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Safety Assessment of Castoreum Extract as a Food Ingredient

G. A. Burdock
Burdock Group, Washington, DC, USA

Castoreum extract (CAS NO. 8023-83-4; FEMA NO. 2261) is a natural product prepared by direct hot-alcohol extraction of castoreum, the dried and macerated castor sac scent glands (and their secretions) from the male or female beaver. It has been used extensively in perfumery and has been added to food as a flavor ingredient for at least 80 years. Both the Flavor and Extract Manufacturers Association (FEMA) and the Food and Drug Administration (FDA) regard castoreum extract as generally recognized as safe (GRAS). Acute toxicity studies in animals indicate that castoreum extract is nontoxic by both oral and dermal routes of administration and is not irritating or phototoxic to skin. Skin sensitization has not been observed in human subject tests. Castoreum extract possesses weak antibacterial activity. A long historical use of castoreum extract as a flavoring and fragrance ingredient has resulted in no reports of human adverse reactions. On the basis of this information, low-level, long-term exposure to castoreum extract does not pose a health risk. The objective of this review is to evaluate the safety-in-use of castoreum extract as a food ingredient.

Keywords Castoreum Extract, Flavor Ingredient, GRAS

Castoreum extract and its derivatives are primarily used as a food flavor ingredient and as a fragrance in cosmetics or as a fixative (stabilizing agent) in soaps, creams, lotions, and perfumes; it has also been used in folk medicine, but has no modern medicinal uses. Castoreum extract (CAS NO. 8023-83-4; FEMA NO. 2261) is a natural product prepared by direct hot-alcohol extraction of castoreum, the dried and macerated castor sac scent glands (and their secretions) of the male or female beaver (Order, Rodentia; Family, Castoridae) (Arctander 1960). Used extensively in perfumery (Opdyke 1973), castoreum extract has also been added to food as a flavor ingredient since at least 1920 (Burdock 1995). It is used in most food and beverage categories and is especially useful as an ingredient in vanilla flavored foods. Castoreum extract has been approved for use by the Flavor and Extract Manufacturers Association (FEMA) and Council of Europe (CoE) and is listed by the Food and Drug Administration (FDA) as generally recognized as safe (GRAS). This review evaluates the safety-in-use of castoreum extract as a food ingredient.

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Address correspondence to George A. Burdock, 888 17th Street NW, Suite 810, Washington, DC 20006, USA. E-mail: gburdock@burdockgroup.com

DESCRIPTION, NATURAL OCCURRENCE, SOURCES

Castoreum is a strong-smelling, brown creamy secretion produced in the paired anal castor sacs of beavers (Tang, Webster, and Muller-Schwarze 1995). The castoreum is mixed with urine and used to coat the fur and tail for water repellence (Lawrence 1977; Walro and Svendsen 1982) and to mark territory, the beaver uses mud piles built at the banks of their ponds, topped with the strong-smelling substance (Muller-Schwarze 1992). Much as trappers have long used castoreum secretion lures to attract beavers, it has also been used since antiquity in perfumes. Castoreum has also been used as a medicant, as it has been reported that the Romans burned castoreum in lamps, believing the fumes to be an abortifacient (Muller-Schwarze 1992), although castoreum or its derivatives are not used in modern medicine.

Castoreum (*castoreum* [Fr.], *bibergeil* [Ger.], *castoreo* [Sp.], *castoreo* [It.]) is the name given to the dried castor sac preputial follicles and glandular secretions from North American (Alaska, Canada) beaver (*Castor canadensis* Kubl.) and Siberian beaver (*Castor fiber* L.), which is often obtained as a by-product of the fur industry. The sacs or pouches are usually sun dried and occasionally dried over burning wood, which adds a "smoky" odor (Dyer 1994). The Canadian pouches are wrinkled, pear shaped, almost flat, 6 to 15 cm long, and 4 to 8 cm wide. Siberian pouches are slightly larger, ovoid, and smooth (Burdock 1995). Canadian castoreum is generally considered superior to the Siberian material (Arctander 1960). Fresh pouches contain a yellowish, butterlike mass, with a sharp, fetid, and aromatic odor. Upon drying, it becomes dark brown, hard, and resinous (Burdock 1995). Castoreum has a warm, animal-sweet odor, becoming more pleasant with dilution. Occasionally a birch, tar-like, musky odor is also perceptible (Burdock 1997).

