Florida Department of Agriculture and Consumer Services
CHARLES H. BRONSON, Commissioner
The Capitol • Tallahassee, FL 32399-0800

August 26, 2004

Please respond to:
Bureau of Pesticides
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Ms. Dorothy Shimer
Research Division
Air Resources Board
P.O. Box 2815
Sacramento, California 95812

Dear Ms. Shimer:

This correspondence contains written comments from the Florida Department of Agriculture and Consumer Services in response to the California Air Resources Board's report (hereafter referred to as the CA-ARB report) entitled, "Draft Report to the California Legislature, Indoor Air Pollution in California in Response to Assembly Bill 1173". In preparing our comments, we reviewed the studies cited in the CA-ARB report. In addition, we conducted a comprehensive search of the available scientific literature regarding the potential health affects resulting from exposure to d-Limonene and related terpenes obtained from citrus fruit. In formulating our opinion, we also reviewed a number of documents on d-Limonene from several authoritative bodies including WHO (World Health Organization); IARC (International Agency for Research on Cancer); EPA (Environmental Protection Agency); FDA (Food and Drug Administration); NTP (National Toxicology Program), and NIOSH (National Institute for Occupational Safety and Health). A copy of our findings is attached.

It is our position that there is no foundation for the CA-ARB report assertion that d-Limonene is a human carcinogen. That view is in stark contrast to conclusions made in the scientific literature and by other governmental agencies addressing this issue, which uniformly agree that d-Limonene is not a human carcinogen.

Further, there is gross deficit of evidence to support the report's recommendation that d-Limonene and other terpenes should be removed from consumer products. The available evidence indicates that d-Limonene is nontoxic by all exposure routes, and that it is present in the air of homes and in occupational settings at levels well below that which could cause any significant health effects. As a natural byproduct of citrus, d-Limonene is an important

alternative to other unrelated chemicals, including chlorinated solvents which can cause harm to human health and the environment, and Freon chemicals which destroy protective ozone in the upper atmosphere.

Advocating the removal of d-Limonene and related citrus terpenes from product formulations could spuriously lead people to associate citrus products with adverse health effects, when in reality citrus consumption is associated with a number of important health benefits. We therefore respectfully urge the CA-ARB to remove statements in the draft report pertaining to d-Limonene and related citrus terpenes.

Thank you for consideration of our comments. If you have any questions in this matter, please contact Dr. Dennis Howard, Chief of the Department's Bureau of Pesticides. Dr. Howard can be reached at (850) 487-0532 or by email at howardd@doacs.state.fl.us.

Sincerely,

CHARLES H. BRONSON
COMMISSIONER

Steven J. Rutz, Director
Division of Agricultural Environmental Services

Enclosure

CC: Ms. Terry Rhodes
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Dr. Davis Daiker
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Florida Department of Agriculture and Consumer Services
Comments on CA-ARB Report Statements Regarding d-Limonene
August 26, 2004

d-Limonene Uses

Food

Terpenes such as d-Limonene occur in nearly every natural food (Wagner and Elmadfa, 2003). It therefore follows that the principle source of human exposure to d-Limonene is food, which accounts for about 96% of d-Limonene intake from all routes of exposure (WHO, 1998). d-Limonene is a natural product obtained from citrus fruits, primarily from the peel of the fruit, but it is also naturally present in the edible fruit. It is naturally present in orange juice at an average concentration of 100 ppm, and it is used as an additive in chewing gum at concentrations of about 2,300 ppm (NTP, 1990). It is also naturally present, along with other terpenes, in a number of herbs and vegetables (HSDB, 2004; NIOSH, 1993; Gould, 1997). d-Limonene is listed on the Food and Drug Administration's (FDA) Generally Recognized as Safe (GRAS) list and it is widely used as a flavor additive in foods and beverages (FDA, 2004).

Consumer Products

d-Limonene is used as a fragrance additive in air fresheners, perfumes, skin cleansers (up to 40% d-Limonene), soaps, household cleaning products, and a number of other consumer products (WHO, 1998; NIOSH, 1993).

