NATIONAL TOXICOLOGY PROGRAM

EXECUTIVE SUMMARY OF SAFETY AND TOXICITY INFORMATION

SESAMOL

CAS Number 533-31-3

February 20, 1991

Submitted to:

NATIONAL TOXICOLOGY PROGRAM

Submitted by:

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Board of Scientific Counselors Draft Report

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OVERVIEW[1]

Nomination History:*Sesamol was nominated for carcinogenicity testing by the National Cancer Institute (NCI) with a moderate to high priority based on the potential for extensive human exposure to sesamol, positive test results in the mouse lymphoma test and the lack of adequate chronic toxicity, epidemiology, and carcinogenicity data available on this compound.*

Chemical and Physical Properties: *Sesamol is an off-white crystalline solid with a melting point of 63-65°C (145-149°F). Sesamol is an excellent antioxidant found in sesame oil. Decomposition products of sesamol include toxic fumes of carbon monoxide and carbon dioxide. This compound is incompatible with strong oxidizing agents.*

Production/Uses/Exposure: *Sesamol is not currently produced in commercial quantities in the United States, however, it can be synthesized upon request. Sesamol is a by-product of sesamolin. No information was found concerning the total U.S. production of sesamol. This compound is not listed in the National Occupational Exposure Survey (NOES). OSHA has not established a permissible exposure limit (PEL) for sesamol. NIOSH and ACGIH have not recommended exposure limits for this compound.*

Toxicological Effects:

Human: *No data were found on the carcinogenic, reproductive, teratogenic, mutagenic, or immunologic effects of sesamol in humans. In addition, no data were found on the chemical*

disposition of this compound in humans.

Fifteen case reports of dermatitis in which sesame oil was implicated as the potential acnegen were found in the literature. In eight of these cases, subjects tested positive to sesamol upon skin patch testing. Sesamol has been found to convert hemoglobin into methemoglobin in vitro.

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[1]The information contained in this executive summary of safety and toxicity information is based on data from current published literature. The summary represents information provided in selected sources and is not claimed to be exhaustive.

Animal: *No data were found concerning the chemical disposition or reproductive effects of sesamol in laboratory animals.*

An intraperitoneal LD_{50} for sesamol was reported to be 470 mg/kg in mice. Sesamol was found to cause necrosis and marked irritation upon intradermal injection in rats and rabbits, respectively. In rabbits, sesamol caused reversible eye irritation when administered in the conjunctival sac. Prechronic and chronic feeding of high doses of sesamol caused a decrease in body weight and an increase in the liver and kidney weights in rats and mice. This compound was not found to have hepatocarcinogenic potential following oral administration to rats in prechronic studies.

Chronic feeding of sesamol to rats caused hyperplastic changes including papillomatous foci in the bladder. In addition, sesamol caused increased pigmentation in the epithelium of the renal convoluted tubules, bronchiectasis, and irregular peribronchial fibrosis of the lung. Sesamol caused hyperplasia and squamous cell carcinomas of the stomach in rats and mice and papillomatous foci in the bladder of mice. Sesame oil was found to be cocarcinogenic in mice. In vitro, sesamol was metabolized to carbon monoxide and inhibited carbon monoxide binding to P-450. In the rabbit nasal mucosa, sesamol formed metabolite complexes with P-450.

Genetic Toxicology: *Sesamol tested positive with and without metabolic activation in the mouse lymphoma assay in the strain L5178Y (Tk+/-). In addition, sesamol was non-mutagenic in Salmonella typhimurium with and without metabolic activation.*

Structure Activity Considerations: *The basic moiety of sesamol, safrole, isosafrole, and dihydrosafrole is methylene dioxyphenyl. The latter three compounds have been shown to be carcinogenic in rats and mice. Safrole and isosafrole produced liver tumors in rats and mice. Safrole also produced lung tumors in infant mice, and dihydrosafrole produced esophagus tumors in rats, and liver and lung tumors in mice.*

I. NOMINATION HISTORY AND REVIEW

A. Nomination History

1. Source: National Cancer Institute (NCI) [NCI, 1989a,b]

2. Date: March 1989

3. Recommendations: Carcinogenicity

4. Priority: Moderate/High

5. Rationale/Remarks:

Common constituent of the diet

Extensive number of humans believed to be exposed

Lack of adequate chronic toxicity, epidemiology and carcinogenicity information available

Positive test results in the mouse lymphoma test

Evidence of cocarcinogenicity

Structural interest

Consider sesamol in conjunction with sesamolin

B. Chemical Evaluation Committee Review

1. Date of Review: March 13, 1991

2. Recommendation: No testing

3. Priority:

4. NTP Chemical Selection Principles:

5. Rationale/Remarks:

Minor component of a naturally occurring product

Sesamol is not produced commercially and has no commercial use

Available data do not indicated any cause for alarm

C. Board of Scientific Counselors Review

1. Date of Review:

2. Recommendations:

3. Priority:

4. Rationale/Remarks

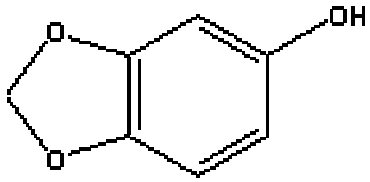
D. Executive Committee Review

1. Date of Review:

2. Decision:

II. CHEMICAL AND PHYSICAL DATA

A. Chemical Identifiers



SESAMOL

Molecular formula: $C_7H_6O_3$ Molecular weight: **138.12**

***CAS No.* 533-31-3**

***RTECS No.* SM0890000**

B. Synonyms and Trade Names

Synonyms: 1,3-benzodioxol-5-ol (9 CI); phenol, 3,4-(methylenedioxy) (8CI); 1,2,4-trihydroxybenzene-1,2-methylene ether; 5-hydroxy-1,3-benzodioxole; methylene ether of oxyquinone

Trade Names: No data were found.

