

**Evaluation of
Cital
for Use as a Cigarette Ingredient**

December 2005

INTRODUCTION

Citral (CAS # 5392-40-5) is currently used worldwide at levels below **5 ppm** in selected cigarette brands manufactured and/or distributed by Philip Morris International. This document is a review of current published toxicology information on citral abstracted from online toxicity databases.

TOXICITY DATA ON UN-BURNED MATERIAL

The following information was generated from the MICROMEDEX database tool <http://csi.micromedex.com> on December 7th 2005, unless otherwise indicated.

Overview

The following information was generated from the HSDB – Hazardous Substances Data Bank, a database of MICROMEDEX Systems (<http://csi.micromedex.com>) on December 7th 2005.

Citral is an aldehyde found to naturally occur in lemon grass, lemons and oranges. It has a strong lemon-like odour and is used as a flavour in perfumery, in cologne and in soaps. It is not endogenous in humans.

As a food flavouring additive, the material has been assessed under the provisions of the *Federal Food, Drug and Cosmetic Act, section 201 (s)*, by the Expert Committee of the USA Flavour and Extract manufacturer's Association (FEMA), to be generally recognized as safe (GRAS) under current conditions of use.

The Joint FAO/WHO Expert Committee on Food Additives has also assessed citral; a group ADI of 0–0.5 mg/kg bw, expressed as citral, was established for citral, citronellol, geranyl acetate, linalool, and linalyl acetate by the Committee at its twenty-third meeting. The daily intake is estimated at 117 µg/kg bw/day in the USA and 114 µg/kg bw/day in Europe¹.

Citral is a common cosmetic ingredient.

This material appears on the list of "Permitted Additives to Tobacco Products in the United Kingdom" (Department of Health, 2003) at a maximum level permitted for inclusion in cigarettes of 0.15 % w/w tobacco.

The following information was generated from the HSDB – Hazardous Substances Data Bank, a database of MICROMEDEX Systems (<http://csi.micromedex.com>) on December 7th 2005.

Non-Human Toxicity Excerpts

1. Citral once was alleged to cause increase in intraocular pressure in monkeys, but this has not been confirmed, nor has an influence on intraocular pressure been found in rabbits. [****PEER REVIEWED****] [Grant, W.M. *Toxicology of the Eye*. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986., p. 241]

¹ Safety evaluations of certain food additives and contaminants, WHO Food Additive Series 52: Aliphatic branched-chain saturated and unsaturated alcohols, aldehydes, acids, and related esters. <http://www.inchem.org/documents/jecfa/jecmono/v52je15.htm>