It is prepared for commercial use in several forms including castoreum extract/tincture[1] (CAS NO. 8023-83-4; FEMA NO. 2261; CoE NO. 3002 (554)) and liquid[2] (CAS NO. 977016-89-9; FEMA NO. 2262; CoE NO. 3002 (554)). Manufacturing intermediates and derivatives are referred to as oil (castorem oil, *oils castoreu*), absolute, and resinoid/concrète.

SPECIFICATIONS

Castoreum extract is prepared by hot-alcohol extraction of the macerated castoreum pods of the beaver, whereas the resinoid/concrète is prepared from dried, ground pouches extracted with benzene (yielding about 20% of a brown "resinoid" [Arctander 1960]) or more often, petroleum ether (Burdock 1995). The "absolute" is a hot-alcohol extract of the resinoid/concrète, which yields 75% to 80% of a dark brown, soft unctuous mass (Arctander 1960; Burdock 1995). The various extracts (whether alcoholic, benzene, or petroleum ether) are complex mixtures consisting of various combinations of an aggregate number of more than 62 compounds identified to date (Maurer and Ohloff 1976; Lederer 1946, 1949; Walbaum and Rosenthal 1927; Tang, Webster, and Muller-Schwarze 1995; Valenta, Khaleque, and Rashid 1960). The castoreum extract has a flash point of $>200^{\circ}$C and a vapor pressure of $\sim$0.3 mm Hg at 20°C (Burdock 1997). The majority ($\leq$80%) of castoreum extract consists of an alcohol-soluble resinoid material containing acidic, basic, phenolic, nitrogenous, and neutral compounds (alcohols, aldehydes, and ketones). It contains a butter-like material made of albumins, fats, urates, and salts (1.4% calcium phosphate) and a layer of castorin (0.33% to 2.5%), a waxy crystalline substance separated from the hot alcoholic extract on cooling. The remainder consists of volatile oils (1% to 2%) and other minor constituents (Leung and Foster 1996; Arctander 1960; List and Horhammer 1976; Poucher 1974).

ECONOMIC USES

Castoreum extracts are used as flavor components in most major categories of foods (particularly vanilla flavored), including alcoholic and nonalcoholic beverages, frozen dairy desserts, candy, baked goods, gelatins and puddings, and meat and meat products (Burdock 1995).

The tincture (maximum use level of 0.4%) is mainly used in cosmetics as a fragrance or as a fixative in soaps, creams, lotions, and perfumes (especially men's and oriental perfumes) (Opdyke 1973). It blends well with other fragrances including ambra notes, calamus, canaga, cedarwood, labdanum products, isoeugenol, oakmoss products, sandalwood oil, veratraldehyde, zingerone, and others (Arctander 1960).

[1]Any extract prepared using alcohol as the extractant may be called a "tincture."

[2]This term is otherwise undefined, but presumably any derivative of the alcoholic extract.

There are no known pharmaceutical uses for castoreum, but it has been used in traditional medicine as an analgesic, analeptic, and nervine agent and to treat conditions such as amenorrhea, dysmenorrhea, hysteria, and restless sleep (Leung and Foster 1996).

REGULATORY HISTORY

The FDA regulates castoreum extract (exclusively from *Castor canadensis* Kubl. and *Castor fiber* L.) as GRAS for use in human food (21 CFR §182.50) and animal food (21 CFR §582.50) (Table 1). The Council of Europe (2000) has established a category 5 rating for castoreum extract (NO. 3002 (554)) in its listing of natural sources of flavorings, setting upper level use limits for food and beverages of 40 mg/kg and 90 mg/kg, respectively. A CoE rating of 5 indicates additional toxicological and/or chemical information is required and that the substance could temporarily be acceptable provided that any limits set for the active principles or the other chemical components are not exceeded. FEMA has recognized castoreum extract as GRAS (NO. 2261) for use as a flavor ingredient (Hall and Oser 1965) (Table 2).

