene, and d/l-limonene) was prepared by the International Programme on Chemical Safety [a cooperative program of the World Health Organization (WHO), the International Labour Organization, and the United Nations Environment Programme]. The CICAD was based primarily on a review prepared in 1993 for the Nordic Expert Group, as well as a review performed under the Nordic Council of Ministers, a preliminary, non peer-reviewed information source on environmental exposure and

effects, and database searches covering the years 1993-1995. Limonene was reported to be a skin irritant in both animals and humans and the liver was reported to be the "critical organ" in animals, that is, the primary target organ most likely to show adverse effects. The report concluded that "food is believed to be the principal source of exposure (96%) to limonene; the contribution from ambient air is approximately 4%. The dermal uptake of limonene has not been estimated." To determine a tolerable intake for humans, data from a 13-week oral-gavage study in the male rat which showed increased relative liver weights was utilized, and a guidance value for ingestion was calculated to be 0.1 mg/kg body weight/day (WHO, 1998).

d-Limonene was included in a report submitted to the EPA HPV Challenge Program by the Flavor and Fragrance High Production Volume Chemical Consortia (The Terpene Consortium, 2002). HPV chemicals are those that are manufactured or imported into the U.S. in production volumes greater than one million pounds per year. The HPV Challenge Program is a voluntary partnership between industry, environmental groups, and the EPA which invites chemical manufacturers and importers to provide basic hazard data on the HPV chemicals they produce/import. The goal of this program is to facilitate the public's right-to-know about the potential hazards of chemicals found in their environment, their homes, their workplace, and in consumer products.

IV. Physical/Chemical Properties:

The physical and chemical properties of d-limonene are provided in Table 2.

Table 2. Physical/Chemical Properties of d-Limonene		
Structure		References: NIOSH, 2001; WHO, 1998
Molecular formula	$C_{10}H_{16}$	
Molecular weight	136.2 g/mole	
Physical state	colorless liquid, with characteristic mild citrus odor	
Melting point	-75 °°C	
Boiling point	176 °C	
Solubility in water	13.8 mg/L at 25°C	
pH	Not applicable	
Density/Specific Gravity	0.84 g/mL	
Vapor Density	Relative vapor density = 4.7 (air = 1)	
Vapor Pressure	0.4 kPa at 14.4°C; 2 mm Hg at 20°C	
Estimated Octanol/Water Coefficient	log Kow: 4.2	
Dissociation Constant	Not applicable	
Estimated Henry's Law constant	34.8 kPa m^3/mol at 25°C	
Estimated Soil Sorption Coefficient	(likely to sorb based on log P)	

V. Hazard Assessment:

Key toxicological data for d-limonene are provided in Table 3. These data were obtained from published studies in peer reviewed journals summarized in two WHO documents (WHO, 1993; 1998). Data cited in the initial tolerance exemption were previously reviewed by the Agency in the 1994 RED.

Table 3. Summary of Toxicity Data for d-Limonene

Test	Species	Route of Administration/ Doses	Results	Reference
Acute Toxicity				
Oral LD_{50}	Mouse	Oral	5600 mg/kg (M)	WHO, 1993
			6600 mg/kg (F)	
	Rat	Oral	4400 mg/kg (M)	
			5100 mg/kg (F)	
Dermal LD_{50}	Rabbit	Dermal	>5000 mg/kg	WHO, 1998
Inhalation LC_{50}	Studies on the acute inhalation of d-limonene in laboratory animals have not been identified.			
Eye Irritation	Rabbits	Eye instillation	Irritation to eyes observed	WHO, 1998
Dermal Irritation	Guinea pigs	Dermal contact	Moderate (guinea pigs)	WHO, 1998
	Rabbits		Low (rabbits)	
	Rat		Irritant at high concentrations	RED, 1994
Dermal Sensitization	Guinea pigs		May cause dermal sensitization	RED, 1994
		Freund's Complete Adjuvant assay	d-Limonene in unoxidized form did not cause sensitization, but its air-oxidized products found to be potent contact allergens	WHO, 1998
Subchronic and Chronic Toxicity				
16-day oral	Mice	Oral-gavage: 0, 413, 825, 1650, 3300, 6600 mg/kg-bw/d	NOAEL: 1650 mg/kg-bw/d LOAEL: 3300 mg/kg-bw/d Deaths at 3300 and 6600 mg/kg-bw/d, but no compound-related clinical signs observed in mice in 1650 mg/kg-bw dose group that lived to end of dosing, plus no compound-related histopathologic effects (NTP, 1990)	WHO, 1993, 1998
13-week oral	Mice	Oral-gavage: 0, 125, 250, 500, 1000, 2000 mg/kg-bw/d	NOAEL: 500 mg/kg-bw/d LOAEL: 1000 mg/kg-bw/d Reduced body weights and death, plus rough hair coats and decreased activity (NTP, 1990)	WHO, 1993, 1998

Test	Species	Route of Administration/ Doses	Results	Reference
103-week oral	Mice	Oral-gavage: Males: 0, 250, and 500 mg/kg-bw/d; Females: 0, 500, 1000 mg/kg-bw/d	NOAEL: 250 mg/kg-bw/d (male) 500 mg/kg-bw/d (female) LOAEL: 500 mg/kg-bw/d (male) 1000 mg/kg-bw/d (female) In males dosed at 500 mg/kg-bw/d, livers exhibited presence of cells with abnormal numbers of nuclei and cytomegaly. (In males dosed at 250 mg/kg-bw/day, lowest dose tested, reduced survival, but not deemed by NTP to be dose-related.) In females, decreased survival and lower body weights (5 - 15%) in highest dose tested, 1000 mg/kg-bw, but no treatment related clinical signs at any dose tested (NTP, 1990)	WHO, 1993, 1998
16-day oral	Rats	Oral-gavage: 0, 413, 825, 1650, 3300, 6600 mg/kg-bw/d	NOAEL: 1650 mg/kg-bw/d LOAEL: 3300 mg/kg-bw/d Deaths at 3300 and 6600 mg/kg-bw/d, but no clinical signs in 1650 mg/kg-bw dose group or lower, and no compound-related histopathological effects seen in any rats (NTP, 1990)	WHO, 1993, 1998
26-day oral	Rats (males only)	Oral-gavage: 0, 75, 150, 300 mg/kg-bw/d	NOAEL: undetermined (kidney) 150 mg/kg-bw/d (liver) LOAEL: 75 mg/kg-bw/d (kidney) 300 mg/kg-bw/d (liver) At lowest dose tested, effects on kidneys of male rats, even after only 6 days; in addition, increased relative kidney and liver weights, even after 6 days, measured in 300 mg/kg-bw/d dosed group, but not in 150 mg/kg-bw/d group; in light microscopy, kidneys showed dose-related hyaline droplet formation, as well as granular casts in outer zone of medulla and chronic nephrosis, but no evident alterations observed in liver sections, even at highest dose tested (Kanerva et al., 1987)	WHO, 1993, 1998
30-day oral	Rats (males only)	Oral-gavage: 400 mg/kg-bw/d	LOAEL: 400 mg/kg-bw/d (males only) At only dose tested, 20-30% increase in amount and activity of different liver enzymes, increase in relative liver weight, and decrease in cholesterol levels; no histopathological examinations conducted (Ariyoshi et al., 1975)	WHO, 1998

Test	Species	Route of Administration/ Doses	Results	Reference
13-week oral	Rats (males only)	Oral-gavage: 0, 2, 5, 10, 30, 75 mg/kg-bw/d	NOAEL: 5 mg/kg-bw/d (kidney) 30 mg/kg-bw/d (liver) LOAEL: 30 mg/kg-bw/d (kidney) 75 mg/kg-bw/d (liver) For kidneys, "incidence and severity of these lesions increased slightly at 10 mg d-limonene/kg body weight although ... a clear 91-day lowest-observable effect (LOEL) was produced at 30 mg d-limonene kg body weight ($P < 0.01$)". For liver, no differences in absolute liver weights, and increase in relative liver weights statistically significant only at 75 mg/kg-bw/d, but no histopathological effects observed (Webb et al., 1989)	WHO, 1993, 1998
13-week oral	Rats	Oral-gavage 0, 150, 300, 600, 1200, 2400 mg/kg-bw/d	NOAEL: undetermined in male 600 mg/kg-bw/d in female LOAEL: 150 mg/kg-bw/d in male 1200 mg/kg-bw/d in female In males, kidneys showed nephropathy at all doses, with severity dose related. In females, at 1200 mg/kg-bw, rough hair coats, lethargy, and excessive lacrimation (NTP, 1990)	WHO, 1993, 1998
103-week oral	Rats	Oral-gavage Males: 0, 75, and 150 mg/kg-bw/d; Females: 0, 300, 600 mg/kg-bw/d	NOAEL: undetermined (male; kidney) 150 mg/kg-bw/d (male; other than kidney, no adverse effects at highest dose tested) 300 mg/kg/bw/d in female LOAEL: 75 mg/kg-bw/d (male: kidney) undetermined (male; other than kidney, no other adverse effects at highest dose tested) 600 mg/kg-bw/d in female In males, effects in kidneys included dose-related increases in incidences of mineralization and epithelial hyperplasia, even at lowest dose tested; however, no other significant adverse effects were observed by NTP in males dosed at 150 mg/kg-bw/d, other than on kidneys. In females, at 600 mg/kg-bw/d, reduced survival, but no adverse effects in low dose group, 300 mg/kg-bw/day (NTP, 1990)	WHO, 1993, 1998

Toxicity to the Kidney of Male Rats:

Note that the WHO CICAD report (1998) listed a "NOEL" of 5 mg/kg-bw/day, based on pathological formation of granular casts at the outer zone of the renal medulla, from a 13-week oral-gavage study in

the rat which tested males only (Webb et al., 1989). This would appear to represent the lowest NOAEL for d-limonene, but the authors of that study (Webb et al., 1989) had indicated that "since the syndrome is dependent on the presence of that alpha$_{2\mu}$-globulin [in male rats], species such as humans, mice, dogs, and guinea-pigs that do not produce this renal protein will probably not develop this specific toxicity following exposure to hydrocarbons like d-limonene," and further that "this toxicity may not be predictive of a similar response in humans." The EPA Risk Assessment Forum (1991) compiled an extensive review of the results of many repeat dosing studies of various chemicals in the male rat, including d-limonene, and similarly concluded that "since humans appear to be more like other laboratory animals than the male rat, in this special situation, the male rat is not a good model for assessing human risk." Thus, the risk assessments in this TRED will not further consider the data obtained from repeat dosing studies causing effects in the kidney of the male rat.