2. Citral was ovicidal to freshly laid eggs of *dysdercus cingulatus*, & inhibited embryonic growth in older eggs, resulting in deformed dead imagoes found in eggshell or imagoes which died while coming out of the eggshell. [**PEER REVIEWED**] [OSMANI Z ET AL; INDIAN J EXP BIOL 15 (8): 666 (1977)]
3. Citral induced microphthalmos in 3-day-old chick embryos by intraamniotic injection, in severe cases changes were in ipsilateral part of head. Corneal epithelium lost its continuity & lens showed degenerative changes with spherophakia hyperplasia of cornea & retina. [**PEER REVIEWED**] [ABRAMOVICI A ET AL; DEV NEUROSCI 1 (3-4): 177 (1978)]
4. Mature female rats treated with citral either topically for 60 or 100 days or by ip injections showed marked decr in number of normal follicles/section, because oocytes degenerated. Reduction in implantation number & litter size & incr post-implantation fetal death. [**PEER REVIEWED**] [TOAFF ME ET AL; J REPROD FERTIL 55 (2): 347 (1979)]
5. Treatment of rats for 3 days with citral incr enzyme & cytochrome P-450 levels. [**PEER REVIEWED**] [PARKE DV, RAHMAN H; BIOCHEM J 113 (2): 12 (1969)]
6. Citral caused teratogenic effect when admin by injection at concn of 0.001-0.1 mol to chick embryos. Morphological malformation occurred mainly in craniofacial area, as well as other parts of body. [**PEER REVIEWED**] [ABRAMOVICI A; ADV EXP MED BIOL 27 161 (1972)]
7. Citral was evaluated for mutagenicity in the Salmonella/microsome preincubation assay using a standard protocol approved by the National Toxicology Program. Citral was tested at doses of 0, 1, 3, 10, 33, 50, 100, and 160 ug/plate in four Salmonella typhimurium strains (TA98, TA100, TA1535, and TA1537) in the presence and absence of Aroclor-induced rat or hamster liver S9. Citral was negative in these tests and the highest ineffective dose level tested without clearing of the background lawn in any Salmonella tester strain was 33 ug/plate. [**PEER REVIEWED**] [Zeiger E et al; Environ Mutagen 9:1-110 (1987)]
8. A study was under taken to investigate the embryofeto-toxic potential of citral in the rat. Citral (60; 125; 250; 500 and 1000 mg/kg) in corn oil was given orally to Wistar rats from day 6 to 15 of pregnancy. On day 21 of pregnancy, the number of resorptions and implantation sites were recorded. A transient decrease in weight gain from days 6 to 11 of gestation at the lowest doses and a reduction in body weight minus uterine weight at term at the highest doses indicated that citral was maternally toxic over the dose range tested. A slight but statistically significant increase in the ratio of resorptions per implantations was observed with 60 and 125 mg/kg body weight. Doses higher than 125 mg/kg reduced dose-dependently the ratio of pregnant per mated female. Signs of fetal growth retardation and a higher incidence of minor skeletal abnormalities were found in doses higher than 60 mg/kg. No increase in the frequency of visceral anomalies was found at any dose level, but an increase in fetal spleen weight was observed in doses higher than 125 mg/kg. The no-observed adverse effect level for embryofeto-toxicity is lower than 60 mg citral/kg body weight p.o. [**PEER REVIEWED**] [Nogueira A C MA et al; Toxicol 96 (2): 105-13 (1995)]
9. A study of the potential effects of microencapsulation on the toxicity of citral was conducted in 14 day continuous feeding studies with both sexes of F344 rats and B6C3F1

mice. Toxicity by the feeding route was compared with that from bolus doses of the neat chemical in corn oil administered by gavage. Both sexes of rats and mice were given diet containing 0, 0.63, 1.25, 2.5, 5 and 10% citral microcapsules. These feed formulations were equivalent to daily doses of 0, 142, 285, 570, 1140 and 2280 mg citral/kg body weight for rats and 0, 534, 1068, 2137, 4275 and 8550 mg citral/kg body weight for mice. The daily gavage doses were 0, 570, 1140 and 2280 mg citral/kg body weight for both sexes of rats, and 0, 534, 1068 and 2137 mg citral/kg body weight for both sexes of mice. Citral microcapsules administered in the diet did not cause mortality in mice or rats. Toxicity was confined to decreases in body weight at the 10% concentration in mice, at the 5 and 10% concentrations in rats, and decreases in absolute weights of the liver, kidney and spleen at the 10% concentration in rats. The only histopathological change observed was minimal to mild hyperplasia and/or squamous metaplasia of the respiratory epithelium in the anterior portion of the nasal passages of rats fed 5 or 10% citral microcapsules. By contrast, citral gavage caused mortality in five out of five male and female mice at 2137 mg/kg body weight, and in two out of five male mice at 1068 mg/kg body weight. There were dose-related increases in absolute liver weights of male and female mice. Cytoplasmic vacuolization of hepatocytes occurred in all female mice gavaged with 1068 and 2137 mg citral/kg body weight, and in male mice from the 2137 mg/kg dose group. Necrosis, ulceration and/or acute inflammation of the forestomach occurred in the high-dose mice of both sexes. Inflammation and/or hyperplasia of the forestomach occurred in about half of the male and female mice dosed with 1068 mg citral/kg. Citral gavage at doses that were equivalent to up to 10% in the diet (2280 mg/kg body weight) did not cause toxicity in rats, except for minimal hyperplasia of the squamous epithelium of the forestomach in high-dose males. [**PEER REVIEWED**] [Dieter MP et al; Food Chem Toxicol 31 (7): 463-74 (1993)]