C. Chemical and Physical Properties

Description: Colorless to off white crystalline solid [Lenga, 1988].

Melting Point: 63.0-65.0°C (145.0-149.0°F) [Aldrich, 1990-1991]

65.8°C (150.4°F) [Johnson and Raymond, 1964; Boeseken *et al.*, 1936]

63.6°C (145.0°F) [Boeseken *et al.*, 1936]

Boiling Point: No data were found.

Density/Specific

Gravity: No data were found.

Refractive Index: No data were found.

Solubility in Water: May be soluble in water [Ambrose *et al.*, 1958].

Solubility in other Solvents: May be soluble in ethanol, methyl ethyl ketone [Neering *et al.*, 1975].

Log Octanol/Water Partition Coefficient: No data were found.

Reactive Chemical Hazards: Decomposition products include toxic fumes of carbon monoxide and carbon dioxide.

Incompatible with strong oxidizing agents [Lenga, 1988].

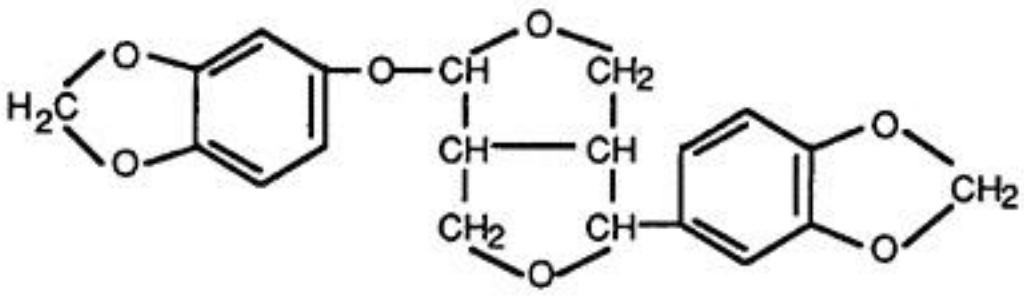
Flammability Hazards: No data were found.

III. PRODUCTION/USE

A. Production

1. Manufacturing Process

Sesamol is not currently produced in commercial quantities in the United States. It is available in research quantities from numerous suppliers. It can be synthesized by specialty manufacturers upon request [NCI, 1989b]. Sesamol can be synthesized by the addition of acetic anhydride and acetic acid to a solution of peracetic acid, followed by addition of sodium acetate and p-toluene sulfonic acid. The resulting solution is combined with piperonal [Boeseken *et al.*, 1936]. Sesamol is liberated from sesamolin (see below) with dilute mineral acids or by bleaching of the oil by acid-type bleaching earths and by hydrogenation [Johnson and Raymond, 1964; Kubo *et al.*, 1986]. In addition, sesamol can be liberated from sesamolin by hydrolysis with concentrated hydrochloric acid and sulfuric acid [Boeseken *et al.*, 1936].



SESAMOLIN

2. Producers and Importers

U.S. Producers	Reference:
Orbis Products Corporation	USEPA, 1990
Newark, New Jersey	-

No information was found on importers of sesamol from the public file of the EPA Toxic Substances Control Act (TSCA) Inventory [USEPA, 1990].

3. Volume

Sesamol is not listed in the United States International Trade Commission's Publication Synthetic Organic Chemicals for the years 1985-1988 [USITC, 1986-1989].

No import volume data specific to sesamol were available from the U.S. Department of Commerce. However, data reported from the U.S. Department of Commerce on the net quantity of sesame oil (inedible and edible) exported to the United States (by country) for the years 1985-1988 are shown in Table 1 [U.S. Department of Commerce, 1986-1989].

Table 1. Net Quantity of Sesame Oil (Inedible and Edible) Exported to the United States By Country 1985-1988

Source	Countries	Net Quantity (lbs)
U.S. Imports for Consumption* 1985	-	-
Inedible	Other	38,614
-	Total	38,614
-	-	-
Edible	Denmark	323,420
-	Fr. Germany	348,800
-	Italy	658,483
-	Lebanon	127,179
-	Thailand	177,479
-	China M	810,586

-	Hong Kong	121,755
-	Hong Kong	210,425
-	China T	125,719
-	Japan	4,762,381
-	Other	221,325
-	Total	7,887,552
-	-	-
U.S. Imports for Consumption 1986	-	-
Inedible	Other	35,644
-	Total	35,644
-	-	-
Edible	Venezuela	221,773
-	Denmark	128,497
-	Fr. Germany	194,100
-	Italy	707,613
-	Lebanon	190,692
-	Thailand	82,463
-	Thailand	134,920
-	China M	872,114
-	Hong Kong	278,794
-	Hong Kong	192,905

-	China T	169,483
-	Japan	4,710,452
-	Other	147,014
-	Total	8,030,820
-	-	-
U.S. Imports for Consumption 1987	-	-
Inedible	Other	78,659
-	Total	78,659
-	-	-
Edible	Mexico	117,129
-	Venezuela	67,422
-	Venezuela	758,930
-	Fr. Germany	228,660
-	Italy	407,972
-	Lebanon	129,381
-	Thailand	155,534
-	Singapore	110,082
-	China M	1,664,633
-	Hong Kong	281,162
-	Hong Kong	381,401
-	China T	359,777
-	Japan	5,083,502

-	Other	191,670
-	Total	9,937,255
-	-	-
U.S. Imports for Consumption 1988	-	-
Inedible	Other	38,614
-	Total	38,614
-	-	-
Edible	Denmark	323,420
-	Fr. Germany	348,800
-	Italy	658,483
-	Lebanon	127,179
-	Thailand	177,479
-	China M	810,586
-	Hong Kong	121,755
-	Hong Kong	210,425
-	China T	125,719
-	Japan	4,762,381
-	Other	221,325
-	Total	7,887,552

*Imports for consumption is a measure of the total of merchandise that has cleared through Customs, whether such merchandise enters consumption channels immediately, or is withdrawn for consumption from warehouses under Customs custody, or is entered into U.S. Customs territory from Foreign Trade Zones.