Although no average daily intake (ADI) *per se* has been promulgated by FDA, the FEMA PADI (possible average daily intake) represents an exposure amount judged generally recognized as safe (GRAS) by FEMA. Flavor ingredients are generally used at two different concentrations, at a lower concentration (i.e., the "usual use level"), where the final flavor is a combination of the organoleptic effects of the combination and not of a single entity, whereas at the higher (maximum) level of use, the final flavor may be distinctive for that one substance used at a greater concentration than other the other constituents. Therefore, FEMA, in its GRAS process, reviews the safety-in-use of the highest use level (average maximum use level), not the average use level or the greatest maximum use level possible. The FEMA PADI is based on maximum use level value, but only mean food consumption values (based on Market Research Corporation of America mean frequency of eating and USDA mean portion size of 34 general food categories). Therefore, the FEMA PADI (given in mg/person/day) is the *mean* consumption of foods containing the *maximum* amount of flavor ingredient. The conservatism of the PADI method assumes that the maximum amount of substance is added to the entire food category, not just the substance within that category. For example, the consumption of a substance added only to marshmallow cream cookies (a rarely eaten food) would account for very little consumption, but the FEMA assumption is that the substance is added to *all* baked goods, not just the small portion of baked goods represented by an exotic cookie. The PADI values for castoreum extract and castoreum liquid are 15.48 and 0.85 mg/day, respectively.

CONSUMPTION

The per capita estimate of intake (maximum survey-derived daily intake or MSDI) is based on "disappearance data" from

TABLE 1
Regulatory status of castoreum extract

Agency	Citation no./title	Food category	Permitted functionality	Use limits
FDA	21 CFR §182.50 (human) 21 CFR§582.50 (animals)	No food category restrictions except as otherwise prohibited by a standard of identity	Certain other spices, seasonings, essential oils, oleoresins and natural extracts that are generally recognized as safe for their intended use	No use limits except as determined by cGMP
CoE	3002 (554)	Category 5: Additional toxicological and/or chemical information is required. Could temporarily be acceptable provided that any limits set for the active principles or the other chemical components are not exceeded	Natural flavoring sources and preparations	Upper levels of use: Food (40 mg/kg) Beverage (90 mg/kg)
FEMA	2261 GRAS List 3		Flavor ingredient	

CoE = Council of Europe; FDA = US Food and Drug Administration; FEMA = Flavor and Extract Manufacturers' Association; cGMP = current Good Manufacturing Practices; GRAS = Generally Recognized As Safe.

periodic surveys conducted by the National Academy of Sciences under contract to FDA (Anonymous 1989). The last survey was conducted in 1987 and was based on voluntary reporting by manufacturers of the volume of ingredients produced during the survey year. The assumption is that there is a finite amount of substance available and it is ingested regardless of source at the retail level. The method is easy to use because it divides the total yearly poundage by the population in the survey year (243.9 million in 1987) and the number of days per year.

TABLE 2
Use levels of castoreum extract and castoreum liquid (Hall and Oser 1965)

	Castoreum extract (FEMA no. 2261)		Castoreum liquid (FEMA no. 2262)	
	Use level (ppm)		Use level (ppm)	
Food category	Usual	Max.	Usual	Max.
Alcoholic beverage	79.59	93.69	NR	NR
Baked goods	62.28	68.47	4.87	4.87
Chewing gum	18.60	42.09	0.01	0.01
Frozen dairy	24.39	26.26	0.70	1.46
Gravies	0.30	0.60	NR	NR
Gelatin pudding	43.58	47.34	0.96	1.25
Hard candy	24.17	24.17	9.09	9.09
Meat products	1.00	2.00	NR	NR
Nonalcoholic beverage	24.21	29.77	1.21	1.72
Soft candy	37.38	44.10	2.92	2.92

FEMA = Flavor and Extract Manufacturers' Association; NR = not reported; ppm = parts per million.