10. To investigate potential mammalian developmental toxicity, pregnant Sprague-Dawley rats were exposed to citral by inhalation for 6 hr/day on gestation days 6-15 at mean concentrations of 0, 10 or 34 ppm as vapor, or 68 ppm as an aerosol/vapor mixture. On gestation day 20, the fetuses were evaluated for gross, visceral and skeletal malformation. Exposure to 68 ppm was maternally toxic, with reduced body-weight gains, ocular opacity, breathing difficulty, nasal discharge and salivation noted in the dams. No maternal toxicity was seen at the lower vapor exposure levels. The number of corpora lutea, implantations, resorptions, fetal viability, litter size, and sex ratio were not adversely affected by citral at any exposure level tested, and no exposure-related malformations were observed. At a maternally toxic exposure level, a slight reduction in mean fetal body weight and a slight increase in the incidence of hypoplastic bones were noted. Citral does not produce developmental toxicity in the rat when administered by inhalation at concentrations up to a maternally toxic exposure level. [**PEER REVIEWED**] [Gaworski CL et al; Food Chem Toxicol 30 (4): 269-75 (1992)]
11. Locally applied retinol is metabolized to retinoic acid in mouse epidermis in vivo. To characterize the oxidation system, the ability of soluble extracts of hairless mouse epidermis to convert retinol and retinal into retinoic acid /was investigated/. The extracts oxidized retinol to retinoic acid in two steps catalyzed by two NAD⁺-dependent enzymes. The first enzyme catalyses the reversible oxidation of retinol to retinal and is an alcohol dehydrogenase isoenzyme. The second enzyme oxidizes retinal to retinoic acid. Retinol oxidation by epidermal extracts was inhibited by the alcohol dehydrogenase inhibitor 4-methylpyrazole and by citral. Citral significantly inhibited retinoic acid formation from retinol in the epidermis in vivo. [**PEER REVIEWED**] [Connor MJ, Smit MH; Biochem J 244 (2): 489-92 (1987)]

12. The short-term effects of citral on the liver have been studied in two strains of rat. Hepatomegaly was accompanied in citral-treated rats by an altered distribution of lipid and glycogen in the liver and peroxisome proliferation occurred in a manner of that associated with some hypolipidaemic compounds. Specific biochemical markers supported the morphological changes in the peroxisomes. Cyanide-insensitive palmitoyl CoA oxidation showed, at the maximum fourfold and threefold inductions in Wistar albino and Long Evans hooded rats, respectively. In addition, induction of cytochrome p450 levels was greater in the Long Evans than in the Wistar rats the maximal increases recorded being 81 and 27% respectively. No alterations in plasma triglycerides or total cholesterol were detected. The differential induction of the mixed-function oxides system and the differential proliferation of peroxisomes in these two strains of rat suggest that citral may be metabolized differently in the two strains. peroxisomal and possibly also mitochondrial changes are involved in the action of citral on lipid metabolism. [**PEER REVIEWED**] [Jackson GM et al; Food Chem Toxicol 25 (7): 505-13 (1987)]
13. Immunocytochemical characterization of several epithelial markers using the PAP technique was analyzed during different stages of induced prostatic hyperplasia in rats. Intact adolescent rats 142 days old were treated with citral (3,7 dimethyl-2,6 octadienal) for 10, 30 and 100 days and their ventral prostate compared to untreated matched-age animals. Among the epithelial markers studied, the prostatic specific acid phosphatase was present in hyperplastic prostates of rats. The immunoreaction showed a fair correlation with the severity of lesion and duration of treatment. The prostatic specific antigen showed equally immunoreactive in both control and treated rats. The hyperplastic and normal rat prostates did not show immunoreactivity towards the other epithelial cell markers such as epithelial membrane antigen, carcinoembryonic antigen and alpha-fetoprotein antisera. Prostatic specific acid phosphatase and to a lesser extent prostatic specific antigen might represent valuable markers for comparative studies of prostatic hyperplasia in rodents. [**PEER REVIEWED**] [Massas R et al; Histol Histopathol 6 (2) 183-9 (1991)]