Other Toxic Effects in Oral Exposure Studies with d-Limonene, including to the Liver:

In addition to effects on the kidney of male rats, Webb et al. (1989) reported effects on the liver. Data from this 91-day subchronic study showed increased relative liver weights and relative kidney weights to be statistically significantly at 75 mg/kg-bw/d, relative to total body weights, although there were no statistically significant increases in absolute weights of either the liver or the kidney. Based on the information reviewed above by the EPA Risk Assessment Forum (1991), the effects on the kidney of the male rat are not considered further. However, the WHO CICAD report (1998) did utilize the increase in relative liver weights from the Webb et al. (1989) study to calculate a tolerable intake, but that report utilized a NOEL of "10 mg/kg-bw/d" of d-limonene, and inferred that the d-limonene "caused increased relative liver weight at 30 and 75 mg/kg body weight per day." However, the increased relative liver weight was not found to be statistically significant at 30 mg/kg-bw/d, with the relative liver weights being only 4.4% greater than the control, while 75 mg/kg-bw/d was statistically significant, but still only 8.3% greater than the controls. While Webb et al. (1989) did not identify a specific NOEL or NOAEL, their paper stressed that there were no treatment-related changes during the in-life 91-day dosing period; moreover, the incidence and type of gross pathological lesions observed at necropsy, and the cumulative body weight gains, feed consumption, and food efficiency for treated males did not differ from control males. In addition, the light microscopic evaluation of liver tissue sections stained with haematoxylin and eosin of the treated male rats revealed no histopathological changes despite the increased relative weights of the liver. Webb et al. (1989) postulated that since the increased relative liver weights were unaccompanied by any changes that could observed using light microscopy, it was likely that microsomal induction had occurred, since mixed function oxidase activity was known to increase in the rat liver following exposure to many of the volatile hydrocarbons.

An earlier d-limonene gavage dosing study in the male rat was conducted over a shorter dosing period, 26 days, and also achieved statistical significance of increased relative liver weights, but at a dose level of 300 mg/kg-bw/d, and did not find statistically significant increases at 150 mg/kg-bw/d (Kanerva et al., 1987). The statistically significant effects were noted in relative liver weights after only 6 days of dosing, with the differences being even more pronounced after 26 days of dosing in the male rat; however, note that even after 26 days of dosing, there were no statistically significant differences between the male rats dosed at 150 mg/kg-bw/d and the male rats in the control. In addition, microscopic examination of liver sections revealed no differences between the vehicle control (corn oil) and male rats which had been dosed with d-limonene at either treatment level, thus Kanerva et al. (1987) also concluded that the increased relative liver weights "were considered to be a probable reflection of microsomal induction, since it is known that certain volatile hydrocarbons will increase mixed function oxidase in the rat."

While the WHO CICAD report (1998) utilized a "NOEL" of 10 mg/kg-bw/d, based on increased relative liver weight data from Webb et al. (1989), an earlier WHO report (1993) had reviewed the data from that study, Ariyoshi et al. (1975), Kanerva et a. (1987), and the NTP (1990) study, and WHO (1993) had not selected the relative liver weight data from Webb et al. (1989) as the key toxic endpoint. Although the NTP (1990) did not report data for liver weights, the WHO (1993) document evaluated the data for the effects on the liver in both the rat and mouse, and discussed the clinical chemistry data for the liver effects reported by Ariyoshi et al. (1975), and then concluded the following: "although liver lesions were not associated with the administration of d-limonene in a 2-year study in rats (doses up to 150 mg/kg bw/day for males; doses up to 600 mg/kg bw/day for females), a daily gavage dose of 500 mg d-limonene/kg bw/day for 2 years was associated with an increased incidence of multinucleated liver hepatocytes and cytomegaly in male mice. The NOEL for these effects was 250 mg/kg bw/day administered by gavage to male mice for 2 years." Note that this NOEL for the male mouse cited in WHO (1993) is approximately 25 times higher than the 10 mg/kg-bw/d based on increased relative liver weights in the male rat that was selected by WHO (1998) to calculate the tolerable intake for humans. Note also that the NTP study did not specifically report any other adverse effects, other that those associated with the effects noted in the kidneys, and especially did not identify any adverse effects to the liver, which the WHO documents have identified as the critical organ, including at 150 mg/kg-bw/d, the high dose tested in male rats over the 2-year gavage study.

The OPP HED TOXicology Science Advisory Council (TOXSAC) prepared a guidance document concerning hepatocellular hypertrophy on October 21, 2002, HED Guidance Document # G0201. This document describes a weight-of-evidence approach to characterizing toxicity to the liver when results of studies show an increase in liver size/weight, which results from an increase in the size of liver parenchymal cells. This is usually an indicator something has changed in the cell, but may not be an adverse effect, but rather only that xenobiotic exposures are causing an increased metabolic response, resulting in the induction of the metabolic enzymes. From these studies, corroborating evidence of toxicity is obtained from clinical chemistry and or histopathology. "Therefore, the dose with only hepatocellular hypertrophy and/or liver size/weight changes should be considered the study No-Observable-Adverse-Effect-Level (NOAEL). The Lowest-Observable-Adverse-Effect-Level (LOAEL) for the study should be the dose which elicits actual hepatotoxicity characterized by toxicologically significant changes in parameters such as clinical chemistry and/or histopathology." Clearly the Kanerva et al. (1987) and Webb et al. (1989) studies showed increased relative liver weights, although not absolute liver weights, but in each study, microscopic examination did not reveal any histopathological changes. While neither of these studies evaluated the clinical chemistry parameters identified in the HED Guidance Document # G0201, the effects at 26 days reported by Kanerva et al. (1987) for the male rat were at doses higher than those tested for 2 years by NTP (300 vs 150 mg/kg-bw/d, respectively), and the NTP study did not report any apparent effects on the liver. Moreover, the increased relative liver weights reported by Webb et al. (1989) after 13 weeks were statistically significant at 75 mg/kg-bw/d, but were only 8.3% higher than those in the controls. Note also that the Kanerva et al. (1987) study only utilized 5 male rats per dose group, while the Webb et al. (1989) utilized more, only 10 male rats were tested for the full 91-day dosing period, whereas the NTP study (1990) utilized 50 rats/dose group/sex, providing an additional data quality aspect to this latter study. Note also that while the NTP study (1990) also reported adverse effects in the liver of male mice at 500 mg/kg-bw/d, specifically cells with abnormal numbers of nuclei and cytomegaly, the no effects were noted in the livers of female rats at doses of 600 mg/kg-bw/d, or in the livers of female mice at 1000 mg/kg-bw/d.

Thus, the critical toxicological endpoint for characterizing the effects of d-limonene would not be the effects of d-limonene on the kidney of the male rat. Instead, this assessment will focus on the liver, but

not on data showing only increased relative liver weights from shorter term studies in the male rat, in the absence of any concomitant histopathological or clinical chemistry effects. Thus, the lowest dose at which an effect has been observed suitable for use as the short-term toxicity endpoint of concern (exposure scenarios of up to 30 days) is the LOAEL of 400 mg/kg/day, from the 30-day, continuous dosing study in the rat, with only males dosed (Ariyoshi et al., 1975, as cited in WHO 1998). (Note that this study was not cited in the WHO (1993) or RED (1994) documents, nor the HPV submission.) The repeated dosing component of this study was conducted at only one dosing level, following single treatments at 200, 400, 800, and 1200 mg/kg, to select doses to evaluate the efficacy of d-limonene to solubilize cholesterol gallstones. After 15 days of dosing in male rats, no effects were observed in the liver parameters measured, but after 30 days of repeated dosing, the following effects were observed: relative liver weight and hepatic phospholipid content had slightly increased; the liver and serum cholesterol values had decreased by 49 and 8%, respectively; changes in the phospholipid fatty acid content (increases in palmitic, lineoleic, and arachidonic acids, and decrease in stearic acid); changes in enzyme activity (aminopyrine demethylase and aniline hydrolase were increased by 26 and 22%, respectively); and changes in cytochrome (P-450 and b_5 increased by 31 and 30%, respectively). Thus, repeated dosing at 400 mg/kg for 30 days was found to have effects on various parameters in the liver of the male rat. Note that Ariyoshi et al. (1975) did not report the results of any histopathological examinations, or whether any were performed. (Note also that Table 3 shows an even lower effects level in the liver of the male rat from a subchronic study of approximately the same duration, with a NOAEL of 150 mg/kg-bw/d and an LOAEL of 300 mg/kg-bw/d, reported by Kanerva et al. (1987) after 6 and 26 days of dosing, but as already stated, these data are for relative liver weights and histopathological examinations of liver sections did reveal any evident alterations in the liver of the male rat.)

Toxicokinetics and Human Volunteer Inhalation Exposures:

Falk-Filipsson et al. (1993) reported on a study to assess the toxicokinetics of d-limonene in human volunteers, exposed by inhalation for 2 hours each, in an exposure chamber. The exposures were at concentrations of approximately 10, 225, or 450 mg/m^3 d-limonene. The relative pulmonary uptake of the d-limonene was high, about 70% of the amount supplied. The blood clearance (1.1 L/kg/hr) indicates that the d-limonene is readily metabolized, although a long half-timer in the blood was observed during the slow elimination phase, suggesting some accumulation in adipose tissues. After the end of the exposure, about 1% of the total d-limonene uptake was eliminated unchanged in the expired air, while 0.003% was eliminated in the urine. It was observed that there was a decrease in the vital capacity after exposure, in those exposed at the highest dose, but that none of the subjects experienced any irritative symptoms nor any symptoms related to the central nervous system.

Mutagenicity/Genotoxicity and Carcinogenicity:

The WHO documents (1993, 1998) and the EPA RED (1994) report that on the basis of available data, there is no evidence that d-limonene causes any genotoxic or mutagenic effects. In addition, those documents, which also include the data from the NTP 1990 study, cite only the renal lesions and kidney tumors in male rats as being the only reported incidences of carcinogenesis due to d-limonene; moreover, in the NTP (1990) report, the conclusions stated that the results indicated there was “no evidence” of carcinogenic activity of d-limonene in the female rat, as well as in either the male or female mice. The WHO (1998) document also reported that the International Agency for Research on Cancer (IARC) has classified d-limonene in “Group 3 (not classifiable as to its carcinogenicity to humans) based on a lack of available data on carcinogenicity to humans and limited evidence for carcinogenicity in experimental animals.” In addition, the NTP also compiles a Report on Carcinogens (RoC), which is the U.S.

government's definitive listing, and the most recent listing, the 10th Report (December 2002) did not list d-limonene (or "limonene").