4. Technical Product Composition

Sesamol is available from Aldrich Chemical Company at a purity of 98% [Aldrich, 1990-1991] and from Sigma Chemical Company at a purity of greater than 99% [Sigma, 1990].

B. Use

Sesame oil is used in the pharmaceutical industry as a solvent and vehicle in fat soluble substances [Ambrose *et al.*, 1958], in the food industry, in the manufacturing of cosmetics, iodized oil, liniments, ointments, and oleomargarine [Gennaro, 1985].

Sesamol is a powerful antioxidant in sesame oil [Johnson and Raymond, 1964] which protects vegetable oils against rancidity [Beroza, 1955]. However, Kikugawa *et al.*, found that other components of sesame oil had stronger antioxidizing properties [Kikugawa *et al.*, 1983].

IV. EXPOSURE/REGULATORY STATUS

A. Consumer Exposure

The estimated potential for human exposure to sesamol is based on several factors including the fact that sesamol content is normally low in unprocessed sesame oil at approximately 0.001-0.005% based on a 0.4% concentration of sesamol/sesamolin in processed sesame oil. The average consumption of sesamol from processed sesame oil in the U.S. in 1981-1986 was estimated to be at least 28,000 pounds. This estimate does not include consumption of oil and substituents derived from imported sesame seeds, therefore, total consumer exposure is expected to be higher [NCI, 1989b].

B. Occupational Exposure

Sesamol is not listed in the National Occupational Exposure Survey (NOES).

C. Environmental Occurrence

Sesamol occurs as a natural component of sesame seed oil. Sesame oil was shown to contain 0.0064% to 0.01% sesamol depending on the detection method employed. Crude sesame oil generally contains < 0.005% sesamol and bleached or hydrogenated oils may contain up to 0.1% free sesamol [Kikugawa *et al.*, 1983]. The concentration of sesamol in processed and unprocessed sesame oils is presented in Table 2 [Budowski *et al.*, 1950; Kikugawa *et al.*, 1983; Yoshida and Kashimoto, 1982; Beroza, 1955; Coors and Montag, 1985].

Table 2. Percent Sesamol in Sesame Oil

-	Budowski et al.	Kikugawa et al.	Yoshida and Kashimoto	Beroza	Coors and Montag
Processed	0.006-0.093[a]	0.064[a]/0.01[b]	---	---	---

Unprocessed	0.001-0.003[a]	0[a/b]	0[b]	0.001-0.005[b]	1 ppm

[a]Spectrophotometric technique

[b]HPLC

D. Regulatory Status

OSHA has not established a permissible exposure limit (PEL) for sesamol.

Sesame oil is a drying oil approved by the FDA as an indirect food additive in resins and polymeric coatings which are food-contact surfaces [Office of the Federal Register, 1990].

E. Exposure Recommendations

ACGIH has not recommended a threshold limit value (TLV) for sesamol.

NIOSH has not recommended an exposure limit (REL) for sesamol.

V. TOXICOLOGICAL EFFECTS

A. Chemical Disposition

1. Human Data

No data were found on the chemical disposition of sesamol in humans.

2. Animal Data

No data were found on the chemical disposition of sesamol in animals.

B. Acute

1. Case Reports

dermal,
human Thirteen patients with contact allergy to sesame oil were patch tested using 5% sesamol, sesamin, and sesamolin in different test vehicles. Each of the materials was dissolved in methyl ethyl ketone and petrolatum. Ethanol was also used as a test vehicle for sesamol. In the standard patch tests, 8 patients tested positive to sesamol and 12 to both sesamin and sesamolin. The sesamin and sesamolin samples were cross-contaminated by approximately 5-10%. Thin layer sheet patch tests were employed, using 250 micrograms of the mixture, to determine whether there were any differences in activity among these

3 materials. The results of the thin layer sheet tests, however, were inconclusive. However, one of the patients reacted to sesamol only. According to the authors this may suggest that sesamol is immunochemically different from sesamin and sesamolin. Neering *et al.* state that some patients seem to be sensitized to either sesamol or the group of sesamin and sesamolin while others

reacted to all 3 substances. Statistical evidence is lacking, however. Because the structures of the three substances are so much alike, the authors thought it useful to perform the thin-layer sheet tests [Neering *et al.*, 1975].

dermal,
human A 35-year-old women who suffered from a deep burn, was treated with a Chinese ointment ("Shiunkoh") composed of 60% sesame oil. After 10 days, the woman experienced edema, erythema, and vesicles around the burn. The women tested positive to skin patch tests with 1% sesamin or 1% sesamolin in petrolatum and negative to 1% sesamol in petrolatum. From these results the authors concluded that sesamin and sesamolin are the primary allergens in sesame oil [Kubo *et al.*, 1986].

dermal,
human A 25-year-old woman developed cheilitis on her lips following the use of a new lipstick. The woman exhibited a strong positive reaction in skin patch tests with the new lipstick and sesame oil at unspecified concentrations. However, no reaction was seen with sesamol at concentrations of 0.1%-5.0% in petrolatum. However, patch tests with sesamin (0.1% pet) and sesamolin (0.3% pet) were positive. Sesamol was not detected in the sesame oil used as an ingredient in the lipstick upon high performance liquid chromatographic (HPLC) analysis [Hayakawa *et al.*, 1987].