Some considerations are necessary in the use of this survey data: (1) because not all producers participate, it is generally held that the amount reported is a fraction of the actual volume and; (2) because not all persons eat all foods each day in each category in which the substance may be found and conversely, some consumers may seek out the substance, therefore, distribution of consumption may be uneven. In order to compensate for these variables, FDA assumes (1) only 60% of the actual value was reported and (2) only 10% of the U.S. population (243.9 million in 1987) consumes 100% of the calculated amount (Anonymous 1997). The annual consumption of castoreum extract (FEMA no. 2261) and castoreum liquid (FEMA no. 2262) determined by National Academy of Sciences (NAS) is given in Table 3.

Table 4 compares the FDA estimated individual consumption and FEMA PADI for castoreum extract and castoreum liquid. Based on the annual consumption for 1987, individual consumption calculated by FDA for castoreum extract or castoreum liquid was 0.00008192 mg/kg/day[3] or 0.0001285 mg/kg/day, respectively (Clydesdale 1997). The estimated consumption values are

[3]Consumption is based on the assumption that an individual weighs 60 kg.

TABLE 3
Annual consumption of castoreum extract and castoreum liquid (Anonymous 1989)

Substance	Year	Poundage
Castoreum extract (FEMA no. 2261)	1970	NR
	1975	NR
	1982	500
	1987	97
Castoreum liquid (FEMA no. 2262)	1970	NR
	1975	NR
	1982	183
	1987	152

FEMA = Flavor and Extract Manufacturers' Association; NR = not reported.

well below the GRAS values determined by FEMA at 0.258 and 0.014 mg/kg/day, respectively.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Of the two acute toxicity studies for castoreum extract reported in the literature, the original data are not available but rather the studies were summarized by Opdyke (1973). In one study, an acute oral LD_{50} >5 g/kg was determined in rats (N = 10 per dose), with a 20% mortality recorded at the highest dose of 5 g/kg (Opdyke 1973). In the second study, an acute dermal LD_{50} >5 g/kg was established in rabbits (N = 6 per dose) as there were no deaths noted at any dose up to the highest dose of 5 g/kg (Opdyke 1973).

Dermatotoxicity

Irritation

Opdyke (1973) reported the results from two separate acute skin irritation studies conducted in hairless mice and rabbits. No irritant effects were observed from castoreum tincture applied to skin on the backs of mice or intact or abraded skin of rabbits (Opdyke 1973).

TABLE 4
FDA individual consumption levels and FEMA PADI for castoreum extract and castoreum liquid

Substance	FDA individual consumption (mg/kg/day)	FEMA PADI (mg/kg/day)
Castoreum extract	0.00008192	0.258
Castoreum liquid	0.0001285	0.014
Total (extract + liquid)	0.00021042	0.272

FDA = US Food and Drug Administration; FEMA = Flavor and Extract Manufacturers' Association; PADI = possible average daily intake.

Phototoxicity

Mice (Skh:hairless1) and miniature swine were used to measure the phototoxicity of 160 fragrance raw materials, including castoreum tincture, by Forbes and coworkers (Forbes, Urbach, and Davies 1977). In this study, mice (N = 12) or swine (N = 2) received a single application of 20 μl castoreum tincture on a 2-cm^2 site on the back. The test sites were then irradiated 30 min after application by fluorescent blacklight (six mice) or Xenon lamp (six mice) and the sites examined at 4, 24, 48, 72 and 96 h. The authors reported that there were no dermal phototoxicity signs observed.