Reproductive/Developmental Effects:

The 1998 WHO document indicated that there were no studies of the reproductive toxicity which had been identified, but presented various study data in the rat, mouse and rabbit, indicating that there was no evidence that limonene has teratogenic or embryotoxic effects in the absence of maternal effects. In addition, a study was reviewed in the RED (1994), and based on the data presented, it is concluded that d-limonene is not a developmental toxicant, because in the rat developmental toxicity study, the NOAEL was determined to be 250 mg/kg/day for both maternal and developmental toxicity. There were small decrements in maternal body weight gain at 500 mg/kg/day, and there were slight, but statistically significant and dose-dependent increases in the number of litters and fetuses with 14 ribs, instead of 13 ribs, at 500 mg/kg/day. The RED considered these effects to be variations in skeletal formation, not accompanied by other effects, and were secondary to the maternal toxicity, so the RED concluded these effects do not represent a concern for the developmental toxicity of limonene.

Maximum Acceptable Daily Intake Recommendations / Tolerable Intake Values:

The WHO (1993) document was the Joint Expert Committee on Food Additives (JECFA) summary report concerning the use of d-limonene as a food additive, and based on statistically significantly reduced body weights in male rats (as well as at higher NOAELs in female rats, male and female mice, and female rabbits), concluded the following:

> "Based on the significant decreases in body weight gain associated with administration of d-limonene to male and female mice and rats and female rabbits, an ADI of 0 - 1.5 mg/kg bw was established for this substance. The Committee considered the known natural occurrence and food additive uses of d-limonene, and concluded that only a small proportion of total intake is likely to be derived from direct additive use. The Committee therefore recommended that food additive intake be restricted to 75 µg/kg bw/day [*i.e., 0.075 mg/kg bw/day*], which represents 5% of the maximum ADI for d-limonene."

It should be noted that the WHO (1998) reported that a subsequent JECFA meeting had withdrawn this 1993 ADI value, and in its place allocated "not specified," and "the establishment of an acceptable daily intake expressed in numerical form was not deemed necessary."

Special Considerations for Infants and Children
At this time, there is no concern for potential sensitivity to infants and children. Based on the data from the study reviewed in the RED (EPA, 1994) and the various teratogenicity and embryotoxicity studies reviewed in the WHO study (1998), it is now again concluded that limonene is not a developmental toxicant. Therefore, a safety factor analysis has not been used to assess the risk. For the same reason, the additional tenfold safety factor is unnecessary, and has been removed.

Toxicity Endpoint Selection:
For this assessment of d-limonene, there are no dermal or inhalation toxicological studies in animals and no dermal absorption studies available in the existing literature. Therefore, to assess short-term dermal and inhalation exposures, an oral LOAEL was used. The dermal dose was conservatively converted to an equivalent oral dose using a 100% dermal and inhalation absorption factor. The oral toxicological

LOAEL endpoint of 400 mg/kg-day was used (Ariyoshi et al. 1975). This LOAEL was based on liver effects (increased enzymes and liver weights) observed in a 30-day rat oral (gavage) study (WHO, 1998). Since this endpoint is based on a LOAEL, an additional safety factor of 3X was applied to the uncertainty factor of 100 (10 for interspecies extrapolation and 10 for intraspecies variation). A Margin of Exposure (MOE) of 300 or greater is protective for these short-term risk assessments.

To assess the long-term dermal and inhalation exposures, an oral NOAEL of 150 mg/kg-bw/d was selected from a 103-week oral gavage study in the male rat (NTP, 1990). At this dose, there were pronounced effects on the kidney, but the EPA Risk Assessment Forum (1991) has indicated these effects on the kidney of male rats are not appropriate for risk characterization. Because the NTP report did not identify any other **adverse** effects on the male rats at this highest dose tested[1], especially on the liver parameters evaluated, this dose is being utilized as the NOAEL, with the clear understanding that there were effects on the kidney of the male rat, but these renal effects would not likely be observed in any other species or sex. In view of the absence of significant effects, other than in the kidney, in the male rats at 150 mg/kg-bw/d, this NOAEL was selected and deemed to be "conservative" (i.e., health-protective), because the other NOAEL values from the NTP (1990) study were even higher for the other test animals, 250 mg/kg-bw/d for the male mice, 300 mg/kg-bw/d for the female rats, and 500 mg/kg-bw/d for the female mice. Note also that other studies had reported effects at lower doses, but the effect reported was increased relative liver weights (Kanerva et al., 1987; Webb et al. 1989), but these effects occurred in the absence any histopathological changes observed with light microscopy and there were no measured enzyme induction changes reported for clinical chemistry parameters. In addition, there were larger sample sizes in the NTP study, thus, based on the weight-of-evidence, the Agency believes that the NTP data are more reliable for assigning an NOAEL. Since this toxicity endpoint selected for long-term exposures is a NOAEL, rather than the LOAEL which was selected for short-term exposures, an additional uncertainty factor is not necessary.

VI. Exposure Assessment

Exposure to d-limonene may occur through the use of certain pesticide products, including insect repellents and dog and cat repellents. In addition, exposure may occur naturally through different foods, or through FDA-approved GRAS uses such as in food products, soaps, and perfumes.

Residential dermal exposure to d-limonene as an active ingredient in various pesticide products was examined for this risk assessment. Postapplication exposure to pesticide products containing d-limonene as the active ingredient were not examined. It was assumed that dermal exposure following application of the pesticide products containing d-limonene would be minimal considering the high vapor pressure of d-limonene (see Table 2). Chemical residues would be expected to dissipate relatively soon after

[1] NTP (1990) did report effects in male rats at 150 mg/kg-bw/d, but the report provided explanations for each effect, as follows: interstitial cell tumors in the testis occurred with a positive trend, but are a commonly occurring neoplasm in aging male F344 rats, and "not considered to be related to chemical exposure;" mononuclear cell leukemia occurred in a positive trend, but "were not significantly different from that in vehicle controls and were not considered to be related to *d*-limonene administration;" three squamous cell papillomas or carcinomas occurred in high dose male rats, but the incidence was not significantly different from vehicle controls and was within the range of historical incidences in NTP studies, and "thus these tumors were not considered related to *d*-limonene administration;" and cataracts were observed at increased incidences in high dose group male and female rats, but "these changes are not believed to be related to the administration of *d*-limonene but rather to the proximity of animal cages to the light source in the animal room."

application, diminishing the possibility of potential exposure to persons after application.

The exposure scenarios chosen for the active ingredient risk assessment were based on the anticipated use patterns and current labeling for d-limonene pesticide products (see Table 4). In addition, application rates were estimated based on information provided on the product labels and these assumptions are listed in Table 4. The average body weight of an adult (70 kg) was assumed. The oral LOAEL of 400 mg/kg/day was used for short-term exposures, while an oral NOAEL of 150 mg/kg/day was used for the long-term exposures. A margin of exposure (MOE) was calculated for each scenario, and when the toxicity endpoint of concern was a LOAEL, the MOE of concern was 300.

The short-term handler MOEs range from a low of 81 for the application of pet dips to a high of 7,300 for the application of liquid pesticides with a watering can (see Table 4). The short-term MOEs for scenarios with the inert ingredient range from a low of 420 for painting to a high of 3,300,000 for back-spraying (see Table 5). The long-term consumer product use MOEs range from a low of 200 for general purpose cleaner inhalation exposure to a high of 46,580 for aerosol spray can inhalation exposure. More detailed information, such as the exposure and dose calculations, are provided in Appendix A.

For exposure to products containing d-limonene as an inert ingredient, the Pesticide Inert Risk Assessment Tool (PIRAT, test version) was used to estimate handler dermal exposure (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 the following formulations: pressurized liquids, ready-to-use liquids, and emulsifiable and soluble concentrates. All product uses for these formulations were examined and the 90th percentile default weight fractions were assumed. In addition, a 100% dermal and inhalation absorption factors were used to convert doses to equivalent oral doses. Default application rates were provided for several scenarios in PIRAT, based on either professional judgement or the Science Advisory Council for Exposure Policy 11 (SAC, 2001). If a default application rate was not provided, it was assumed that 10 lb of product per acre (0.00023 lb/ft^2) was applied.

The scenarios, application rates, areas treated or amounts used and calculated MOEs are provided in Table 5. MOEs for inert uses ranged from a low of 420 for ready-to-use outdoor paints/stains that are applied by airless sprayer to a high of 3,300,000 for emulsifiable concentrates applied using a backpack sprayer. Exposure outputs from the PIRAT model are provided in Appendix B.

In terms of consumer use exposure to products containing d-limonene, the Consumer Exposure Module (CEM) (Versar, 1999) was used to determine the possible residential exposure to d-limonene. The exposure scenario examined was the use of a general purpose cleaner assuming a weight fraction range of 12.5% to 25%. Table 6 provides the CEM dermal MOE estimates. Exposure output information from the CEM model is provided in Appendix C. Using the oral NOAEL of 150 mg/kg-day and assuming 100% dermal absorption, the MOE was calculated to be 2,600.

To assess inhalation exposure, two scenarios representing the expected highest exposures for the overall use pattern, were evaluated for this assessment: (1) general purpose cleaner, and (2) aerosol spray can. In both scenarios it was assumed that the use takes place indoors. Using the Consumer Exposure Module of the E-FAST model, inhalation MOEs of 200 for the general purpose cleaner, and 124,200 for the aerosol can scenario have been calculated. See Table 6 for a breakdown of the inhalation MOE calculation, and see Appendix C for more details of the model run.

