Toxicological Evaluation of Myristicin

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ABSTRACT   Myristicin, or methoxysafrole, is the principal aromatic constituent of the volatile oil of nutmeg, the dried ripe seed of *Myristica fragrans.* Myristicin is also found in several members of the carrot family (*Umbelliferae*). Several intoxications have been reported after an ingestion of approximately 5 g of nutmeg, corresponding to 1–2 mg myristicin/kg body weight (b.w.). Although these intoxications may be ascribed to the actions of myristicin, it is likely that other components of nutmeg may also be involved. The metabolism of myristicin resembles that of safrole. No information is available, however, concerning the quantitative importance of the different metabolic pathways. The acute toxicity of myristicin appears to be low. No toxic effects were observed in rats administered myristicin perorally at a dose of 10 mg/kg b.w., while 6–7 mg/kg b.w. may be enough to cause psychopharmacological effects in man. A weak DNA-binding capacity has been demonstrated, but there are no indications that myristicin exerts carcinogenic activity in short-term assays using mice. Intake estimations indicate that nonalcoholic drinks may be the most important single source of myristicin intake. Based on available data, it seems unlikely that the intake of myristicin from essential oils and spices in food, estimated to a few mg per person and day in this report, would cause adverse effects in humans. It is, however, at present not possible to make a complete risk assessment, as studies regarding genotoxicity and chronic toxicity, including reproductive toxicity and carcinogenicity, are still lacking. *Nat. Toxins 5:186–192, 1997.*   © 1998 Wiley-Liss, Inc.

INTRODUCTION

Myristicin, or methoxysafrole, is the principal aromatic constituent of the volatile oil in nutmeg, the dried ripe seed of *Myristica fragrans* (Fam. *Myristicaceae*). The seed yields 7–16% volatile oil [List and Hörhammer, 1976]. The content of myristicin in the oil is approximately 4–8% [Leung, 1980]. In addition to isolation from natural sources, it is also possible to obtain myristicin synthetically [Shulgin, 1966].

Apart from nutmeg and mace (the aril surrounding the shell enclosing the nutmeg seed), myristicin has been reported to be present in a number of members of the carrot (*Umbelliferae)* family: for instance, in dill (*Anethum graveolens),* celery (*Apium graveolens),* parsnip (*Pastinaca sativa*), parsley (*Petroselium crispum*), and carrot (*Daucus carota*) [Hall, 1973]. Myristicin has also been reported to occur as a minor constituent in oil of black pepper (*Piper nigrum)* [Richards and Jennings, 1971], but no quantitative data have been found. In addition to the spices and edible plants mentioned above, myristicin has also been reported to be present in some plants that are unlikely to be used for flavouring purposes, such as Scotch lovage (*Levisticum scoticum),* Harvest fennel (*Ridolfia segetum),* and *Oenanthe stolonifera* [Shulgin, 1966].

Toxic effects have been experienced by individuals consuming nutmeg in quantities exceeding 5 g [Green, 1959; Mack, 1982]. Such intoxications have occurred by accident or voluntarily, often in order to achieve a mind-altering

experience, since myristicin, and probably also other components of nutmeg, have hallucinogenic effects. Since the Middle Ages, nutmeg has been used as a carminative, stimulant, narcotic, emmenagogue, and abortifacient [Hall, 1973]. At present, the use of nutmeg is confined largely to exploitation of its properties as a flavouring agent.

The purpose of this report has been to estimate the daily intake of myristicin, to review the available toxicity data, and to assess the risk which may be associated with consumption of essential oils and spices that contain myristicin. The evaluation was prepared for the Council of Europe Committee of Experts on Flavouring Substances.

PHYSICAL AND CHEMICAL DATA

Chemical name: 1-allyl-5-methoxy-3,4 methylene-dioxybenzene (Fig. 1); CAS No: 607-91-0; Empirical formula: $C_{11}H_{12}O_3$; Molecular weight: 192.22 [Merck Index, 1989]; Description: Colorless oil [Merck Index, 1989].

HUMAN INTAKE

The highest levels of myristicin are found in nutmeg (*Myristica fragrans*). As can be concluded from Table I, nutmeg contains approximately 1.3% and mace 2.7% myris-

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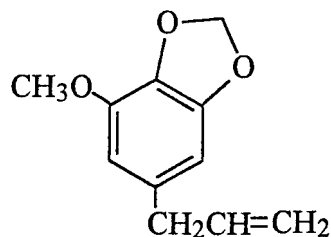
Fig. 1. Structural formula of myristicin.

ticin if the content is calculated from the highest reported levels. The contents of myristicin in some other edible plants are also included in Table I.