TSCA Test Submissions

1. 3,7-Dimethyl-2,6-Octadienal (CAS # 5392-40-5) was evaluated for primary dermal irritation. The test substance was applied (undiluted) at a dosage level of 0.5 ml to 6 New Zealand albino rabbits for 24 hours. Clinical signs included moderate erythema and edema, and loosening of the scab edges in 14-17 days, showing injury in depth. The test substance was determined to be corrosive. [**NOT REVIEWED**] [MONSANTO CO; Initial Submission: Toxicity Studies on: Citral with Cover Letter Dated 08/13/92; 06/12/78; EPA Doc. No. 88-920007532; Fiche No. OTS0538615]
2. 3,7-Dimethyl-2,6-Octadienal (CAS # 5392-40-5) was evaluated for genotoxicity. Tests for cytogenetic effects were performed in chinese hamster ovary cells. The test substance was negative for induction of chromosome aberrations (CA) and positive for induction of sister chromatid exchanges (SCE). No further information was submitted. [**NOT REVIEWED**] [GIVAUDAN CORP; National Toxicology Program Fiscal Year 1985 Annual Plan; 03/01/85; EPA Doc. No. 86-870001798; Fiche No. OTS0516404]

The following information was generated from the RTECS – Registry of Toxic Effects of Chemical Substances, a database of MICROMEDEX Systems (<http://csi.micromedex.com>) on December 7th 2005.

Health hazard data

Acute toxicity

LD50/LC50 - LETHAL DOSE/CONC 50% KILL

Rat

LD50 - ROUTE: Intraperitoneal; DOSE: 460 mg/kg [Journal of Reproduction and Fertility. (Biochemical Soc. Book Depot, POB 32, Commerce Way, Colchester, Essex CO2 8HP, UK) V.1- 1960- (55,347,1979)]

LD50 - ROUTE: Oral; DOSE: 3.45 gm/kg ['Vrednie chemichescie veshstva. Prirodnie organicheskie soedinenia' (Hazardous substances. Nature products.) Volkova N.V. et al., Sankt-Peterburg, 1998. (-,291,1998)]

TOXIC EFFECTS:

Liver - Changes in liver weight

Kidney, Ureter, and Bladder - Changes in kidney weight

LD50 - ROUTE: Oral; DOSE: 4960 mg/kg [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (2,327,1964)]

TOXIC EFFECTS:

Behavioral - Somnolence (general depressed activity)

Mouse

LD50 - ROUTE: Oral; DOSE: 6 gm/kg [Biochemical Journal. (Biochemical Soc. Book Depot, POB 32, Commerce Way, Colchester, Essex CO2 8HP, UK) V.1- 1906- (34,1196,1940)]

TOXIC EFFECTS:

Tumorigenic - Active as anti-cancer agent

LD50 - ROUTE: Oral; DOSE: 1.67 gm/kg ['Vrednie chemichescie veshstva. Prirodnie organicheskie soedinenia' (Hazardous substances. Nature products.) Volkova N.V. et al., Sankt-Peterburg, 1998. (-,291,1998)]

Rabbit

LD50 - ROUTE: Skin; DOSE: 2250 mg/kg [Food and Chemical Toxicology. (Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, NY 10523) V.20- 1982- (25,505,1987)]

Irritation

SKIN - STANDARD DRAIZE TEST

Rabbit

ROUTE: Skin; DOSE: 100 mg/24H; REACTION: Severe [Cosmetics and Toiletries. (Allured Pub. Corp., POB 318, Wheaton, IL 60189) V.91- 1976- (94(8),41,1979)]

ROUTE: Skin; DOSE: 500 mg/24H; REACTION: Moderate [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (17,259,1979)]

Guinea Pig

ROUTE: Skin; DOSE: 100 mg/24H; REACTION: Severe [Cosmetics and Toiletries. (Allured Pub. Corp., POB 318, Wheaton, IL 60189) V.91- 1976- (94(8),41,1979)]