Table 4. Residential Handler Risks Due to Exposure to d-Limonene as an Active Ingredient						
Exposure Scenario	Assumptions for estimating product application rate	Percent active ingredient	Calculations of product application rate (AR)	Application Rate	Area Treated or Amount Handled Daily[a]	Baseline Dermal MOE[b]
Loading/Applying Granulars by Hand	From product label – apply 1 lb/800 ft^2	4	AR = (1 lb/800 ft^2)*0.04	0.00005 lb ai/ft^2	1000 ft^2/day	1,300
Mixing/loading/applying emulsifiable concentrates with a watering can	From product label, max application rate is 8 fl. oz and 5.6 lb ai/gallon	78.2	AR = 5.6 lb ai/gal *1 gal/128 oz * 8 oz/1000 ft^2	0.00035 lb ai/ft^2	1000 ft^2/day	7,300
Applying RTU (Ready to Use) Formulations via Pump-Trigger Spray	Assume 0.125 gallons of product applied per day and assume density is 1.0 g/mL	5.8	AR = (1.0 g/mL * 0.0022 lb/g * 3785 mL/gal) * 0.058	0.48 lb ai/gallon	0.125 gal/day	2,100
Applying RTU Formula-tions via Shampoo	Average size of shampoo bottle is 12 oz; use ½ bottle when shampooing pet; assume density is 1.0 g/mL	5	AR = (1.0 g/mL * 1000mL/L * 1L/33.8 oz * 1000 mg/g * 6 oz/day) * 0.05	8,876 mg ai/day	NA	320
Applying RTU Formulations via Dip	From product label – use 1.5 oz/gallon of water; assume density is 1.0 g/mL	78.2	AR = (1.0 g/mL * 1000mL/L * 1L/33.8 oz * 1000 mg/g * 1.5 oz/day) * 0.782	34,704 mg ai/day	NA	81

a Amount handled per day values are EPA estimates of amount treated based on revised Residential SOPs (2/01).

b Baseline Dermal MOE = LOAEL (400 mg/kg/day) / dermal daily dose (mg/kg/day), where dermal dose = daily unit exposure (µg/lb ai) x application rate x amount handled per day x conversion factor (if needed) / body weight (70 kg adult).

Table 5. Residential Handler Risks Due to Exposure to d-Limonene as an Inert Ingredient					
Formulation Type	Application method	Crop Treated	Application Rate	Area treated or Amount Used	Dermal MOE
Emulsifiable Concentrate	Low pressure handwand	Turf, Garden, Trees, Outdoor Perimeter Treatment	0.00023 lb/ft^2	1000 ft^2	170,000
		Crack and Crevice	0.12 lb/gal	0.5 gal/day	660,000
	Backpack	Turf, Garden, Trees, Outdoor Perimeter Treatment	0.00023 lb/ft^2	1000 ft^2	3,300,000
	Hose-end sprayer	Turf	0.00023 lb/ft^2	20000 ft^2	28,000
		Garden and Trees		1000 ft^2	550,000
Pressurized liquid	Aerosol	Crack and Crevice	0.094 gal/day	NA	56,000
		Outdoor paint and stain	0.28 gal/day		8,100
Ready to Use liquid	Pump-trigger	Turf and Garden	1.0 gal/day	NA	2,300
		Crack and Crevice	0.50 gal/day	NA	10,000
	Paintbrush	Trees and Outdoor Paint and Stains	1.0 gal/day	NA	2,200
	Airless sprayer	Outdoor Paint and Stains	15 gal/day	NA	420
	Backpack		5 gal/day	NA	20,000
	Low pressure handwand		5 gal/day	NA	1,000
		Crack and Crevice	0.50 gal/day	NA	10,000
	Pump-trigger	Crack and Crevice	0.13 gal/day	NA	18,000
	Low pressure handwand		0.50 gal/day	NA	10,000
Soluble Concentrate	Low pressure handwand	Turf	0.00023 lb/ft^2	1000 ft^2	410,000
		Garden and Trees			120,000
		Crack and Crevice			490,000
	Backpack	Turf, Garden, Trees and Outdoor Perimeter Treatment	0.00023 lb/ft^2	1000 ft^2	2,400,000
	Hose-end sprayer	Turf	0.00023 lb/ft^2	20000 ft^2	21,000
		Garden and Trees		1000 ft^2	410,000
	Low pressure handwand	Crack and Crevice	0.12 lb/gal	0.5 gal/day	490,000
		Outdoor Perimeter Treatment	0.00023 lb/ft^2	1000 ft^2	120,000

Table 6. Summary of Consumer Dermal and Inhalation Exposure					
Scenario[a]	Weight Fractions	Dermal Dose[b] (mg/kg-day)	Dermal MOE[c]	Inhalation Dose[b] (mg/kg-day)	Inhalation MOE
General Purpose Cleaner	0.125	5.77e-02	2,600	7.53E-01	200[c]
Aerosol Spray Can	0.000734	NA[e]	NA	3.22E-03	124,200[d]

a This model run was developed using the Office of Pollution, Prevention, and Toxics (OPPT). The general purpose cleaner scenario was run with Standard New Chemicals Program assumptions and defaults. While the aerosol spray can scenario was modified to assess 60 days of use over a year.
b Modeled for chronic dose rates.
c MOE = NOAEL (150 mg/kg-day)/ Average Daily Dose (mg/kg/day).
d MOE = LOAEL (400 mg/kg-day)/ Average Daily Dose (mg/kg/day).
e NA = Not available. EFAST Consumer Exposure Module does not have a dermal exposure scenario for aerosol paint.

VII. Dietary (Food) Exposure

Screening-level dietary modeling was performed to determine the potential exposure for d-limonene in the food supply as a result of applications of a pesticide product containing d-limonene as an inert ingredient. The following assumptions were used for the DEEM modeling:

- Actual crop-specific residue data for active ingredients can be utilized as surrogate data for inert ingredient residue levels (including secondary residues in meat, milk, poultry and eggs)
- Inert ingredients are used on all crops and 100% of all crops are "treated" with inert ingredients
- No adjustment made for % of inert in formulation, application rate, or multiple applications of different active ingredient formulations
- Considers only preharvest applications

Dietary modeling was performed utilizing the highest established tolerance level residue for each commodity.

Table 7. Estimated Chronic Dietary Exposure[a] and Risk[b] for a Generic Inert Ingredient		
Population Subgroup[c]	Estimated Exposure, mg/kg/day	MOE
U.S. Population (total)	0.120	1250
All infants (< 1 year)	0.245	610
Children (1-2 years)	0.422	360
Children (3-5 years)	0.310	480
Children (6-12 years)	0.174	860
Youth (13-19 years)	0.100	1500
Adults (20-49 years)	0.087	1720
Adults (50+ years)	0.086	1740
Females (13-49 years)	0.087	1720

a Exposure estimates are based on highest-tolerance-level residues of high-use active ingredients for all food forms, including meat, milk, poultry, and eggs.
b MOE = NOAEL (150 mg/kg/day) / Estimated Exposure (mg/kg/day)
c Only representative population subgroups are shown.

For chronic dietary assessments, a NOAEL of 150 mg/kg-bw/d was selected, based on an 103-week oral gavage study in the male rat. For all populations addressed, the MOEs for d-limonene were greater than the MOE of concern of 100.

VIII. Drinking Water Considerations

d-Limonene is only somewhat soluble in water (13.8 mg/L) and has an estimated octanol/water partition coefficient of 4.2. d-Limonene is expected to rapidly volatilize from water to the atmosphere, with an estimated half-life for volatilization from a model river of 3.4 hr, although adsorption to sediment and suspended organic matter may attenuate the rate of this process. Based on these data, it is unlikely that d-limonene will occur in drinking water sources resulting from any of the registered and proposed uses as an active ingredient or when used as an inert ingredient as discussed above.

IX. Aggregate Assessment

d-Limonene is naturally-occurring in citrus and certain fruits, vegetables, meats and spices. And d-limonene is classified by the US FDA as a GRAS food additive. It is present in baked goods, ice cream products, gelatins, puddings and chewing gum at levels ranging from 68 to 2300 ppm from the direct food additive use.

Given the physical/chemical properties of d-limonene, it is unlikely that d-limonene will occur in drinking water sources. However, the Agency has conducted screening-level exposure assessments for dietary exposures as a result of agricultural applications, and residential exposures. Various screening-level models were used to estimate some of the existing levels of exposure that could occur. To assure protectiveness, these models create estimates that are deliberately intended to over-estimate exposure.

As an inert ingredient, d-limonene can be applied to agricultural crops. So, the Agency's screening level dietary assessment was performed based on a use pattern that considered uses on all crops. The generic modeling was performed using data derived from chemicals that are solids. But, for d-limonene, the vapor pressure is 2 mm Hg, thus indicative of significant evaporation.

One of the greatest uncertainties of using this generic dietary assessment for a volatile chemical such a d-limonene, is the potential for d-limonene to enter the food supply as a result of agricultural applications. Based on the vapor pressure (1) it is unlikely that any significant amount of residues of a volatile chemical would remain on the surface of the plant or edible commodity and (2) it is also unlikely that residues of such a volatile chemical would be incorporated into the raw agricultural commodity that is eventually harvested. While there is a logic to this rationale, the Agency also acknowledges a great deal of uncertainty on this issue.

Generally, the Agency has advocated a position that if a pesticide chemical is used on a food crop, residues of that chemical substance are assumed to be present unless there is compelling data to the contrary. Such data could be a radiolabelled uptake study of sufficient sensitivity to ascertain whether or not the residues exist in the edible commodity. The Agency is unaware of such data for a chemical such

as d-limonene. Therefore, the generic dietary exposure estimates used in this assessment are overly conservative for a chemical such as d-limonene, and the estimated MOEs could be even larger.

To judge the potential aggregate exposures for d-limonene the Agency is performing an aggregate assessment for two residential scenarios: use in a cleaning product, and RTU formulations via shampoo. The cleaning product represents the use of d-limonene as an inert ingredient in a product that could be used in and around the home. Cleaning products also tend to be used in a repetitive manner, and are more of a chronic type of scenario. The RTU formulation represents the use of d-limonene as an active ingredient in a product that could be used in and around the home. The RTU formulation also represents a very short-term scenario that could be measured in minutes that is of a non-repetitive nature.

Given that these two scenarios bracket the inert and active uses, as well as the short-term and more chronic types of scenarios, and that these two scenarios have the lowest residential MOEs estimated for d-limonene, all other aggregate MOEs should be greater than the target MOE.

Table 8: Aggregate MOEs

Scenario	Type of Assessment	Exposure (dietary + residential) (mg/kg/day)	MOE
RTU via shampoo	short-term LOAEL = 400 mg/kg/day target MOE is 300	0.12 + 1.25 = 1.37	290
		0.06 + 1.25 = 1.31	305
general cleaner	long-term NOAEL = 150 mg/kg/day target MOE is 100	0.12 + 0.753 = 0.873	171

The MOE of 290 is less than the target MOE of 300. However, as previously discussed the dietary exposures are considered to be much over-estimated due to the volatile nature of d-limonene. If the dietary exposure is divided by 2 (0.12/2 = 0.06), then the MOE is 305. This indicates that the driver for the aggregate exposure is not the dietary exposure that occurs as a result of applications of a pesticide product, but the residential exposure, which in and of itself is considered to be over-estimated.