The intake of myristicin from spices (Table II) and essential oils (Table III) was estimated using food intake data from the British adult study [Gregory et al., 1990]. Food items spiced with nutmeg or dill were considered to be the main sources of myristicin. As can be seen in Table II, the myristicin intake from dill appears to be very limited. The highest levels of myristicin are found in food spiced with mace, with nonalcoholic drinks as the most important single source of intake. Due to its lower content of myristicin, food spiced with nutmeg generally contains lower levels of myristicin than food spiced with mace.

In addition to the food groups listed in Table II, which were considered to contribute most to the intake of myristicin, mace and nutmeg are also reported to be used in soups, snack foods, gravies, condiments, breakfast cereals, fats, oils, milk products, fruit juices, sweet sauce, gelatins, puddings, and alcoholic beverages [Burdock, 1995].

The intake of myristicin from essential oils seems to be lower than that from spices (Table III). In accordance with the intake from spices, dill essential oil contributes to a very minor degree to the total intake of myristicin, and again mace appears to be the main source of intake, with nonalcoholic drinks giving the largest contributon to the total intake. Apart from the food groups included in Table III, which were considered to result in the largest intakes of myristicin, mace and nutmeg essential oils are also reported to be used in gelatins, puddings, sweet sauce, condiments, alcoholic beverages, and chewing gum [Burdock, 1995].

In conclusion, an approximate estimate of the average total intake of myristicin from all sources appears to be in the order of a few mg per person and day.

KINETICS AND METABOLISM DATA
In vitro

The metabolism of myristicin has been investigated in several types of in vitro systems [Braun and Kalbhen, 1973; Casida et al.,1966; Kamienski and Casida, 1970; Scheline, 1991].

In one experiment, using perfused liver or rat liver homogenates, it was shown that myristicin was converted to an amphetamine derivative, 3-methoxy-4,5-methylene-

dioxyamphetamine, by both preparations [Braun et al., 1973]. Oxygenation increased the yield of the metabolite indicating that an oxidation reaction precedes the transamination.

In vivo

The metabolism of myristicin in vivo has been studied in guinea pigs, rats, and mice. Single doses of myristicin in the range of 5–20 mg/kg b.w. were administered by the intraperitonel route (i.p.) to rats and guinea pigs [Oswald et al., 1971], which resulted in the following metabolites in the urine: 1) 3-piperidyl-1-(3′-metoxy-4, 5′- methylenedioxyphenyl)-1-propanon (the major metabolite in rat), and 2) 3-pyrrolindinyl-1-(3′-methoxy-4′, 5′-methylendioxyphenyl)-1-propanone (the major metabolite in guinea pig). In addition, the rat and guinea pig excrete trace quantities of the pyrrolidinyl ketone, and the piperidyl ketone, respectively. No amphetamine-type compounds were detected. The proposed pathway for the formation of these tertiary aminopropiophenones is allylic oxidation of the allylbenzene compounds followed by condensation with a secondary amine to produce the tertiary aminoketone.

The excretion of ^{14}-C-labeled myristicin has been studied in rats and mice [Casida et al., 1966; Kamienski and Casida,1970; Peele, 1976]. In both species the excretion was rapid, as it was nearly completed within 48 hours. Excretion occurred largely via the urinary route in rats [Kamienski and Casida,1970], and via the respiratory air in mice [Braun and Kalbhen, 1973; Casida et al., 1966]. In mice, 61–76% of the administered radioactivity (the methylenedioxy group was labelled) was recovered as CO_2 in the expired air. In contrast, only 25% of the the label was expired as CO_2 in rats. Even less (2%) was expired via this route when 3-^{14}C-myristicin (ringlabelled myristicin) was administered to rats [Peele, 1976]. In rats, very little retention of myristicin was observed in the tissues, after 48 hours [Peele, 1976]. Of the radioactivity remaining in the tissues half of the activity was localized in the liver [Peele, 1976]. No information is available regarding kinetics or metabolism of myristicin in humans.

The following metabolic pathways have been described.

In vitro:

1. Addition of ammonia to the allyl group resulting in an amphetamine derivative (3-methoxy-4,5-methylenedioxyamphetamine) [Braun and Kalbhen, 1973].

2. Demethylation leading to formate and the corresponding cathecol (=5′-hydroxyeugenol) [Casida et al., 1966].

In vivo:

1. Extensive demethylation resulting in formate and the corresponding cathecol (=5′-hydroxyeugenol) [Casida et al., 1966; Kamienski and Casida,1970; Peele, 1976].