Tumor Promotion

The tumor-promoting capacity of cigarette smoke condensate (CSC) prepared from cigarettes containing 150 flavor ingredients including castoreum extract (0.1 ppm) was evaluated in female SENCAR mice (Gaworski et al. 1999). Mice (N = 35–50) were initiated with a single 50 μg dose of 7,12-dimethylbenz(a)anthracene (DMBA) in 0.1 ml acetone applied to a shaved 2 × 3-cm dorsal skin site. Beginning 1 week after DMBA initiation, mice were treated three times per week for 26 consecutive weeks with 10 or 20 mg CSC in 0.1 ml acetone and examined at 27 weeks post DMBA initiation. The investigators reported no substantial changes in tumor promotion capacity from CSC prepared from cigarettes with flavor ingredients, including castoreum extract, compared with CSC prepared from cigarettes without flavor ingredients (Gaworski et al. 1999).

Antimicrobial Activity Studies

The antimicrobial activity of 512 fragrance materials, including castoreum absolute, was evaluated by Morris, Khettry, and Seitz (1979) using a standardized Petri plate procedure. A single dose of 50% castoreum absolute (~1 mg) diluted into 10% ethanol spotted onto a 10-mm paper disk was tested for its ability to retard the growth on agar plates around the disk of *Staphloccocus aureus*, *Echerichia coli*, *Candida albicans,* and, if active in the others, a *Diphtheroid* (possibly *Corynebacterium* but not confirmed). The results showed that castoreum absolute was positive in retarding the growth of *S. aureus*, but not the others. No further testing was conducted to determine minimum inhibitory concentration (Morris, Khettry, and Seitz 1979).

Human Studies

Opdyke (1973) described two separate human studies on the dermal effects of castoreum. No irritant effect was found from application of a 4% solution of castoreum in petrolatum on a 48-h skin irritation patch test on the backs of five male volunteers (Opdyke 1973). Additionally, no skin sensitization was observed when a 4% solution of castoreum in petrolatum was studied in a maximization provocative patch test (Opdyke 1973). In this experiment, 25 male volunteers were patched on the volar forearms

for five alternate 48-h periods. Prior to the castoreum challenges, they were pretreated for 24 h with 5% aqueous sodium lauryl sulphate (SLS) and for 1 h with 10% aqueous SLS at challenge.

SUMMARY

Castoreum extract is approved by FDA and FEMA as a GRAS substance for direct addition to food as a flavoring agent. It is also approved by the Council of Europe as a food flavoring. The FEMA approved average use level (i.e., the PADI) represents a possible intake of castoreum extract or castoreum liquid of 15.48 mg/day or 0.85 mg/day, respectively. FDA per capita estimate of daily intake is 0.00008192 mg/kg/day (0.0049 mg/day) and 0.0001285 mg/kg/day (0.00771 mg/day) for castoreum extract and castoreum liquid, respectively. Therefore, the per capita estimates of daily intake of both substances are well below amounts deemed generally recognized as safe by FEMA.

Castoreum is primarily used as a food flavor ingredient and as a fragrance in cosmetics or as a fixative in soaps, creams, lotions and perfumes. There are reports of castoreum used as a traditional medicine as an analgesic, analeptic, and nervine agent and to treat conditions such as amenorrhea, dysmenorrhea, hysteria, and restless sleep (Leung and Foster 1996). However, castoreum is not used in modern pharmaceuticals.

The biological and toxicological data reported for castoreum extract or other castoreum products are minimal. The acute oral and dermal toxicity of castoreum is low. Oral administration of 5 g/kg to rats resulted in 20% lethality, whereas dermal application of 5 g/kg to the back of rabbits did not cause any deaths. It is nonirritating to the skin of humans, mice, and rabbits and is not phototoxic to mice or miniature swine. No carcinogenicity or mutagenicity studies were identified, but one tumor promoter study did report that cigarette smoke condensate prepared from cigarettes containing 150 flavor enhancers, including 0.1 ppm castoreum extract, did not alter tumor promotion. It was also identified as possessing a weak antibacterial activity.

CONCLUSION

On the basis of the above, consumption of castoreum extract is considered safe at present levels of use. Long historical use of castoreum extract as a flavoring and fragrance ingredient has resulted in no reports of human adverse reactions. Although the toxicological database is limited, existing data suggest that castoreum extract is nontoxic. On the basis of data presented herein, consumption of castoreum extract, at historical levels of use, presents no concern for its safe use.

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