X. Risk Characterization

d-Limonene is naturally-occurring in food and is classified by the US FDA as a GRAS food additive. It is present in baked goods, ice cream products, gelatins, puddings and chewing gum at levels ranging from 68 to 2300 ppm. d-Limonene is expected to rapidly volatilize from dry soil, wet soil and water, therefore exposure through the drinking water routes is considered very unlikely. Exposure through the dietary route as a result of application of a pesticide product is considered to be also unlikely due to the volatile nature of d-limonene. The dietary estimates presented are considered to be over-estimates for a chemical such as d-limonene. The driver for aggregate exposure for d-limonene is the residential exposure.

In this assessment forty nine exposure scenarios were evaluated. Of these forty nine ,and considering only the residential exposure component, only one scenario (the dermal exposure pet dip scenario) resulted in an MOE that was less than the target MOE of 300. The MOE for residential exposures from

the use of pet dips containing limonene was calculated to be 81. While this is less than the target MOE of 300, several factors need to be considered when interpreting this MOE, including:

- The assessment is based on the OPP Health Effects Division's Standard Operating Procedures (SOP) for Residential Exposure Assessments. In that pet dip SOP, the Agency states: "The uncertainties associated with this assessment stem from assumptions regarding amount of chemical handled and the percentage of which humans are exposed. The estimated doses are believed to be reasonable bounding estimates based on professional judgement."

- The toxicity endpoint chosen for this assessment was a 30-day feeding study (oral-gavage) administered to rats. It was from a 1975 study and was the lowest (i.e. most conservative) of the NOAELs and LOAELs in the liver in oral studies conducted for 30 days or less. There are also 16-day studies, both rat and mice, in which there were NOAELs of 1650 mg/kg/day. However, all of these studies are multi-day (continuously dosing endpoint) which was then compared to a pet dip scenario for which the Agency believes that it is most likely that there will only be a single event exposure for less than an hour's duration.

- The dermal absorption rate for this assessment is assumed to be 100%, which may be conservative for this particular chemical.

- There is only one product currently registered with this use pattern, EPA Reg. No. 4758-144. On the label in question, there is a specific recommendation that users wear rubber gloves while performing the pet dip activity. The Agency does not require personal protective equipment for residential use labels; however, the Agency also does not typically request that registrants remove PPE from their existing labels, when the use of such PPE is protective for users.

Taken together, these factors make a strong case that the resulting estimate significantly overestimate exposures and risks for this pet dip scenario.

Several uncertainties and limitations, in addition to the ones mentioned above for the pet dip scenario, are associated with this assessment. For the granular, emulsifiable concentrate and ready-to-use liquid formulation scenarios, uncertainties exist from the use of surrogate exposure data (PHED data) and from the assumptions regarding the amount of chemical that is handled. However, it is believed that the doses estimated based on these assumption are reasonable central tendency to high-end estimates based on observations from chemical-specific studies and professional judgement (SAC, 2001).

The Agency believes that these considerations are sufficient to determine that there is a reasonable certainty that no harm to any population subgroup will result from exposure to limonene when considering dietary exposure and all other non-occupational sources of pesticide exposure for which there is reliable information.

XI. Environmental Fate/Ecotoxicity

d-Limonene is only somewhat soluble in water (13.8 mg/L), and it is somewhat resistant to aerobic and anaerobic biodegradation in water and soil. Based on its water solubility and estimated octanol/water partition coefficient (4.2), its predicted soil adsorption coefficient indicates that it will display low mobility in soil. However, it is expected to rapidly volatilize from both dry and moist soil to the atmosphere, although adsorption to soil may attenuate the rate of this process. Once in the atmosphere,

limonene is expected to rapidly undergo gas-phase oxidation reactions with photochemically produced hydroxyl radicals, ozone, and at night with nitrate radicals, with calculated half-lives for these processes on the order of a two hours or less.

Toxicity studies have been performed with both the technical form of d-limonene and its formulated products, as well as products which contain d-limonene as an inert ingredient. Based on the data from these studies, d-limonene has been shown to be practically nontoxic to birds and slightly toxic to freshwater species, both fish and invertebrates. Studies on rats have also shown d-limonene to be practically non-toxic to mammals (EPA, 1994).

XII. Cumulative Exposure

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to d-limonene and any other substances, and d-limonene 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 d-limonene 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/.

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APPENDIX A

Active Ingredient Residential Handler Exposure

Exposure Scenario	Application Rate	Area Treated Daily	Dermal Unit Exposure (mg/lb ai)	Dermal Exposure (mg/day)[a]	Dermal Dose (mg/kg-day)	Dermal MOE
Mixer/Loader/Applicator						
Mixing/Loading/Applying Emulsifiable Concentrates with a Watering Can	0.00035 lb ai/ft^2	1000 ft^2/day	11	3.9	0.055[b]	7,300
Loading/Applying Granulars by Hand	0.00005 lb ai/ft^2	1000 ft^2/day	430	22	0.31[b]	1,300
Applying Ready to Use Formulations via Trigger-Pump Sprayer	0.48 lb ai/gallon	0.125 gal/day	220	13	0.19[b]	2,100
Applying Ready to Use Formulations via Shampoo	8876 mg ai/day	NA	NA	NA	1.3[c]	320
Applying Ready to Use Formulations via Dip	34704 mg ai/day	NA	NA	NA	5[c]	81

a Dermal Exposure = (Application rate)*(Area treated daily)*(Dermal unit exposure)
b Dermal Dose = (Dermal exposure)/(Adult body weight)
c Dermal Dose = (Application rate)*(Fraction exposed, 0.01)/(Adult body weight)

APPENDIX B

Inert Ingredient Residential Handler Exposure

PiRat Handler Report for Formulation Type Emulsifiable Concentrate

Functional Use: Fragrance (perfume, fragrance)
Toxicity Value: 400
Body Weight: 70.0 kg

Weight Fraction: 7.34E-03
Duration: Short Term
Absorption Value: 100 %

	Scenario #1	Scenario #2	Scenario #3
Product Use:	turf	turf	turf
Application Method:	low pressure handwand; MLAP	backpack: MLAP	sprinkling can; MLAP
Dermal PDR (mg/kg/day):	3.25E-03	1.23E-04	7.24E-04
Inhalation PDR (mg/kg/day)	N/A	N/A	N/A
Dermal Unit Exposure (mg/lb):	100.00 Low 9-80 reps	5.10 Low 9-11 reps	30.00 Low 8 reps
Inhalation Unit Exposure (mg/lb):	N/A	N/A	N/A
Application Rate:	2.30E-04* lb/ft2	2.30E-04* lb/ft2	2.30E-04* lb/ft2
Fraction Exposed:	N/A	N/A	N/A
Amount used:	1000.00 ft2/day (spot)	1000.00 ft2/day (spot)	1000.00 ft2/day (spot)
Density (lb/gal):	N/A	N/A	N/A
MOE:	120000	3300000	550000
Exposure Frequency (yrs)	N/A	N/A	N/A
Exposure Duration (yrs)	N/A	N/A	N/A
Averaging Time (yrs)	N/A	N/A	N/A
LADD	N/A	N/A	N/A
Cancer Risk	N/A	N/A	N/A

Dose Calculation:
Scenario #1 PDR=(UE*AR*WF*A)/BW
Scenario #2 PDR=(UE*AR*WF*A)/BW
Scenario #3 PDR=(UE*AR*WF*A)/BW

Assumptions:
Scenario #1 1,000 ft2/day assumed to be equivalent to 5 gal/day; SAC Policy 11
Scenario #2 1,000 ft2/day assumed to be equivalent to 5 gal/day; SAC Policy 11
Scenario #3 assumed based on hose-end; SOPs

* Modified by user

PiRat Handler Report for Formulation Type Emulsifiable Concentrate

Functional Use: Fragrance (perfume, fragrance)
Toxicity Value: 400
Body Weight: 70.0 kg
Weight Fraction: 7.34E-03
Duration: Short Term
Absorption Value: 100 %

	Scenario #4	Scenario #5	Scenario #6
Product Use:	turf	garden	garden
Application Method:	hose end sprayer; MLAP	low pressure handwand; MLAP	backpack: MLAP
Dermal PDR (mg/kg/day):	1.45E-02	2.41E-03	1.23E-04
Inhalation PDR (mg/kg/day)	N/A	N/A	N/A
Dermal Unit Exposure (mg/lb):	30.00 Low 8 reps	100.00 Low 9-80 reps	5.10 Low 9-11 reps
Inhalation Unit Exposure (mg/lb):	N/A	N/A	N/A
Application Rate:	2.30E-04* lb/ft2	2.30E-04* lb/ft2	2.30E-04* lb/ft2
Fraction Exposed:	N/A	N/A	N/A
Amount used:	2.00E+04 ft2/day (full broadcast)	1000.00 ft2/day (spot)	1000.00 ft2/day (spot)
Density (lb/gal):	N/A	N/A	N/A
MOE:	28000	170000	3300000
Exposure Frequency (yrs)	N/A	N/A	N/A
Exposure Duration (yrs)	N/A	N/A	N/A
Averaging Time (yrs)	N/A	N/A	N/A
LADD	N/A	N/A	N/A
Cancer Risk	N/A	N/A	N/A

Dose Calculation:
Scenario #1 PDR=(UE*AR*WF*A)/BW
Scenario #2 PDR=(UE*AR*WF*A)/BW
Scenario #3 PDR=(UE*AR*WF*A)/BW

Assumptions:
Scenario #1 upper percentile lawn size (SAC Policy 11)
Scenario #2 1,000 ft2/day assumed to be equivalent to 5 gal/day; SAC Policy 11
Scenario #3 1,000 ft2/day assumed to be equivalent to 5 gal/day; SAC Policy 11

* Modified by user

PiRat Handler Report for Formulation Type Emulsifiable Concentrate

Functional Use: Fragrance (perfume, fragrance)
Toxicity Value: 400
Body Weight: 70.0 kg
Weight Fraction: 7.34E-03
Duration: Short Term
Absorption Value: 100 %