2. Animal Data

intraperitoneal,
mouse Male Swiss albino mice (ICR/Ha) (6-8 weeks of age) (n=8 each) were injected intraperitoneally with 0.1 milliliters of a suspension of 1% tween 20 (v/v) with 2.5, 10, 40, 160, or 640 mg/kg sesamol. Controls received solvent only. This initial injection was followed by an immediate intraperitoneal injection with 0.1 milliliters of a solution of hexobarbital (75 mg/kg) or zoxazolamine (80 mg/kg). An LD_{50} of 470 mg/kg was determined for sesamol. Sesamol was found to reduce activity in the hexobarbital sleeping time assay, as shown by the decrease of the dose response slope. The activity in the zoxazolamine paralysis time assay was not affected by sesamol [Fujii *et al.*, 1970].

intradermal,
rat Ten rats of unspecified strain and sex were injected intradermally with 0.1 milliliters of an aqueous solution containing 5 milligrams of sesamol. Six rats developed necrosis at the site of injection within 4 days [Ambrose *et al.*, 1958].

intradermal,
rabbit Rabbits of unspecified strain and sex were injected intradermally via the abdomen with 0.16-5 milligrams of sesamol dissolved in 0.1 milliliters of water. Control rabbits received water and 0.05 milliliters of a 4% solution of formaldehyde. Irritation was seen in the formaldehyde dosed rabbits but not the water treated rabbits. Rabbits dosed with 0.5 milligrams or greater sesamol developed marked irritation within 30 minutes of injection [Ambrose *et al.*, 1958].

dermal,
rabbit A 5% aqueous solution of sesamol, equivalent to 50 mg/kg, was applied to the shaved right flank of 3 rabbits of unspecified sex and strain for 4 days. No local or systemic effects were

observed [Ambrose *et al.*, 1958].

eye,
rabbit Rabbits of unspecified strain and sex were administered 1.2 milligrams (n=6), 2.3 milligrams (n=4), and 4.6 milligrams (n=6) sesamol in the conjunctival sac. The other eye of each rabbit served as the control and was exposed to water only. Within 4 hours of application, all rabbits in each group experienced the same symptomatology including edema of the nictitating membrane, swelling of the palpebral folds, and conjunctivitis. Twenty-four hours later, slight chemosis of the eye was seen in rabbits treated with 2.3 and 4.6 milligrams sesamol. However, eyes of rabbits treated with 1.2 milligrams sesamol appeared normal. After 48 hours, the eyes of rabbits treated with 1.2 and 2.3 milligrams sesamol appeared normal. Three of the 6 rabbits treated with 4.6 milligrams sesamol experienced a slight nictitating membrane at 48 hours, but the eyes of these rabbits were otherwise normal [Ambrose *et al.*, 1958].

C. Prechronic

1. Human Data

dermal,
human Five human subjects received applications of 9 sensitizing doses of 1.25 milligrams of sesamol dissolved in alcohol to the anterior cubital surface of the right arm, 24 hours apart. A challenge dose was applied 12 days after the last sensitizing dose. No signs of hyperemia or irritation were observed after either the sensitizing or the challenging doses [Ambrose *et al.*, 1958].

2. Animal Data

oral,
rat Groups of 5, 6 week old male F344 rats were fed 1% or 2% sesamol in a basal diet for 4 weeks. Five control rats received the basal diet only. Following treatment, body weights of the sesamol treated rats were 10% to 15% less than controls. The 2% sesamol diet induced large ulcers with thickened epithelium in the central region of the forestomach. The 2% sesamol diet induced mild (83%) to moderate (67%) hyperplasia in rats in the prefundic region of the stomach. In the central region of the stomach, the 2% sesamol diet induced mild (100%), moderate (100%), and severe (33%) hyperplasia. In addition, epithelial necrosis and vesicle formation with infiltration of inflammatory cells were observed in rats treated with the 2% sesamol diet. No lesions were seen in the 1% sesamol fed rats [Hirose *et al.*, 1987].

oral, rat The hepatocarcinogenic potential of sesamol was determined using 3 groups of male Fischer rats treated as follows: group 1 (n=19) received a single intraperitoneal injection of 200 mg/kg diethylnitrosamine (DEN) dissolved in 0.9% sodium chloride (NaCl). After 2 weeks on a basal diet, 5000 ppm sesamol was added to the basal diet. Group 2 rats received the same treatment as group 1, however, they did not receive sesamol in the diet. Group 3 rats (n=24) were treated the same as group 1, however, they were injected with 0.9% NaCl in place of DEN. All animals were subject to 2/3 partial hepatectomy at week 3 and sacrificed at week 8. The rats receiving a 5000 ppm dietary concentration of sesamol experienced a significant ($P < 0.01$) inhibition of glutathione S-transferase placental form-positive foci (GST-P+ foci) in the liver. Based on the results of this "medium term" bioassay, it is predicted that sesamol does not have

hepatocarcinogenic potential [Ito *et al.*, 1988].

oral, rat An unspecified number of six week-old male F344/DuCrj rats were given saline injections followed by 2 weeks of basal diet prior to receiving 5000 ppm sesamol in the diet for 1 week. The rats were partially hepatectomized at week 3, and then continued on the sesamol test diet for an additional 5 weeks. Sesamol which had previously been found to inhibit glutathione-S-transferase placental form positive foci (GST-P+ foci), was not found to be hepatotoxic, did not enhance formation of GST-P+ foci and inhibited *N*-nitrosodiethylamine induced carcinogenesis. Although the number of animals in the study was not specified, the authors indicated that liver histopathology studies on 5-20 rats in each treatment group were reviewed in a blind fashion [Ward *et al.*, 1989].

dermal,
rat Rats of unspecified strain, sex, and number were given topical applications of 50 mg/kg sesamol in cotton seed oil or ethyl alcohol daily for 30 days to the depilated skin. No local or systemic effects were observed [Ambrose *et al.*, 1958].