Industrial Uses

While d-Limonene finds its principle uses in foods and fragrances, it is also currently used as a solvent, degreaser, and wetting agent, and is an important industrial alternative to toxic halogenated solvents and ozone-depleting chlorofluorocarbons used for those purposes (NIOSH, 1993; HSDB, 2004).

Medical Uses

d-Limonene is used in various medical procedures. d-Limonene is demonstrating success as a chemotherapeutic agent in human clinical trials in patients with advanced cancer (Vigushin et al., 1998; Wagner et al., 2002). Infusions of d-Limonene have also been shown to be effective in dissolving gallstones *in vivo* in humans (NIOSH, 1993).

Inhalation therapy of essential oils containing d-Limonene and other terpenes are used to treat acute and chronic bronchitis and acute sinusitis. Inhalation of vapors of essential oils augments the output of respiratory tract fluid, maintains the ventilation and drainage of the sinuses, and has an anti-inflammatory effect on the trachea and reduces asthmatic symptoms (Inouye et al., 2001). In a multi-centre, randomized, double-blind, placebo-controlled parallel group clinical trial, myrtol standardized (consisting of the monoterpenes d-Limonene, alpha-pinene, and 1,8-cineole) was shown to be a safe and effective alternative to commonly used antibiotics in treating acute bronchitis (Matthys et al., 2000). Other studies have also supported the efficacy and safety of using this product containing d-Limonene to treat children with acute and chronic sinus infections (Sengespeik et al., 1998; Federspil et al., 1997).

Potential Health Effects from d-Limonene

d-Limonene is of low toxicity by all routes of exposure in both human and animal studies. It is not a human carcinogen, a mutagen, a neurotoxin, or a teratogen (HSDB, 2004; WHO, 1998; NIOSH, 2004; NICNAS, 2002).

Inhalation Exposure

The CA-ARB report cites a study (Delfino, 2002) which cites yet another study (Norback et al., 1995) that implies that d-Limonene and other terpenes were associated with asthma. The CA-ARB reports, "Delfino (2002) published a review of the epidemiological evidence for links between air toxics and asthma. Delfino cites Swedish studies that showed that self-reported asthma prevalence in schoolchildren increased with increasing VOC levels, and asthmatic adult symptoms occurred in association with toluene, C8-aromatics, terpenes, formaldehyde, and Limonene." It is apparent from the CA-ARB draft report that the CA-ARB did not review the primary reference when including this in the report. It is noteworthy that the study was based largely on subjective interviews, and it included a small number (88) of study participants (Norback, 1995). The CA-ARB study failed to include in their draft report mention of other studies (see above "Medical Uses") reporting that d-Limonene and other terpenes are used to alleviate asthmatic and respiratory symptoms.

The CA-ARB report cites a study by Girman et al. (1999) to support the position that d-Limonene causes indoor problems. However, while that study did indicate that d-Limonene was among the compounds having the highest median indoor concentration, the paper indicates that these buildings did not have indoor air problems. The authors of the study state, "The results from this study provide normative data on VOCs in U.S. office buildings that can be used to compare to data from complaint buildings." The d-Limonene levels reported in the study ranged from 0.3 to 140 ug/m3. In contrast to the conclusions drawn by the CA-ARB, this study actually lends support to the position that d-Limonene in the air of typical office work areas is at levels insufficient to cause any health concerns.

The intake of Limonene from indoor and outdoor air for the general population is estimated to be 10 and 0.1 ug/kg (or 0.01 and 0.0001 mg/kg) body weight per day, respectively. Inhalation of d-Limonene from air is believed to account for only about 4% of total d-Limonene exposure, with most exposure coming from ingesting food (WHO, 1998).