	Scenario #7	Scenario #8	Scenario #9
Product Use:	garden	garden	trees
Application Method:	sprinkling can; MLAP	hose end sprayer; MLAP	low pressure handwand; MLAP
Dermal PDR (mg/kg/day):	7.24E-04	7.24E-04	2.41E-03
Inhalation PDR (mg/kg/day)	N/A	N/A	N/A
Dermal Unit Exposure (mg/lb):	30.00 Low 8 reps	30.00 Low 8 reps	100.00 Low 9-80 reps
Inhalation Unit Exposure (mg/lb):	N/A	N/A	N/A
Application Rate:	2.30E-04* lb/ft2	2.30E-04* lb/ft2	2.30E-04* lb/ft2
Fraction Exposed:	N/A	N/A	N/A
Amount used:	1000.00 ft2/day (spot)	1000.00 ft2/day	1000.00 ft2/day (spot)
Density (lb/gal):	N/A	N/A	N/A
MOE:	550000	550000	170000
Exposure Frequency (yrs)	N/A	N/A	N/A
Exposure Duration (yrs)	N/A	N/A	N/A
Averaging Time (yrs)	N/A	N/A	N/A
LADD	N/A	N/A	N/A
Cancer Risk	N/A	N/A	N/A

Dose Calculation:
Scenario #1 PDR=(UE*AR*WF*A)/BW
Scenario #2 PDR=(UE*AR*WF*A)/BW
Scenario #3 PDR=(UE*AR*WF*A)/BW

Assumptions:
Scenario #1 assumed based on hose-end; SOPs
Scenario #2 SAC Policy 11
Scenario #3 1,000 ft2/day assumed to be equivalent to 5 gal/day; SAC Policy 11

* Modified by user

PiRat Handler Report for Formulation Type Emulsifiable Concentrate

Functional Use: Fragrance (perfume, fragrance)
Toxicity Value: 400
Body Weight: 70.0 kg

Weight Fraction: 7.34E-03
Duration: Short Term
Absorption Value: 100 %

	Scenario #10	Scenario #11	Scenario #12
Product Use:	trees	trees	trees
Application Method:	backpack: MLAP	sprinkling can; MLAP	hose end sprayer; MLAP
Dermal PDR (mg/kg/day):	1.23E-04	7.24E-04	7.24E-04
Inhalation PDR (mg/kg/day)	N/A	N/A	N/A
Dermal Unit Exposure (mg/lb):	5.10 Low 9-11 reps	30.00 Low 8 reps	30.00 Low 8 reps
Inhalation Unit Exposure (mg/lb):	N/A	N/A	N/A
Application Rate:	2.30E-04* lb/ft2	2.30E-04* lb/ft2	2.30E-04* lb/ft2
Fraction Exposed:	N/A	N/A	N/A
Amount used:	1000.00 ft2/day (spot)	1000.00 ft2/day (spot)	1000.00 ft2/day
Density (lb/gal):	N/A	N/A	N/A
MOE:	3300000	550000	550000
Exposure Frequency (yrs)	N/A	N/A	N/A
Exposure Duration (yrs)	N/A	N/A	N/A
Averaging Time (yrs)	N/A	N/A	N/A
LADD	N/A	N/A	N/A
Cancer Risk	N/A	N/A	N/A

Dose Calculation:
Scenario #1 PDR=(UE*AR*WF*A)/BW
Scenario #2 PDR=(UE*AR*WF*A)/BW
Scenario #3 PDR=(UE*AR*WF*A)/BW

Assumptions:
Scenario #1 1,000 ft2/day assumed to be equivalent to 5 gal/day; SAC Policy 11
Scenario #2 assumed based on hose-end; SOPs
Scenario #3 SAC Policy 11

* Modified by user

PiRat Handler Report for Formulation Type Emulsifiable Concentrate

Functional Use: Fragrance (perfume, fragrance)
Toxicity Value: 400
Body Weight: 70.0 kg

Weight Fraction: 7.34E-03
Duration: Short Term
Absorption Value: 100 %

	Scenario #13	Scenario #14	Scenario #15
Product Use:	crack & crevice	outdoor perimeter treatment	outdoor perimeter treatment
Application Method:	low pressure handwand; MLAP	low pressure handwand; MLAP	backpack: MLAP
Dermal PDR (mg/kg/day):	1.21E-06	2.41E-03	1.23E-04
Inhalation PDR (mg/kg/day)	N/A	N/A	N/A
Dermal Unit Exposure (mg/lb):	100.00 Low 9-80 reps	100.00 Low 9-80 reps	5.10 Low 9-11 reps
Inhalation Unit Exposure (mg/lb):	N/A	N/A	N/A
Application Rate:	2.30E-04* lb/gal	2.30E-04* lb/ft2	2.30E-04* lb/ft2
Fraction Exposed:	N/A	N/A	N/A
Amount used:	0.50 gal/day	1000.00 ft2/day (spot)	1000.00 ft2/day (spot)
Density (lb/gal):	N/A	N/A	N/A
MOE:	330000000	170000	3300000
Exposure Frequency (yrs)	N/A	N/A	N/A
Exposure Duration (yrs)	N/A	N/A	N/A
Averaging Time (yrs)	N/A	N/A	N/A
LADD	N/A	N/A	N/A
Cancer Risk	N/A	N/A	N/A

Dose Calculation:
Scenario #1 PDR=(UE*AR*WF*A)/BW
Scenario #2 PDR=(UE*AR*WF*A)/BW
Scenario #3 PDR=(UE*AR*WF*A)/BW

Assumptions:
Scenario #1 SAC Policy 11
Scenario #2 1,000 ft2/day assumed to be equivalent to 5 gal/day; SAC Policy 11
Scenario #3 1,000 ft2/day assumed to be equivalent to 5 gal/day; SAC Policy 11

* Modified by user

PiRat Handler Report for Formulation Type Pressurized Liquid

Functional Use: Fragrance (deodorant, perfume, fragrance)
Toxicity Value: 400
Body Weight: 70.0 kg

Weight Fraction: 3.00E-03
Duration: Short Term
Absorption Value: 100 %

	Scenario #1	Scenario #2	
Product Use:	outdoor spray paints/stains	crack & crevice	
Application Method:	aerosol; APP	aerosol; APP	
Dermal PDR (mg/kg/day):	4.93E-02	7.09E-03	
Inhalation PDR (mg/kg/day)	N/A	N/A	
Dermal Unit Exposure (mg/lb):	220.00 Medium 15-30 reps	220.00 Medium 15-30 reps	
Inhalation Unit Exposure (mg/lb):	N/A	N/A	
Application Rate:	0.28 gal/day	9.40E-02 gal/day	
Fraction Exposed:	N/A	N/A	
Amount used:	N/A	N/A	
Density (lb/gal):	8.00	8.00	
MOE:	8100	56000	
Exposure Frequency (yrs)	N/A	N/A	
Exposure Duration (yrs)	N/A	N/A	
Averaging Time (yrs)	N/A	N/A	
LADD	N/A	N/A	
Cancer Risk	N/A	N/A	

Dose Calculation:
Scenario #1 PDR=(UE*AR*WF*D)/BW
Scenario #2 PDR=(UE*AR*WF*D)/BW

Assumptions:
Scenario #1 assumed to use three 12-oz. cans per event (90th percentile amount of spray
Scenario #2 assumed to use one 12 oz. cans 1 aerosol cans per event; SAC Policy 11

* Modified by user

PiRat Handler Report for Formulation Type Ready to Use Liquid

Functional Use: Fragrance (deodorant, perfume, odor masking agent, fragrance)
Toxicity Value: 400
Body Weight: 70.0 kg

Weight Fraction: 7.00E-03
Duration: Short Term
Absorption Value: 100 %

	Scenario #1	Scenario #2	Scenario #3
Product Use:	turf	garden	trees
Application Method:	pump-trigger; APP	pump-trigger; APP	paintbrush; APP
Dermal PDR (mg/kg/day):	0.18	0.18	0.18
Inhalation PDR (mg/kg/day)	N/A	N/A	N/A
Dermal Unit Exposure (mg/lb):	220.00 Medium 15-30 reps	220.00 Medium 15-30 reps	230.00 Medium 14-15 reps
Inhalation Unit Exposure (mg/lb):	N/A	N/A	N/A
Application Rate:	1.00 gal/day (spot)	1.00 gal/day (spot)	1.00 mg/kg/day
Fraction Exposed:	N/A	N/A	N/A
Amount used:	N/A	N/A	N/A
Density (lb/gal):	8.00	8.00	8.00
MOE:	2300	2300	2200
Exposure Frequency (yrs)	N/A	N/A	N/A
Exposure Duration (yrs)	N/A	N/A	N/A
Averaging Time (yrs)	N/A	N/A	N/A
LADD	N/A	N/A	N/A
Cancer Risk	N/A	N/A	N/A

Dose Calculation:
Scenario #1 PDR=(UE*AR*WF*D)/BW
Scenario #2 PDR=(UE*AR*WF*D)/BW
Scenario #3 PDR=(UE*AR*WF*D)/BW

Assumptions:
Scenario #1 professional judgement
Scenario #2 professional judgement
Scenario #3 assumed to be highest amt. individual would brush on; SAC Policy 11

* Modified by user

PiRat Handler Report for Formulation Type Ready to Use Liquid

Functional Use: Fragrance (deodorant, perfume, odor masking agent, fragrance)
Toxicity Value: 400
Body Weight: 70.0 kg

Weight Fraction: 7.00E-03
Duration: Short Term
Absorption Value: 100 %

	Scenario #4	Scenario #5	Scenario #6
Product Use:	outdoor paints/stains	outdoor paints/stains	outdoor paints/stains
Application Method:	paintbrush; APP	airless sprayer; APP	backpack; APP
Dermal PDR (mg/kg/day):	0.18	0.95	2.04E-02
Inhalation PDR (mg/kg/day)	N/A	N/A	N/A
Dermal Unit Exposure (mg/lb):	230.00 Medium 14-15 reps	79.00 High 15 reps	5.10 Low 9-11 reps
Inhalation Unit Exposure (mg/lb):	N/A	N/A	N/A
Application Rate:	1.00 gal/day	15.00 gal/day	5.00 gal/day
Fraction Exposed:	N/A	N/A	N/A
Amount used:	N/A	N/A	N/A
Density (lb/gal):	8.00	8.00	8.00
MOE:	2200	420	20000
Exposure Frequency (yrs)	N/A	N/A	N/A
Exposure Duration (yrs)	N/A	N/A	N/A
Averaging Time (yrs)	N/A	N/A	N/A
LADD	N/A	N/A	N/A
Cancer Risk	N/A	N/A	N/A

Dose Calculation:
Scenario #1 PDR=(UE*AR*WF*D)/BW
Scenario #2 PDR=(UE*AR*WF*D)/BW
Scenario #3 PDR=(UE*AR*WF*D)/BW

Assumptions:
Scenario #1 assumed to use 2 1-gal. cans based on 90th percentile value of 8 gal. of latex
Scenario #2 assumed to use three 5-gal. cans, based on coverage rate of 200 ft2/gal; and a
Scenario #3 assumed value based on idea that more would be used by this method than by