dermal, guinea
pig Twelve albino guinea pigs of unspecified strain and sex were divided into 3 groups of 4 and received either intracutaneous injections of 0.1 milliliters of a 0.1% solution of sesamol in 0.8% sodium chloride; topical applications of 0.1 milliliters of a 1.0% solution of sesamol in ethyl alcohol; or topical applications of 0.1 milliliters of a 1.0% solution of sesamol in cotton seed oil on alternating days, until 100 applications were given. Fifteen days after the last application, a challenge dose of sesamol in the respective carrier vehicle was injected slightly below the sensitized area. No irritation was produced by the sensitizing doses. No reactions were observed after the challenge doses other than a slight hyperemia in 2 guinea pigs. The hyperemia was still present at 24 hours but was questionable at 48 hours [Ambrose *et al.*, 1958].

D. Chronic/Carcinogenicity

1. Human Data

No information was found on the chronic toxicity or carcinogenicity of sesamol in humans. Epidemiological studies are being conducted in areas of high sesame seed/oil consumption such as China, Lebanon, Cairo, and Korea. However, these studies are not investigating sesame oil as a causative agent [NCI, 1989b].

2. Animal Data

oral,
rat Groups of weanling rats (5 male and 5 female per group) from the Western Utilization Research and Development Division, Agricultural Research Service colonies, were fed a basal diet containing either pure (recrystallized twice) or commercial (recrystallized once) sesamol for 13 months and 21 months at the following concentrations: 0.008%, 0.016%, 0.03%, 0.06%, 0.125%, 0.25%, 0.5% or 1.0%. Control rats were fed the basal diet only. Body weights were determined, hematological studies conducted, and gross and microscopic examinations were performed on the surviving rats. Mortality was found to be unrelated to the dietary levels of either sample of sesamol. Rats receiving all doses of the commercial sesamol and the 1% pure

sesamol were sacrificed after 13 months and rats receiving all other doses of pure sesamol were sacrificed after 21 months. Neither the commercial nor the pure sesamol had any effect on body or organ weights in the male rats at any dose level. The highest doses of commercial sesamol (0.25%, 0.5% and 1.0%) caused a slight decrease in the final body weights of female rats. The only significant ($P=0.05$) decreased body weight was observed in the 1.0% dosed females. In female rats fed commercial sesamol, a significant increase in liver weights occurred in the 3 highest dose groups ($P < 0.01$, $P < 0.05$, and $P < 0.01$, respectively). In addition, the body and organ weights of female rats fed pure sesamol was not affected. Body weight and liver weight changes were not observed in female rats that received pure sesamol, indicating the presence of an impurity in the commercial sample. No adverse effects were seen regarding hemoglobin, erythrocyte or leukocyte levels.

The rats fed commercial sesamol for 13 months experienced the following adverse effects. One rat in the 0.25% sesamol group had an ovarian cyst. A kidney cyst was seen in 1 female rat in the 1% sesamol group. Several female rats (unspecified number) experienced more pigmentation in the epithelium of the renal convoluted tubules than controls. However, the amount of pigmentation varied from one animal to another, and there was little relationship to the dosage administered. Lungs of male and female rats had a 10% increased incidence of well-developed non-dose dependent inflammatory changes compared to controls. A number of these lungs had bronchiectasis and some had irregular peribronchial fibrosis. Several sesamol fed rats had hemorrhagic lungs unrelated to sex or sesamol dose. A summary of the hyperplastic lesions observed in the treated rats is presented in Table 3. No lesions were observed in the controls or rats that received the 2 lowest dose levels.

The rats fed pure sesamol experienced the following adverse effects. Gross pathological effects occurred in male rats that received 1% sesamol, including bladder stones (1 rat) and consolidation of the lung (2 rats). Among rats fed 0.5% sesamol or less, an occasional rat at each dosage level had bladder stones, browning of the uterine horns, and lung consolidation. One kidney of each of 2 female rats had a cyst. Micropathological examination revealed that the kidneys of females treated with sesamol had brown pigment in some epithelial cells of the proximal convoluted tubules. The kidney of one female control rat contained a small amount of this pigment which was about the same amount of pigment noted in about half of the treated female rats. The kidneys of male rats contained almost no deposited pigment. Chronic inflammatory lesions of lungs were seen in one quarter of the rats. These changes were unrelated to the dose of sesamol administered. The hyperplastic lesions observed are summarized in Table 3 [Ambrose *et al.*, 1958].

Table 3. Hyperplastic Changes in Rats Fed Sesamol				
Type of Lesion	**No. of Males**	**No. of Females**	**Dietary Level of Sesamol**	**Days on Diet**
	Lesions in Rats Fed Commercial Sesamol 400 Days			
Papillomatous foci in bladder	1	-	0.06%	-
-	2	-	0.13%	-
Adenoma of lung	-	1	0.03%	-
Glandular tumor of stomach	-	1	1.0%	-
Uterine polyp	-	1	1.0%	-
Ovarian lipoma	-	1	0.5%	-
	Lesions in Rats Fed Pure Sesamol 400-634 Days			
Papillomatous foci in bladder	1	-	1.0%	400
Benign uterine polyp	-	1	0.03%	632
-	-	1	0.06%	634
-	-	1	0.25%	634
Adenoma of pancreas	-	1	0.25%	634
Adrenal medullary nodule	-	1	0.5%	632
Adenoma of adrenal cortex	-	1	0.25%	634
Mammary adenoma	-	1	0.016%	576
-	-	1	0.03%	576
-	-	1	0.125%	578
-	-	1	0.25%	578
Subcutaneous lipoma	1	-	0.016%	576

Fibrosarcoma of ovary	-	1	0.5%	410

Reference: Abrose *et al.*, 1958

oral, rat and mouse Groups of 30, 6-week old male and female F344 rats and B6C3F1 mice (male {M} and female {F}) were fed 2% sesamol in a basal diet, or a basal diet alone for 104 weeks (rats) or 96 weeks (mice). Animals were sacrificed and tissues were examined.