ROUTE: Skin; DOSE: 1%/48H; REACTION: Moderate [Journal of the Society of Cosmetic Chemists. (Soc. of Cosmetic Chemists, 1995 Broadway, Suite 1701, New York, NY 10023) V.1- 1947- (28,357,1977)]

Pig

ROUTE: Skin; DOSE: 50 mg/48H; REACTION: Severe [Cosmetics and Toiletries. (Allured Pub. Corp., POB 318, Wheaton, IL 60189) V.91- 1976- (94(8),41,1979)]

Reproductive effects

Rat

TDL_o - ROUTE: Intraperitoneal; DOSE: 1800 mg/kg; DURATION: female 22W prior to mating [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (18,547,1980)]

TOXIC EFFECTS:

Maternal Effects - Oogenesis

Effects on Fertility - Pre-implantation mortality (e.g., reduction in number of implants per female; total number of implants per corpora lutea)

Effects on Fertility - Post-implantation mortality (e.g., dead and or resorbed implants per total number of implants)

TDL_o - ROUTE: Intraperitoneal; DOSE: 1800 mg/kg; DURATION: female 6D prior to mating [Journal of Reproduction and Fertility. (Biochemical Soc. Book Depot, POB 32, Commerce Way, Colchester, Essex CO2 8HP, UK) V.1- 1960- (55,347,1979)]

TOXIC EFFECTS:

Maternal Effects - Ovaries, fallopian tubes

Effects on Newborn - Live birth index (similar to T26, except measured after birth)

TDL_o - ROUTE: Intraperitoneal; DOSE: 1800 mg/kg; DURATION: female 6D prior to mating ['Vrednie chemicheskije veshstva. Prirodnie organicheskie soedinenia' (Hazardous substances. Nature products.) Volkova N.V. et al., Sankt-Peterburg, 1998. (-,286,1998)]

TOXIC EFFECTS:

Effects on Fertility - Post-implantation mortality (e.g., dead and or resorbed implants per total number of implants)

Effects on Newborn - Other postnatal measures or effects

TDL_o - ROUTE: Oral; DOSE: 1250 mg/kg; DURATION: female 6-15D of pregnancy [Toxicology. (Elsevier Scientific Pub. Ireland, Ltd., POB 85, Limerick, Ireland) V.1- 1973- (96,105,1995)]

TOXIC EFFECTS:

Effects on Embryo or Fetus - Fetotoxicity (except death, e.g., stunted fetus)

TDL_o - ROUTE: Oral; DOSE: 2500 mg/kg; DURATION: female 6-15D of pregnancy [Toxicology. (Elsevier Scientific Pub. Ireland, Ltd., POB 85, Limerick, Ireland) V.1- 1973- (96,105,1995)]

TOXIC EFFECTS:

Effects on Fertility - Female fertility index (e.g., # females pregnant per # sperm positive females; # females pregnant per # females mated)

Specific Developmental Abnormalities - Other developmental abnormalities

TDLo - ROUTE: Oral; DOSE: 10 gm/kg; DURATION: female 6-15D of pregnancy [Toxicology. (Elsevier Scientific Pub. Ireland, Ltd., POB 85, Limerick, Ireland) V.1- 1973-(96,105,1995)]

TOXIC EFFECTS:

Maternal Effects - Other effects

Effects on Fertility - Pre-implantation mortality (e.g., reduction in number of implants per female; total number of implants per corpora lutea)

Effects on Embryo or Fetus - Fetal death

TDLo - ROUTE: Oral; DOSE: 10 gm/kg; DURATION: female 6-15D of pregnancy [Toxicology. (Elsevier Scientific Pub. Ireland, Ltd., POB 85, Limerick, Ireland) V.1- 1973-(96,105,1995)]

TOXIC EFFECTS:

Specific Developmental Abnormalities - Musculoskeletal system

Effects on Newborn - Sex ratio

TDLo - ROUTE: Skin; DOSE: 46 gm/kg; DURATION: female 14W prior to mating [Journal of Reproduction and Fertility. (Biochemical Soc. Book Depot, POB 32, Commerce Way, Colchester, Essex CO2 8HP, UK) V.1- 1960- (55,347,1979)]

TOXIC EFFECTS:

Maternal Effects - Ovaries, fallopian tubes

Effects on Fertility - Other measures of fertility

Effects on Newborn - Viability index (e.g., # alive at day 4 per # born alive)

TDLo - ROUTE: Skin; DOSE: 27600 mg/kg; DURATION: female 60D prior to mating [Journal of Reproduction and Fertility. (Biochemical Soc. Book Depot, POB 32, Commerce Way, Colchester, Essex CO2 8HP, UK) V.1- 1960- (55,347,1979)]

TOXIC EFFECTS:

Effects on Newborn - Live birth index (similar to T26, except measured after birth)

TDLo - ROUTE: Skin; DOSE: 27.6 gm/kg; DURATION: female 60D prior to mating ['Vrednie chemicheskije veshstva. Prirodnie organicheskie soedinenia' (Hazardous substances. Nature products.) Volkova N.V. et al., Sankt-Peterburg, 1998. (-,286,1998)]

TOXIC EFFECTS:

Effects on Fertility - Post-implantation mortality (e.g., dead and or resorbed implants per total number of implants)

Effects on Newborn - Other postnatal measures or effects

TDLo - ROUTE: Skin; DOSE: 28 gm/kg; DURATION: female 60D prior to mating [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (18,547,1980)]

TOXIC EFFECTS:

Maternal Effects - Oogenesis

Effects on Fertility - Pre-implantation mortality (e.g., reduction in number of implants per female; total number of implants per corpora lutea)

Effects on Fertility - Post-implantation mortality (e.g., dead and or resorbed implants per total number of implants)

TDL_o - ROUTE: Skin; DOSE: 46 gm/kg; DURATION: female 14W prior to mating [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (18,547,1980)]

TOXIC EFFECTS:

Effects on Newborn - Viability index (e.g., # alive at day 4 per # born alive)

Genetic effects

DNA REPAIR

Bacteria - B Subtilis

DOSE: 2222 ug/disc [Osaka-shi Igakkai Zasshi. Journal of Osaka City Medical Association. (Osaka-shi Igakkai, c/o Osaka-shiritsu Daigaku Igakubu, 1-4-54 Asahi-cho, Abeno-ku, Osaka, 545, Japan) V.24- 1975- (34,267,1985)]

Other multiple dose toxicity data

Rat

TDL_o - ROUTE: Intraperitoneal; DOSE: 1800 mg/kg/6D intermittent ['Vrednie chemichescie veshstva. Prirodnie organicheskie soedinenia' (Hazardous substances. Nature products.) Volkova N.V. et al., Sankt-Peterburg, 1998. (-,291,1998)]

TOXIC EFFECTS:

Maternal Effects - Ovaries, fallopian tubes

Others - Changes in ovarian weight

TDL_o - ROUTE: Oral; DOSE: 24 gm/kg/10D intermittent [Food and Chemical Toxicology. (Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, NY 10523) V.20- 1982- (25,505,1987)]

TOXIC EFFECTS:

Liver - Changes in liver weight

Biochemical - Hepatic microsomal mixed oxidase (dealkylation, hydroxylation, etc.)

Biochemical - CoA

TDL_o - ROUTE: Skin; DOSE: 12648 mg/kg/17W intermittent [Urological Research. (Springer Verlag New York, Inc., Service Center, 44 Hartz Way, Secaucus, NJ 07094) V.1- 1973- (20,139,1992)]

TOXIC EFFECTS:

Skin and Appendages - Dermatitis, other

Skin and Appendages - Hair

TDL_o - ROUTE: Skin; DOSE: 3720 mg/kg/5W intermittent [Urological Research. (Springer Verlag New York, Inc., Service Center, 44 Hartz Way, Secaucus, NJ 07094) V.1- 1973- (20,139,1992)]

TOXIC EFFECTS:

Paternal Effects - Prostate, seminal vesicle, Cowper's gland, accessory glands

TDL_o - ROUTE: Skin; DOSE: 5550 mg/kg/30D intermittent [Comparative Biochemistry and Physiology, C: Pharmacology, Toxicology and Endocrinology. (Elsevier Science, 660 White Plains Rd., Tarrytown, NY 10591) V.74- 1983- (115,169,1996)]

TOXIC EFFECTS:

Endocrine - Other changes

TDL_o - ROUTE: Skin; DOSE: 27.6 gm/kg/60D intermittent ['Vrednie chemicheskije veshstva. Prirodnie organicheskie soedinenia' (Hazardous substances. Nature products.) Volkova N.V. et al., Sankt-Peterburg, 1998. (-,291,1998)]

TOXIC EFFECTS:

Maternal Effects - Ovaries, fallopian tubes

Others - Changes in ovarian weight

Mouse

TDL_o - ROUTE: Oral; DOSE: 14952 mg/kg/14D intermittent [Food and Chemical Toxicology. (Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, NY 10523) V.20- 1982- (31,463,1993)]

TOXIC EFFECTS:

Liver - Other changes

Liver - Changes in liver weight

Others - Death

Rabbit

TDL_o - ROUTE: Oral; DOSE: 255 mg/kg/13W intermittent [FAO Nutrition Meetings Report Series. (Rome, Italy) No.?-57, 1948-77. Discontinued. (44A,1,1967)]

TOXIC EFFECTS:

Kidney, Ureter, and Bladder - Interstitial nephritis

Kidney, Ureter, and Bladder - Proteinuria

Blood - Other changes

TOXICITY DATA ON BURNT MATERIAL

Data on the toxicity of citral as a cigarette ingredient has been evaluated in a series of studies. The results of these studies may be found in the following references:

E.L. Carmines, 2002, "Evaluation of the Potential Effects of Ingredients Added to Cigarettes. Part I: Cigarette Design, Testing Approach and Review of Results," Food and Chemical Toxicology, 40:77-91. **PEER REVIEWED**

K. Rustemeier et al, 2002, "Evaluation of the Potential Effects of Ingredients Added to Cigarettes Part II. Chemical Smoke Composition," Food and Chemical Toxicology, 40:93 - 104. **PEER REVIEWED**

Roemer et al, 2002, "Evaluation of the Potential Effects of Flavor Ingredients Added to Cigarettes. Part 3. In Vitro Genotoxicity and Cytotoxicity," Food and Chemical Toxicology, 40:105-111. **PEER REVIEWED**

P.M. Vanscheeuwijck et al, 2002, "Toxicological Evaluation of Cigarettes without and with the Addition of Flavor Ingredients to the Tobacco. Part 4. Subchronic Inhalation Toxicity," Food and Chemical Toxicology, 40:113-131. **PEER REVIEWED**

These studies indicate that the ingredients used in the production of cigarettes do not increase the overall toxicity of cigarette smoke.

DATA ON THE EFFECTS ON HUMAN HEALTH

The following information was generated from the HSDB – Hazardous Substances Data Bank, a database of MICROMEDEX Systems (<http://csi.micromedex.com>) on December 7th 2005.

Human Toxicity Excerpts

1. Irritant effect of 19 oils & 20 synthetic perfumes used in cosmetics were tested on skin of 50 male volunteers. Citral @ 32% concn was the most irritating of perfumes in human patch test. **[**PEER REVIEWED**]** [MOTOYOSHI K ET AL; COSMET TOILET 94 (AUG): 41 (1979)]
2. The low molecular weight aldehydes, the halogenated aliphatic aldehydes, and the unsaturated aldehydes are particularly irritating. The mucus membranes of the nasal and oral passages and the upper respiratory tract are affected, producing a burning sensation, an increased ventilation rate, bronchial constriction, choking, and coughing. The eyes tear, and a burning sensation is noted on the skin of the face. During low exposures, the initial discomfort may abate after 5 to 10 minutes but will recur if exposure is resumed after an interruption. /Aldehydes/ [Peer reviewed] [Clayton, G. D. and F. E. Clayton (eds.). Patty's Industrial Hygiene and Toxicology: Volume 2A, 2B, 2C: Toxicology. 3rd ed. New York: John Wiley Sons, 1981-1982., p. 2633]
3. Recent outbreak of hand eczema amongst cleaning personnel after introduction of new, lemon-scented detergent. Citral proved to be strong primary irritant @ higher temp. **[**PEER REVIEWED**]** [ROTHENBORG HW ET AL; CONTACT DERMATITIS 3 (1): 37 (1977)]