* Modified by user

PiRat Handler Report for Formulation Type Ready to Use Liquid

Functional Use: Fragrance (deodorant, perfume, odor masking agent, fragrance)
Toxicity Value: 400
Body Weight: 70.0 kg

Weight Fraction: 7.00E-03
Duration: Short Term
Absorption Value: 100 %

	Scenario #7	Scenario #8	Scenario #9
Product Use:	outdoor paints/stains	crack & crevice	crack & crevice
Application Method:	low pressure handwand; APP	pump-trigger; APP	low pressure handwand; APP
Dermal PDR (mg/kg/day):	0.40	2.20E-02	4.00E-02
Inhalation PDR (mg/kg/day)	N/A	N/A	N/A
Dermal Unit Exposure (mg/lb):	100.00 Low 9-80 reps	220.00 Medium 15-30 reps	100.00 Low 9-80 reps
Inhalation Unit Exposure (mg/lb):	N/A	N/A	N/A
Application Rate:	5.00 gal/day	0.13 gal/day	0.50 gal/day
Fraction Exposed:	N/A	N/A	N/A
Amount used:	N/A	N/A	N/A
Density (lb/gal):	8.00	8.00	8.00
MOE:	1000	18000	10000
Exposure Frequency (yrs)	N/A	N/A	N/A
Exposure Duration (yrs)	N/A	N/A	N/A
Averaging Time (yrs)	N/A	N/A	N/A
LADD	N/A	N/A	N/A
Cancer Risk	N/A	N/A	N/A

Dose Calculation:
Scenario #1 PDR=(UE*AR*WF*D)/BW
Scenario #2 PDR=(UE*AR*WF*D)/BW
Scenario #3 PDR=(UE*AR*WF*D)/BW

Assumptions:
Scenario #1 assumed value based on idea that more would be used by this method than one 16 oz bottle; SAC Policy 11
Scenario #2
Scenario #3 based on professional judgement; SAC Policy 11

* Modified by user

PiRat Handler Report for Formulation Type Soluble Concentrate

Functional Use: Fragrance (perfume, fragrance)
Toxicity Value: 400
Body Weight: 70.0 kg

Weight Fraction: 9.88E-03
Duration: Short Term
Absorption Value: 100 %

	Scenario #1	Scenario #2	Scenario #3
Product Use:	turf	turf	turf
Application Method:	low pressure handwand; MLAP	backpack; MLAP	sprinkling can; MLAP
Dermal PDR (mg/kg/day):	9.86E-04	1.66E-04	9.74E-04
Inhalation PDR (mg/kg/day)	N/A	N/A	N/A
Dermal Unit Exposure (mg/lb):	100.00 Low 9-80 reps	5.10 Low 9-11 reps	30.00 Low 8 reps
Inhalation Unit Exposure (mg/lb):	N/A	N/A	N/A
Application Rate:	2.30E-04* lb/ft2	2.30E-04* lb/ft2	2.30E-04* lb/ft2
Fraction Exposed:	N/A	N/A	N/A
Amount used:	1000.00 ft2/day (spot)	1000.00 ft2/day (spot)	1000.00 ft2/day
Density (lb/gal):	N/A	N/A	N/A
MOE:	410000	2400000	410000
Exposure Frequency (yrs)	N/A	N/A	N/A
Exposure Duration (yrs)	N/A	N/A	N/A
Averaging Time (yrs)	N/A	N/A	N/A
LADD	N/A	N/A	N/A
Cancer Risk	N/A	N/A	N/A

Dose Calculation:
Scenario #1 PDR=(UE*AR*WF*A)/BW
Scenario #2 PDR=(UE*AR*WF*A)/BW
Scenario #3 PDR=(UE*AR*WF*A)/BW

Assumptions:
Scenario #1 1,000 ft2/day assumed to be equivalent to 5 gal/day; SAC Policy 11
Scenario #2 1,000 ft2/day assumed to be equivalent to 5 gal/day; SAC Policy 11
Scenario #3 assumed based on hose-end; SOPs

* Modified by user

PiRat Handler Report for Formulation Type Soluble Concentrate

Functional Use: Fragrance (perfume, fragrance)
Toxicity Value: 400
Body Weight: 70.0 kg
Weight Fraction: 9.88E-03
Duration: Short Term
Absorption Value: 100 %

	Scenario #4	Scenario #5	Scenario #6
Product Use:	turf	garden	garden
Application Method:	hose end sprayer; MLAP	low pressure handwand; MLAP	backpack; MLAP
Dermal PDR (mg/kg/day):	1.95E-02	3.25E-03	1.66E-04
Inhalation PDR (mg/kg/day)	N/A	N/A	N/A
Dermal Unit Exposure (mg/lb):	30.00 Low 8 reps	100.00 Low 9-80 reps	5.10 Low 9-11 reps
Inhalation Unit Exposure (mg/lb):	N/A	N/A	N/A
Application Rate:	2.30E-04* lb/ft2	2.30E-04* lb/ft2	2.30E-04* lb/ft2
Fraction Exposed:	N/A	N/A	N/A
Amount used:	2.00E+04 ft2/day (full broadcast)	1000.00 ft2/day (spot)	1000.00 ft2/day (spot)
Density (lb/gal):	N/A	N/A	N/A
MOE:	21000	120000	2400000
Exposure Frequency (yrs)	N/A	N/A	N/A
Exposure Duration (yrs)	N/A	N/A	N/A
Averaging Time (yrs)	N/A	N/A	N/A
LADD	N/A	N/A	N/A
Cancer Risk	N/A	N/A	N/A

Dose Calculation:
Scenario #1 PDR=(UE*AR*WF*A)/BW
Scenario #2 PDR=(UE*AR*WF*A)/BW
Scenario #3 PDR=(UE*AR*WF*A)/BW

Assumptions:
Scenario #1 upper percentile lawn size (SAC Policy 11)
Scenario #2 1,000 ft2/day assumed to be equivalent to 5 gal/day; SAC Policy 11
Scenario #3 1,000 ft2/day assumed to be equivalent to 5 gal/day; SAC Policy 11;

* Modified by user

PiRat Handler Report for Formulation Type Soluble Concentrate

Functional Use: Fragrance (perfume, fragrance)
Toxicity Value: 400
Body Weight: 70.0 kg
Weight Fraction: 9.88E-03
Duration: Short Term
Absorption Value: 100 %

	Scenario #7	Scenario #8	Scenario #9
Product Use:	garden	garden	trees
Application Method:	sprinkling can, MLAP	hose end sprayer; MLAP	low pressure handwand; MLAP
Dermal PDR (mg/kg/day):	9.74E-04	9.74E-04	3.25E-03
Inhalation PDR (mg/kg/day)	N/A	N/A	N/A
Dermal Unit Exposure (mg/lb):	30.00 Low 8 reps	30.00 Low 8 reps	100.00 Low 9-80 reps
Inhalation Unit Exposure (mg/lb):	N/A	N/A	N/A
Application Rate:	2.30E-04* lb/ft2	2.30E-04* lb/ft2	2.30E-04* lb/ft2
Fraction Exposed:	N/A	N/A	N/A
Amount used:	1000.00 ft2/day	1000.00 ft2/day	1000.00 ft2/day (spot)
Density (lb/gal):	N/A	N/A	N/A
MOE:	410000	410000	120000
Exposure Frequency (yrs)	N/A	N/A	N/A
Exposure Duration (yrs)	N/A	N/A	N/A
Averaging Time (yrs)	N/A	N/A	N/A
LADD	N/A	N/A	N/A
Cancer Risk	N/A	N/A	N/A

Dose Calculation:
Scenario #1 PDR=(UE*AR*WF*A)/BW
Scenario #2 PDR=(UE*AR*WF*A)/BW
Scenario #3 PDR=(UE*AR*WF*A)/BW

Assumptions:
Scenario #1 assumed based on hose-end; SOPs
Scenario #2 SAC Policy 11
Scenario #3 1,000 ft2/day assumed to be equivalent to 5 gal/day; SAC Policy 11

* Modified by user

PiRat Handler Report for Formulation Type Soluble Concentrate

Functional Use: Fragrance (perfume, fragrance)
Toxicity Value: 400
Body Weight: 70.0 kg

Weight Fraction: 9.88E-03
Duration: Short Term
Absorption Value: 100 %

	Scenario #10	Scenario #11	Scenario #12
Product Use:	trees	trees	trees
Application Method:	backpack; MLAP	sprinkling can; MLAP	hose end sprayer; MLAP
Dermal PDR (mg/kg/day):	1.66E-04	9.74E-04	9.74E-04
Inhalation PDR (mg/kg/day)	N/A	N/A	N/A
Dermal Unit Exposure (mg/lb):	5.10 Low 9-11 reps	30.00 Low 8 reps	30.00 Low 8 reps
Inhalation Unit Exposure (mg/lb):	N/A	N/A	N/A
Application Rate:	2.30E-04* lb/ft2	2.30E-04* lb/ft2	2.30E-04* lb/ft2
Fraction Exposed:	N/A	N/A	N/A
Amount used:	1000.00 ft2/day (spot)	1000.00 ft2/day	1000.00 ft2/day
Density (lb/gal):	N/A	N/A	N/A
MOE:	2400000	410000	410000
Exposure Frequency (yrs)	N/A	N/A	N/A
Exposure Duration (yrs)	N/A	N/A	N/A
Averaging Time (yrs)	N/A	N/A	N/A
LADD	N/A	N/A	N/A
Cancer Risk	N/A	N/A	N/A

Dose Calculation:
Scenario #1 PDR=(UE*AR*WF*A)/BW
Scenario #2 PDR=(UE*AR*WF*A)/BW
Scenario #3 PDR=(UE*AR*WF*A)/BW

Assumptions:
Scenario #1 1,000 ft2/day assumed to be equivalent to 5 gal/day; SAC Policy 11
Scenario #2 assumed based on hose-end; SOPs
Scenario #3 SAC Policy 11

* Modified by user

PiRat Handler Report for Formulation Type Soluble Concentrate

Functional Use: Fragrance (perfume, fragrance)
Toxicity Value: 400
Body Weight: 70.0 kg
Weight Fraction: 9.88E-03
Duration: Short Term
Absorption Value: 100 %