Body weights were lower in both treated mice and rats compared to controls; relative kidney and liver weights were higher. Upon histopathological examination, the number of male and female rats with hyperplasia, papillomas, and squamous cell carcinoma in the forestomach was found to be 29M, 30F (100%/100%); 10M, 14F (34%, 47%); and 9M, 3F (31%, 10%), respectively. These effects were all significant ($P < 0.001$) with the exception of the occurrence of squamous cell carcinoma in female rats. Sarcomas were not observed. The number of treated male and female mice with hyperplasia, papillomas, and squamous cell carcinoma was found to be 29M, 28F (100%, 93%); 0M, 0F; and 11M, 5F (38%, 17%), respectively. These effects were significant ($P < 0.001$) for hyperplasia and squamous cell carcinoma ($P < 0.05$). Sarcoma of the glandular stomach was observed in one female mouse. Five female mice (17%) had significant ($P < 0.05$) submucosal growth of the glandular stomach compared to controls. One male rat had adenomatous hyperplasia. Hyperplasia induced by sesamol in rats was characterized by downward basal growth, while hyperplasia in mice was characterized by downward spinal growth [Hirose *et al.*, 1990].

testicular, mice In an abstract of an unpublished study, it was reported that 3 groups of male Marsh mice were used to study the local inflammatory response factor prompted by unspecified concentrations of sesamol and cholesterol α-oxide (n=33), 10 mg/mouse cholesterol α-oxide in saline (n=33), or 0.4 milligrams of sesamol in saline (n=34). The mice were given testicular injections of each substance. One and 2 mice developed sarcomas in the cholesterol α-oxide and cholesterol and sesamol treated groups, respectively. No tumors were seen among the mice treated with sesamol only. However, sesamol produced focal areas of calcification and fibrosis in 35% of the dosed mice. Aspermatogenesis was also observed [Bryson and Bischoff, 1963].

subcutaneous, mice The carcinogenic activity of "sesame oil" was evaluated in Marsh buffalo mice. Thirty-day old male (castrated or intact) and female mice were injected subcutaneously in the dorsal region with cholesterol oxidation products dissolved in sesame oil or aqueous solutions. Mice (n=30) receiving cholesterol oxidation products in sesame oil were injected once at 3 months of age and again with 1 or 2 subsequent injections at 2 month intervals. The sesame oil solution was heated on the water bath for 10 minutes. The total amount of cholesterol oxidation products in sesame oil administered was 15 to 20 milligrams. Mice (n=30) receiving cholesterol oxidative products in aqueous solutions were administered 5 to 15 milligrams per mouse. Three hundred and fifty-five male (castrated and intact) and female mice served as controls and received subcutaneous

doses of sesame oil only at age 17 to 18 months. The incidence of fibrosarcoma in mice that were administered sesame oil only was 1.4 percent. The authors concluded that sesame oil was not carcinogenic following subcutaneous injection, but it was cocarcinogenic. This conclusion was based on the following results: 1) sesame oil was found to be noncarcinogenic; 2) heated or oxidized sesame oil was mildly carcinogenic; 3) certain oxidation products of cholesterol were highly carcinogenic when administered in sesame oil, and non-carcinogenic when administered in aqueous suspensions, 4) certain steroids which are normal body constituents were carcinogenic when administered in sesame oil [Bischoff, 1957].

E. Reproductive Effects and Teratogenicity

1. Human Data

No information was found on the reproductive or teratogenic effects of sesamol in humans.

2. Animal Data

No studies were found in the literature concerning the reproductive or teratogenic effects of sesamol in animals. However, it was reported that this compound caused aspermatogenesis following testicular injection in mice (see V.D.).

F. Genetic Toxicology

1. Procaryotic Data

Salmonella typhimurium The mutagenicity of sesamol was evaluated in the Ames test using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538. In the presence of metabolic activation, sesamol at a concentration of 33-3333 µg/plate, dissolved in dimethylsulfoxide, was non-mutagenic. In addition, sesamol was non-mutagenic without metabolic activation at a concentration of 100-5000 µg/plate [CCRIS, 1990].

2. Eukaryotic Data

mouse lymphoma In the mouse lymphoma assay in strain L5178Y (TK+/-), sesamol at a concentration of 35-215 µg/ml, dissolved in dimethylsulfoxide, was found to be mutagenic in the absence of metabolic activation [CCRIS, 1990]. Sesamol at a concentration of 8-26 µg/ml dissolved in dimethyl sulfoxide was also mutagenic in the presence of metabolic activation [CCRIS, 1990].

G. Other Toxicological Effects

1. Immunotoxicity

No information was found on the immunotoxicity of sesamol in humans or animals.

2. Neurotoxicity

No information was found on the neurotoxicity of sesamol in humans or animals.