Nevertheless, d-Limonene and other terpenes are ubiquitous in the atmosphere as a result of emissions in very large amounts from natural sources such as California western sagebrush, oranges, tomatoes, kiwi, grasses, wax myrtle, sweet acacia and many other plant sources (HSDB, 2004). d-Limonene and other monoterpenes comprise a significant proportion of flower scent composition (Jurgens, 2004; Rapparini et al., 2001). Muller et al. (2002) reported that d-Limonene comprised a significant portion of flowering rape plant emissions in agricultural land. Global annual emissions of biogenic monoterpenes are estimated to be in the range of 145 to 825 million tons (WHO, 1998). Mean emission rates of Limonene from different plant species (e.g., lemon, orange, pistachio, and walnut) in the Central Valley of California reportedly ranged from 0.4 to 2.5 mg/g dry leaf weight per hour (WHO, 1998).

Measured concentrations of d-Limonene in outdoor air vary greatly, but are typically in the range of 0.1 to 2 parts per billion (ppb), (or about 0.6 to 11 ug/m3, using the conversion factor of 1 ug/m3 = 0.177 ppb; WHO, 1998). d-Limonene has been detected in the air of office buildings at levels ranging from 7.6 to 11.2 ppb (43 to 63 ug/m3; HSDB, 2004). Indoor Limonene concentrations ranged from 1.6 to 78 ug/m3 in Ruston, Washington, and were reportedly present in indoor air at an arithmetic mean level of 40 ug/m3 (7.1 ppb, or 0.0071 ppm) in Los Angeles, California (WHO, 1998).

California has not established acute or chronic Reference Exposure Levels for d-Limonene (CA-OEHHA, 2004). While OSHA has set an occupational 8 hour time-weighted average (TWA) value of 100 parts per million (100 ppm or 100,000 ppb) for turpentine, which contains significant amounts of d-Limonene as well as other monoterpenes, occupational exposure limits have not been established specifically for d-Limonene by either OSHA, NIOSH, or ACGIH (NIOSH, 2003; NIOSH, 1993). However, the AIHA has suggested a guideline level for d-Limonene exposure in workplaces (8 hour TWA) of 30 ppm (30,000 ppb; AIHA, 2004). Investigators in Finland also arrived at a "Recommended Indoor Level" (RIL) for d-Limonene of about 30 ppm based on potential respiratory irritation (Kasanen et al., 1999). Those researchers commented in their study that concentrations of d-Limonene measured indoors in homes or offices are far less than that which could cause irritation. Sweden has established an occupational exposure limit (8-hour TWA) for d-Limonene of 150 mg/m3 (or about 27 ppm). The intake of Limonene associated with working at the Swedish occupational exposure limit was estimated as 17 mg/kg body weight per day (WHO, 1998). According to research conducted by scientists at the Danish National Institute of Occupational Health, the sensory irritation threshold for d-Limonene in humans is above 80 ppm (80,000 ppb; Larsen et al., 2000). The California Department of Health Services published a report in which d-Limonene was listed as a substance likely emitted from building materials and cleaning products, and while the list in that report categorized a number of other chemicals as irritants, d-Limonene was not among them (CDHS, 1999).

Human volunteers were exposed to d-Limonene by inhalation for two hours on three different occasions with exposure concentrations of 10, 225, and 450 mg/m3 (1.8, 39.8, and 79.7 ppm). While a temporary decrease in vital capacity was observed at the highest level, the subjects did not experience any symptoms of irritation or symptoms related to the central nervous system (Falk-Filipsson et al., 1993). Further, levels of d-Limonene in that study reportedly having any effect are well above that typically reported in indoor environments in the U.S.

NIOSH conducted a study in which workers employed at two aircraft maintenance facilities were exposed to fairly high amounts of d-Limonene (NIOSH, 1993; Tharr, 1994). Very large open tanks and spray products containing highly concentrated d-Limonene were used at these work areas. Workers manually washed parts with d-Limonene, and in many cases did not have adequate ventilation or did not take safety precautions, such as wearing gloves. Despite air levels of d-Limonene reported at levels considerably higher than in home environments or at other types of work settings (personal air sampling d-Limonene values of 5.2 to 114.3 ppm), no Limonene related medical problems were identified in the exposed workers.