TSCA Test Submissions

1. 3,7-Dimethyl-2,6-octadienal (CAS # 5392-40-5) was evaluated for dermal sensitization. The test substance was applied at a dosage of 0.5 ml to the occluded upper arms of 42 human subjects. The final challenge application applied two patches, one to the original site and one to a site not previously sensitized. No evidence of primary irritation or sensitization was observed. **[**NOT REVIEWED**]** [Repeated Insult Patch Test of Group Number 79, NRA-01-0229(----)C (Final Report) with Attachments and Cover Letter Dated 112591 (Sanitized); 02/23/72; EPA Doc. No. 86-920000249S; Fiche No. OTS0535066]
2. A case report for 3,7-Dimethyl-2,6-Octadienal (CAS # 5392-40-5) was submitted because of an adverse health effect from an Exxon employee who complained of 'congestion, nausea, headaches, sore throat, eyes burning, tightness in chest', during the run of lemon scent bags containing the product 'lemon scent resin concentrate'. The product contains one material, Citral, which is know to have sensitizing potential. Citral is a skin irritant and may be capable of eliciting skin allergies (delayed contact hypersensitivity). Further claims of adverse health effects were alleged from a clerical employee in the Clinton, Massachusetts plant who suffered a 'distinct allergic reaction' to the scent of a raw material used in the manufacture of the subject chemical. The employee saw a physician at the time of the incident, who 'administered a shot which reduced the swelling, and after a few minutes returned her breathing to normal'. The allergic response is similar to 'anaphylactic shock'. **[**NOT REVIEWED**]**

[QUANTUM CHEMICAL CORP; Letter From Quantum Chemical Corp to USEPA Regarding Adverse Health Effects as a Result of Exposure to Lemon Scent Resin with Attachments and Cover Letters Dated 04/07/88 & 11/16/87; 04/07/88; EPA Doc. No. FYI-OTS-0488-0609P; Fiche No. OTS0000609-0]

The following information was generated from the RTECS – Registry of Toxic Effects of Chemical Substances, a database of MICROMEDEX Systems (<http://csi.micromedex.com>) on December 7th 2005.

Health hazard data

Irritation

SKIN - STANDARD DRAIZE TEST

Human

ROUTE: Skin; DOSE: 40 mg/24H; REACTION: Mild [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (17,259,1979)]

Man

ROUTE: Skin; DOSE: 16 mg/48H; REACTION: Severe [Cosmetics and Toiletries. (Allured Pub. Corp., POB 318, Wheaton, IL 60189) V.91- 1976- (94(8),41,1979)]

CONCLUSION

Cigarette smoking causes lung cancer, heart disease, emphysema and other serious diseases in smokers. Smokers are far more likely to develop serious diseases, like lung cancer, than non-smokers. There is no "safe" cigarette. Government health warnings about smoking apply to all cigarettes, regardless of the ingredients added, including those containing only tobacco and paper.

While Philip Morris International has not conducted human studies on the health effects of ingredients used in cigarette manufacture, studies have been conducted using scientifically accepted in vitro and in vivo toxicity assays with various ingredient mixtures (see Toxicity Data on Burnt Material above). These studies show there is no meaningful difference in the composition or toxicity of smoke when the smoke from cigarettes with added ingredients is compared to the smoke from cigarettes without added ingredients. These findings are supported by similar studies from the published literature. It is our scientific judgment, based on the best available data, that the ingredients used in our cigarettes do not increase the overall toxicity of cigarette smoke.