3. Biochemical Toxicology

in vivo,
human In a study concerning the transport mechanism of sesamol in the human body, an equilibrium distribution of sesamol between human blood plasma and cellular constituents in plasma-red blood cells was determined to be in the range of 0.2 to 2.0 micrograms sesamol/ml . The distribution of sesamol in plasma-red cells (1:1) was found to be 55% by albumin of plasma proteins, 15% by plasma water, 20% by hemoglobin, and 10% by red cell water. Distribution ratios of sesamol for red cells/saline varied from 1.9 to 2.7 in the pH range of 6.7-8.5 [Bryson and Bischoff, 1970].

in vitro,
in vivo, *humans*,
rats Sesamol was found to convert oxymethemoglobin (HbO_2) into methemoglobin (metHb) *in vitro* at pH 7 at 25°C in human red blood cells. Sesamol transformed HbO_2 and deoxyhemoglobin into metHb at pH 6 and 8 but the process was faster at pH 6. The amount of metHb formed was proportional to the HbO_2 concentration. *In vivo*, no apparent formation of metHb from hemoglobin occurred in rats at a single dose of 50 to 60 mg/kg sesamol [Kikugawa *et al.*, 1981].

in vitro,
human Sesamol produced methemoglobin (metHb) from hemoglobin A (oxyhemoglobin {oxyHb} and deoxyhemoglobin) and from red blood cells. MetHb formation was proportional to the concentration of oxyHb at pH 7. Sesamol induced metHb formation was influenced by inositol hexaphosphate (IHP) which enhanced the transformation of oxyHb and inhibiting the transformation of deoxyhemoglobin [Kurechi *et al.*, 1980].

in vitro,
rat Sesamol was metabolized to carbon monoxide *in vitro* by NADPH-reduced male Sprague-Dawley rat liver microsomes [Yu *et al.*, 1979].

in vitro,
rabbit The inhibitory effect of sesamol and other methylene dioxyphenyl (MDP) compounds on nasal cytochrome P-450-dependent hexamethylphosphoramide N-demethylase in male white New Zealand rabbits was investigated. The nasal mucosa contains high concentrations of cytochrome P-450 dependent activities. These are important in the removal of deposited odorants. If this activity is inhibited the metabolism of concurrently or subsequently inhaled compounds may be altered. The results from using nasal microsomes were compared with results using liver microsomes. Ten microliters of a 700 mM solution of sesamol in ether was combined with 10 mM nicotinamide-adenine dinucleotide phosphate (NADPH), and added to microsomes prepared from the nasal tissues of rabbits. An apparent type III spectrum formed upon the addition of NADPH to nasal microsomes in the presence of sesamol. This does not occur in liver microsomes, where an oxidized minus reduced type spectrum has been observed. This has been explained as possibly the result of benzoquinone formation [Dahl and Brezinski, 1985].

in vitro,*species unspecified* The rate at which nitrate in dilute aqueous solutions is decreased due to reaction with sesamol by combining 0.1 mM NaNO2 in citrate buffer with 1.0 mM of sesamol at a pH of 2 and 3 was determined. Sesamol reacted with most of the nitrite after 20 minutes at pH 2.0 and 60 minutes at pH 3.0 producing a nitrosesamol (3,4-methylene dioxy-6-nitrosophenol). In order to achieve a quantitative formation of nitrosesamol, the authors stated

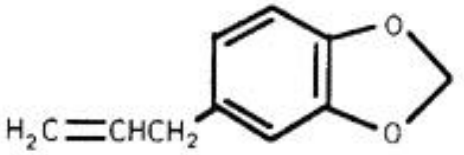
that there needed to be an excess of sesamol [Kurechi *et al.*, 1979].

in vitro, species unspecified The effect of sesamol on n-nitrosamine formation has been studied *in vitro* using dimethylamine, which slowly undergoes n-nitrosation in the presence of nitrite under acidic conditions. Dimethylamine and nitrite were incubated at pH 3 and 5 with sesamol at a concentration of 1, 20, 50, or 100 mM. Sesamol was found to inhibit the n-nitrosation of dimethylamine by 40-50%. A low concentration of 1 mM sesamol accelerated nitrosamine formation at pH 5, but had no effect on its formation at pH 3 [Kurechi *et al.*, 1979].

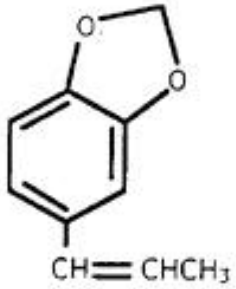
intraperitoneal, rat Male Wister albino rats received daily intraperitoneal injections of 150 mg/kg sesamol in corn oil for 3 days. Sesamol did not form a metabolic complex with cytochrome P450 [Fennel and Bridges, 1979].

VI. STRUCTURE ACTIVITY CONSIDERATIONS

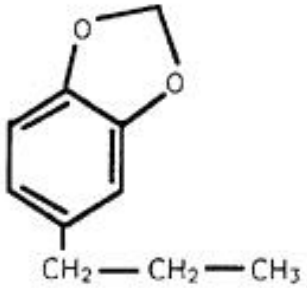
The basic moiety of sesamol, safrole, isosafrole, and dihydrosafrole is methylenedioxyphenyl (see below). The latter 3 compounds have been shown to be carcinogenic in mice and rats. Safrole and isosafrole produced liver tumors following oral administration in rats and mice. Safrole also produced liver and lung tumors following subcutaneous injection into infant male mice. Oral administration of dihydrosafrole produced tumors of the esophagus in rats, liver tumors in male mice, and an increased incidence of lung tumors in both male and female mice [IARC, 1976].