Guinea pigs exposed to d-Limonene in air did not experience any allergic reactions until the d-Limonene was exposed to air for two months and Limonene oxide was produced in sufficient quantities to cause sensitization to the oxidation product. While some of the test animals developed sensitivity to the oxidation product, they did not become sensitized to d-Limonene (Karlberg et al., 1991; 1992). Sensory irritation was reported in a study in which mice were exposed to reaction byproducts of 48 ppm Limonene and 4 ppm ozone (Clausen et al, 2001). However, the level of Limonene used in this study is well above levels reported under typical use scenarios, and equally important is that the concomitant presence of ozone, or other known respiratory irritants (e.g. nitric oxide free radicals), is apparently a prerequisite for the formation of sensory irritants from Limonene. By itself, Limonene does not produce such effects (Fan et al., 2003; WHO, 1998; HSDB, 2004). Wilkins et al. (2003) conducted experimental inhalation studies using mice exposed to Limonene at 50 ppm. Those researchers reported that mice experienced signs of irritation only when ozone was also present at a concentration of 0.5 ppm or more.

Dermal Exposure

The intake of Limonene from dermal exposure is likely to be low compared with other routes of exposure (WHO, 1998). d-Limonene and other terpenes are noncorrosive and nonreactive. However, dermal exposure to sufficiently high levels of d-Limonene may cause superficial drying of the skin (NIOSH, 1993).

d-Limonene is reportedly a mild skin and eye irritant (NIOSH, 2003; HSDB, 2004). Application of 20% mixture of d-Limonene and l-Limonene under a patch to the skin of volunteers did not cause irritation after 48 hours (CCOHS, 2004). Solvents containing 20 to 30% d-Limonene have been used in copious amounts to remove tar and asphalt from the eyes and skin of burn injury victims presenting to the emergency room. No adverse reactions have been reported in these cases (NIOSH, 1993).

d-Limonene by itself not a contact sensitizer (WHO, 1998). It must undergo an enzymatic or chemical oxidation before it is converted into a different compound (e.g., a haptan compound), which may exhibit contact allergenic properties in a small proportion of allergic individuals (NIOSH, 1993; Karlberg and Dooms-Goossens, 1997; HSDB, 2004). Patch testing of thousands of patients having dermatitis was conducted to determine the rate of allergy to oxidation products of Limonene and other terpenes, and only a very small proportion of these patients (in the range of a few percent) had a positive reaction to the patch tests (Matura et al., 2003; Jancin, 2004). Consumer products containing d-

Limonene typically have antioxidant additives that prevent or reduce the likelihood of this oxidation reaction occurring (Nilsson et al., 1999; FCCI, 2004). Further, it has been reported that when products containing Limonene are stored in closed containers in cool dark storage areas, they produce no oxidation products for up to a year or more, even without addition of antioxidants (Karlberg et al., 1994). In addition, there is limited evidence from some studies that d-Limonene may actually prevent sensitizing compounds (e.g., cinnamic aldehyde) from exerting their allergenic effects (WHO, 1998).

Oral Exposure

As previously mentioned, Limonene from food constitutes the overwhelming contribution to total Limonene intake. In fact, the intake of Limonene in food may be unavoidable due to its widespread presence in foods. Limonene has been detected in breast milk of non-occupationally exposed mothers (WHO, 1998).

Limonene in foods presents little if any risk to human health (WHO, 1998). To the contrary, d-Limonene is the principle constituent of the volatile oil of citrus fruits and it is also present in other foods associated with beneficial health effects including reduced rates of cancer and heart disease (Wattenberg, 1990; Hakim and Harris, 2001). Based on daily U.S. consumption of d-Limonene per capita, the intake of d-Limonene from food for the general public has been estimated to be 0.27 mg/kg body weight per day (WHO, 1998). LD50 values for the oral administration of d-Limonene in rats and mice are in the range of 5 to 6 g/kg body weight (or 5,000 to 6,000 mg/kg body weight), making d-Limonene a compound of exceptionally low toxicity (WHO, 1998).