	Scenario #13	Scenario #14	Scenario #15
Product Use:	crack & crevice	outdoor perimeter treatment	outdoor perimeter treatment
Application Method:	low pressure handwand; MLAP	low pressure handwand; MLAP	backpack; MLAP
Dermal PDR (mg/kg/day):	1.62E-06	3.25E-03	1.66E-04
Inhalation PDR (mg/kg/day)	N/A	N/A	N/A
Dermal Unit Exposure (mg/lb):	100.00 Low 9-80 reps	100.00 Low 9-80 reps	5.10 Low 9-11 reps
Inhalation Unit Exposure (mg/lb):	N/A	N/A	N/A
Application Rate:	2.30E-04* lb/gal	2.30E-04* lb/ft2	2.30E-04* lb/ft2
Fraction Exposed:	N/A	N/A	N/A
Amount used:	0.50 gal/day	1000.00 ft2/day (spot)	1000.00 ft2/day (spot)
Density (lb/gal):	N/A	N/A	N/A
MOE:	250000000	120000	2400000
Exposure Frequency (yrs)	N/A	N/A	N/A
Exposure Duration (yrs)	N/A	N/A	N/A
Averaging Time (yrs)	N/A	N/A	N/A
LADD	N/A	N/A	N/A
Cancer Risk	N/A	N/A	N/A

Dose Calculation:
Scenario #1 PDR=(UE*AR*WF*A)/BW
Scenario #2 PDR=(UE*AR*WF*A)/BW
Scenario #3 PDR=(UE*AR*WF*A)/BW

Assumptions:
Scenario #1 SAC Policy 11
Scenario #2 1,000 ft2/day assumed to be equivalent to 5 gal/day; SAC Policy 11
Scenario #3 1,000 ft2/day assumed to be equivalent to 5 gal/day; SAC Policy 11

* Modified by user

APPENDIX C

Inert Ingredient Consumer Use Residential Exposure

CEM Inputs		ID Number: Unknown	
Product: d-limonene		Chemical Name: d-limonene	
Scenario: General Purpose Cleaner		Population: Adult	
Molecular Weight (g/mole):	136.2		
Weight Fraction - Median (unitless):	0.125	Weight Fraction - 90% (unitless):	0.25
Dermal Inputs			
Frequency of Use - Body (events/yr):	300	SA/BW - Body (cm2/kg):	15.6
Amount Retained / Absorbed to Skin (g/cm2-event):		3.6e-05	
Avg. Time, $LADD_{pot}$, $LADC_{pot}$ (days):	2.74e+04	Avg. Time, ADD_{pot}, ADC_{pot} (days):	2.08e+04
Avg. Time, ADR_{pot}, Cp_{pot} (days):	1.00e+00		

CEM Dermal Exposure Estimates

ID Number: Unknown

Scenario: General Purpose Cleaner Population: Adult

Years of Use (years): 57

SA/BW Body (cm^2/kg): 15.6

Frequency of Use (events/year): 300

Exposure Units	Result	AT (days)
Chronic Cancer		
$LADD_{pot}$ (mg/kg-day)	4.39e-02	2.74e+04
Chronic Non-Cancer		
ADD_{pot} (mg/kg-day)	5.77e-02	2.08e+04
Acute		
ADR_{pot} (mg/kg-day)	1.40e-01	1.00e+00

LADD - Lifetime Average Daily Dose (mg/kg-day)

ADD - Average Daily Dose (mg/kg-day)

ADR - Acute Dose Rate (mg/kg-day)

Note: 75 years = 2.738e+04 days pot - potential dose

Note: The general Agency guidance for assessing short-term, infrequent events (for most chemicals, an exposure of less than 24 hours that occurs no more frequently than monthly) is to treat such events as independent, acute exposures rather than as chronic exposure. Thus, estimates of long-term average exposure like ADD or ADC may not be appropriate for use in assessing risks associated with this type of exposure pattern. (Methods for Exposure-Response Analysis for Acute Inhalation Exposure to Chemicals (External Review Draft). EPA/600/R-98/051. April 1998

CEM Inputs		ID Number: Unknown	
Product: Unknown		Chemical Name: d-Limonene	
Scenario: General Purpose Cleaner		Population: Adult	
Molecular Weight (g/mole):	136.2	Vapor Pressure (torr):	2
Weight Fraction - Median (unitless):	0.125	Weight Fraction - 90% (unitless):	0.125
Inhalation Inputs			
Frequency of Use (events/yr):	300	Years of Use:	57
Mass of Product Used per Event - Median (g):	61.5	Mass of Product Used per Event -90% (g):	123
Inhalation Rate During Use (m^3/hr):	0.55	Duration of Use - Median (hours/event):	0.667
Inhalation Rate After Use (m^3/hr):	0.55	Duration of Use - 90% (hours/event):	1.42
Zone 1 Volume (m^3):	20	Whole House Volume (m^3):	369
Air Exchange Rate (air exchanges/hr):	0.45	Body Weight (kg):	71.8
Activity Patterns			
User:	111111122154246742274411	Start Time: 7	
Non-User:	111111113244247742274411	Room of Use: 2. Kitchen	
Hour:	0 6 12 18		
Dermal Inputs			
Frequency of Use - Body (events/yr):	300	SA/BW - Body (cm2/kg):	15.6
Amount Retained / Absorbed to Skin (g/cm2-event):		3.6e-05	
Avg. Time, $LADD_{pot}$, $LADC_{pot}$ (days):	2.74e+04	Avg. Time, ADD_{pot}, ADC_{pot} (days):	2.08e+04
Avg. Time, ADR_{pot}, Cp_{pot} (days):	1.00e+00		

CEM Inhalation Exposure Estimates	
ID Number: Unknown	
Scenario: General Purpose Cleaner	Population: Adult

Inhalation Rate (m^3/day): 0.55 Years of Use (years): 57

Body Weight (kg): 71.8 Frequency of Use (events/year): 300

Exposure Units	Result	AT (days)
Chronic Cancer		
$LADD_{pot}$ (mg/kg-day)	5.72e-01	2.74e+04
$LADC_{pot}$ (mg/m^3)	3.11e+00	2.74e+04
Chronic Non-Cancer		
ADD_{pot} (mg/kg-day)	7.53e-01	2.08e+04
ADC_{pot} (mg/m^3)	4.10e+00	2.08e+04
Acute		
ADR_{pot} (mg/kg-day)	1.75e+00	1.00e+00
Cp_{pot} (mg/m^3)	1.30e+02	1.00e+00

LADD - Lifetime Average Daily Dose (mg/kg-day) LADC - Lifetime Average Daily Concentration (mg/m^3)

ADD - Average Daily Dose (mg/kg-day) ADC - Average Daily Concentration (mug/m^3)

ADR - Acute Dose Rate (mg/kg-day) Cp - Peak Concentration (mg/m^3)

Note: 75 years = 2.738e+04 days pot - potential dose

Note: The general Agency guidance for assessing short-term, infrequent events (for most chemicals, an exposure of less than 24 hours that occurs no more frequently than monthly) is to treat such events as independent, acute exposures rather than as chronic exposure. Thus, estimates of long-term average exposure like ADD or ADC may not be appropriate for use in assessing risks associated with this type of exposure pattern. (Methods for Exposure-Response Analysis for Acute Inhalation Exposure to Chemicals (External Review Draft). EPA/600/R-98/051. April 1998

CEM Inputs		ID Number: Unknown	
Product: Unknown		Chemical Name: None	
Scenario: Aerosol Paint		Population: Adult	
Molecular Weight (g/mole):	136.2	Vapor Pressure (torr):	2
Weight Fraction - Median (unitless):	0.000734	Weight Fraction - 90% (unitless):	0.000734
Inhalation Inputs			
Frequency of Use (events/yr):	60	Years of Use:	11
Mass of Product Used per Event - Median (g):	227	Mass of Product Used per Event -90% (g):	738
Inhalation Rate During Use (m^3/hr):	0.55	Duration of Use - Median (hours/event):	0.333
Inhalation Rate After Use (m^3/hr):	0.55	Duration of Use - 90% (hours/event):	1
Zone 1 Volume (m^3):	20	Whole House Volume (m^3):	369
Air Exchange Rate (air exchanges/hr):	0.45	Body Weight (kg):	71.8
Portion of Aerosol in Air (unitless):	0.01		
Activity Patterns			
User:	1 1 1 1 1 1 1 2 3 5 5 4 2 4 6 7 4 2 2 7 4 4 4 1	Start Time: 9	
Non-User:	1 1 1 1 1 1 1 1 3 2 4 4 2 4 7 7 4 2 2 7 4 4 4 1	Room of Use: 5. Utility Room	
Hour:	0 6 12 18		
Dermal Inputs			
There are no Dermal inputs for this scenario.			
Avg. Time, $LADD_{pot}$, $LADC_{pot}$ (days):	2.74e+04	Avg. Time, ADD_{pot}, ADC_{pot} (days):	4.02e+03
Avg. Time, ADR_{pot}, Cp_{pot} (days):	1.00e+00		

CEM Inhalation Exposure Estimates

ID Number: Unknown

Scenario: Aerosol Paint | Population: Adult

Inhalation Rate (m^3/day): 0.55 | Years of Use (years): 11

Body Weight (kg): 71.8 | Frequency of Use (events/year): 60

Exposure Units	Result	AT (days)
Chronic Cancer		
$LADD_{pot}$ (mg/kg-day)	4.72e-04	2.74e+04
$LADC_{pot}$ (mg/m^3)	2.57e-03	2.74e+04
Chronic Non-Cancer		
ADD_{pot} (mg/kg-day)	3.22e-03	4.02e+03
ADC_{pot} (mg/m^3)	1.75e-02	4.02e+03
Acute		
ADR_{pot} (mg/kg-day)	6.24e-02	1.00e+00
Cp_{pot} (mg/m^3)	5.76e+00	1.00e+00

LADD - Lifetime Average Daily Dose (mg/kg-day) | LADC - Lifetime Average Daily Concentration (mg/m^3)

ADD - Average Daily Dose (mg/kg-day) | ADC - Average Daily Concentration (mg/m^3)

ADR - Acute Dose Rate (mg/kg-day) | Cp - Peak Concentration (mg/m^3)

Note: 75 years = 2.738e+04 days pot - potential dose

Note: The general Agency guidance for assessing short-term, infrequent events (for most chemicals, an exposure of less than 24 hours that occurs no more frequently than monthly) is to treat such events as independent, acute exposures rather than as chronic exposure. Thus, estimates of long-term average exposure like ADD or ADC may not be appropriate for use in assessing risks associated with this type of exposure pattern. (Methods for Exposure-Response Analysis for Acute Inhalation Exposure to Chemicals (External Review Draft). EPA/600/R-98/051. April 1998