Safrole



Isosafrole



Dihydrosafrole

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APPENDIX I. ON-LINE DATABASES SEARCHED		
-	DATE OF SEARCH	TIME PERIOD
BRS:	-	-
HZDB	September, 1990	-
DIALOG:	-	-
Agricola	September, 1990	1970-1990
Agris International	September, 1990	1974-1990
Aquatic Sciences Abstracts	September, 1990	1974-1990
Biosis Previews	September, 1990	1969-1990
CAB Abstracts	September, 1990	1972-1990
Cancerlit	September, 1990	1963-1990
Chem Bus Newsbase	September, 1990	1984-1990
Chemical Exposure	September, 1990	1974-1987
Compendex Plus	September, 1990	1970-1990
CRIS USDA	September, 1990	-
Embase	September, 1990	1974-1990
Environline	September, 1990	1970-1990
Environmental Bibliography	September, 1990	1974-1990
Federal Register	September, 1990	1977-1990
Foods Adlibra	September, 1990	1974-1990
FSTA	September, 1990	1969-1990
Life Sciences Collection	September, 1990	1978-1990
Medline	September, 1990	1966-1990
NTIS	September, 1990	1964-1987

Occupational Safety and Health	September, 1990	1973-1990
PTS Newsletter	September, 1990	1987-1990
PTS Prompt	September, 1990	1972-1990
Pollution Abstracts	September, 1990	1970-1990
Trade and Industry ASAP	September, 1990	1983-1990
-	-	-
MEAD:	-	-
Nexis/Lexis-BNA ENV	August, 1990	-
-	-	-
NLM:	-	-
Chemline	August, 1990	-
HSDB	August, 1990	-
RTECS	August, 1990	-
Toxline 65	September, 1990	1965-1980
Toxline	August, 1990	1981-1990
Toxlit	August, 1990	1981-1990
Toxlit 65	August, 1990	1965-1990
-	-	-
STN:	-	-
CA	August, 1990	1967-1990
Chemlist	August, 1990	-
CCRIS	November, 1990	-

APPENDIX II. SAFETY INFORMATION

HANDLING AND STORAGE

Sesamol is stable under normal laboratory conditions. It is incompatible with strong oxidizing agents [Lenga, 1988].

EMERGENCY FIRST AID PROCEDURES

Eye: First check the victim for contact lenses and remove if present. Flush victim's eyes with water or normal saline solution for 20 to 30 minutes while simultaneously calling a hospital or poison control center. Do not put any ointments, oils, or medication in the victim's eyes without specific instructions from a physician. Immediately transport the victim to a hospital even if no symptoms (such as redness or irritation) develop.

Skin: IMMEDIATELY flood affected skin with water while removing and isolating all contaminated clothing. Gently was affected skin areas thoroughly with soap and water. If symptoms such as inflammation or irritation develop, IMMEDIATELY call a physician or go to a hospital for treatment.

Inhalation: IMMEDIATELY leave the contaminated area and take deep breaths of fresh air. If symptoms (such as wheezing, coughing, shortness of breath, or burning in the mouth, throat, or chest) develop, call a physician and be prepared to transport the victim to a hospital.

Provide proper respiratory protection to rescuers entering an unknown atmosphere. Whenever possible, Self-Contained Breathing Apparatus (SCBA) should be used.

Ingestion: If the victim is conscious and not convulsing, give 1 or 2 glasses of water to dilute the chemical and IMMEDIATELY call a hospital or poison control center. Be prepared to transport the victim to a hospital if advised by a physician.

If the victim is convulsing or unconscious, do not give anything by mouth, ensure that the victim's airway is open and lay the victim on his/her side with the head lower than the body. DO NOT INDUCE VOMITING. IMMEDIATELY TRANSPORT THE VICTIM TO A HOSPITAL.

PROTECTIVE EQUIPMENT

Eye: Safety goggles

Gloves: Two pairs of dissimilar protective gloves shall be worn when handling the neat chemical, otherwise one pair. When contact with this chemical has been known to occur, change gloves immediately.

Clothing: Minimally, a disposable laboratory suit (e.g. Tyvek ®) shall be worn, as specified in the most current NTP Statement of Work or NTP Health and Safety Minimum Requirements.

Respiratory A NIOSH-approved chemical cartridge respirator with an

Protection: organic vapor and high-efficiency particulate filter cartridge.

EXTINGUISHANT

Dry chemical, carbon dioxide or halon extinguisher

MONITORING PROCEDURES

There is no NIOSH analytical method reported in the NIOSH Manual of Analytical Methods for sesamol.

SPILLS AND LEAKAGE

Persons not wearing the appropriate protective equipment and clothing shall be restricted from areas of spills until cleanup has been completed. When exposure to unknown concentrations may occur, air-purifying respirators may not be used. Chemical cartridge respirators with organic vapor cartridges may not be used when airborne concentrations exceed 1000 ppm.

If sesamol is spilled the following steps shall be taken:

1. In order to prevent dust formation, use moistened paper towels to clean up a solid spill. Avoid dry sweeping.

2. Clean the spill area with dilute alcohol (approximately 60-70%) followed by a strong soap and warm water washing.

3. Dispose of all absorbed material as hazardous waste.

DECONTAMINATION OF LABORATORY EQUIPMENT

TDMS Terminal: Whenever feasible, a protective covering (e.g.,plastic wrap) shall be placed over the keyboard when in use.

General Equipment: Before removing general laboratory equipment (i.e., lab carts, portable hoods and balances) from animal dosing rooms and/or chemical preparation areas, a decontamination process shall be conducted in addition to routine housekeeping procedures.

WASTE MANAGEMENT AND DISPOSAL PROCEDURES

Waste Management:If an inhalation study is to be conducted, all exhaust air from the inhalation chamber must be cleaned with appropriate air cleaning devices unless the laboratory has informed local and state air pollution regulatory agencies of both the laboratory's operating practices and the potential hazards of the chemical's in use. Compliance with all federal, state and local air pollution laws and regulations is required. A specific air cleaning system design must consider the specific conditions of the laboratory (eg., air flow rates and volumes, mixing of exhaust streams, size of inhalation chamber, etc.) and the dosing regimen selected. Air cleaning systems designs must be described by the laboratory and approved by the NTP Office of Laboratory Health and Safety.

Waste Disposal: Securely package and label, in double bags, all waste material. All potentially contaminated material (i.e., carcasses, bedding, disposable cages, labware) shall be disposed of by incineration in a manner consistent with federal (EPA), state, and local regulations or disposed of in a licensed hazardous waste landfill.