Carcinogenicity

Page 18 of the draft CA-ARB report states that, “Reformulation of other products, such as cleaning agents to remove terpenes, could go far to reduce irritant and carcinogenic effects.” That supposition is speculative and is not supported by the scientific literature.

d-Limonene has not been shown to be a human carcinogen (IARC, 1999). In fact, d-Limonene and other terpenes have been shown to prevent carcinogenesis at the initiation, promotion, and progression stages, and d-Limonene is being evaluated for its effectiveness as a cancer chemotherapeutic agent in human clinical trials (IARC, 1999; Gould, 1997).

Male F344/N rats orally dosed with highly elevated doses of d-Limonene far greater than that which humans are exposed developed adenomas and adenocarcinomas of the kidney (NTP, 1992). However, it is widely accepted by a number of authoritative bodies that this isolated effect occurs only in males of this particular rat strain because of a specific protein that they carry (alpha 2u-globulin), and that it is therefore not relevant to humans (IARC, 1999; WHO, 1998; NIOSH, 1993; HSDB, 2004; Whysner and Williams, 1996; Webb et al., 1990).

Other animal studies have shown that d-Limonene has anti-carcinogenic effects. d-Limonene inhibits the development of mammary tumors in rats fed the carcinogens DMBA and nitrosomethylurea. In mice, d-Limonene inhibits carcinogenesis of forestomach and lung tumors induced by NDEA and the potent tobacco-specific carcinogen NNK (NIOSH, 1993). In other animal experiments, d-Limonene has been shown to be effective in treating leukemias, neuroblastomas, and cancers of the liver, colon, and pancreas, and in some cases with complete regression of tumors in advanced cancers (IARC, 1999; WHO, 1998; ACS, 2003; Gould, 1997; AICR, 2001; Chow et al., 2002; Crowell et al., 1999, 1997, 1996; Elson et al., 1988). d-Limonene and other monoterpenes reportedly reduce adduct formation in rats exposed to aflatoxin B1 (Elegbede and Gould, 2002).

Conclusions

On page 31 of the draft report, the CA-ARB states, "Risk is dependent on the amount of a pollutant people actually inhale, which depends on the air concentration of the pollutant in a given environment, the length of time a person is in that environment, and the person's breathing rate during that time." The Limonene levels measured in indoor air environments, including in California, are apparently thousands of times less than any of the lowest occupational exposure limits established by any authoritative body.

According to the World Health Organization, vegetation is the primary source of d-Limonene and other related terpenes in air, and global biogenic emissions likely exceed those from anthropogenic sources. However, it has not yet been suggested by the CA-ARB that trees constitute a significant source of pollution that warrants removal. In the aggregate, just as trees benefit human and environmental health, consumer products containing Limonene can mitigate the need for the use of toxic solvents in those products. Direct health benefits from d-Limonene (e.g., anti-carcinogenic and antimicrobial properties) must also be weighed against any possible adverse health effects.

Limonene is of very low toxicity, and it is not a human carcinogen. The transformation of d-Limonene to oxidation products which could potentially cause minor irritation in some individuals depends to a large extent on the presence of other chemicals known to be respiratory irritants. Therefore, the CA-ARB and other health and environmental agencies should focus their attention on the reduction of those known air pollutants rather than on d-Limonene.

In the absence of ambient air criteria or enforceable occupational limits for d-Limonene in the U.S., and without quantitative data to assess risk, it is inappropriate for the CA-ARB to recommend the removal of d-Limonene from consumer products. The California Air Resources Board stands alone in opposition to other governing bodies in advocating that d-Limonene should be removed, and therefore the Florida Department of Agriculture and Consumer Services opines that the CA-ARB should delete these unsubstantiated claims pertaining to d-Limonene and related citrus terpenes from the draft report.

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