TABLE I. Myristicin Content in Some Edible Plants

Botanical name	English name	Essential oil in plant (%)	Myristicin in essential oil (%)	Myristicin (mg/kg)
Anethum graveolens	Dill	2.5–4 in seed[a]	0.7–12 in seed oil[b]	
		0.6–1.5 in herb[a]	2.8–7.6 in herb oil[b]	1,200 in herb (calculated)
Apium graveolens	Celery			0.33 in root[d]
Daucus carota	Carrot	0.4 in root[e]	0.004 in root oil[e]	0.16 in root (calculated)
Myristica fragrans	Nutmeg	7–16 in nutmeg[a]	4–8 in nutmeg oil[b]	13,000 in nutmeg (calculated)
		4–15 in mace[a]	7–18 in mace oil[a]	27,000 in mace (calculated)
Pastinaca sativa	Parsnip			0.002 in root[f]
Petroselium crispum	Parsley	2–7 in seed[a]		727 in plant[c]
		0.06 in leaf[b]		

[a]List and Hörhammer [1976].
[b]Huopalahti and Linko [1983].
[c]Data provided by the International Organization of the Flavour Industry (IOFI), 1995.
[d]MacLeod et al. [1988].
[e]Buttery [1968].
[f]Shulgin [1966].

TABLE II. Estimated Intake of Myristicin from Species*

Species	Food	Level of use of spices (mg/kg)[a]	Myristicin (mg/kg food)[b,c,d]	Intake of food (g)[e] Mean	Intake of food (g)[e] Extreme[f]	Myristicin intake (mg/day) Mean	Myristicin intake (mg/day) Extreme
Dill	Condiments	1,100	1.3	12	32	0.02	0.04
	Meats (fish)	650	0.8	24	78	0.02	0.06
	Pickles (processed vegetables)	310	0.4	5.7	24	0.002	0.01
Mace	Nonalcoholic beverages	1,000	27	130	530	3.5	14
	Backed goods	1,500	40	52	154	2.1	6.2
	Picles (processed vegetables)	360	9.7	5.7	24	0.06	0.2
	Meats	470	13	25	86	0.3	1.1
Nutmeg	Nonalcoholic beverages	350	4.6	130	530	0.6	2.4
	Frozen dairy	1,600	21	18	62	0.4	1.3
	Baked goods	2,600	34	52	154	1.8	5.2
	Pickles (processed vegetables)	990	13	5.7	24	0.07	0.3
	Meats	1,200	16	25	86	0.4	1.4

*The following assumptions were made in the estimations of the myristicin intake: All foods in the food groups listed contain myristicin. This will obviously result in an overestimate. Intake data for ''Condiments'' refers to intake of white sauce. Intake data for ''Meats (fish)'' refers to intake of white fish. Intake data for ''Meats'' containing mace and nutmeg refers to intake of sausages, meat spreads, pates, bolognaise sauce, and curry sauce. ''Nonalcholic beverages'' exclude fruit juice, tea, and coffee. ''Baked goods'' are biscuits, fruit pies, buns, cakes, and pastries.
[a]According to Burdock [1995].
[b]Assuming 0.12% myritistcin in dill.
[c]Assuming 2.7% myristicin in mace.
[d]Assuming 1.3% myristicin in nutmeg.
[e]Intake data were obtained from the British Adult Study [Gregory et al., 1990].
[f]Extreme intake refers to the 97.5%th percentile consumer.

2. Epoxidation leading to several epoxides and their resultant diols, for example: myristin glycol and finally a methylendioxy derivative of phenylacetic acid [Peele, 1976].

3. Allylic hydroxylation to 1′-hydroxymyristicin, 3′-hydroxymyristicin, and finally piperonylic acid (also described as the metylendioxyderivative of benzoic acid [Peele, 1976].

4. Allylic oxidation followed by condensation with a secondary amine to produce a tertiary aminoketone (3-piperidyl-1-(3′-methoxy-4′,5′-methylenedioxylphenyl)-I-propanone and 3-pyrrolidinyl-1-(3′-methoxy-4′,5′-methylene-dioxy-phenyl)-1-propanone)[Peele, 1976; Oswald et al., 1971].

5. Possibly a reduction of the allylic double bond to dihydromyristicin may occur [Peele, 1976].

In conclusion, the metabolism of myristicin broadly seems to resemble that of safrole. No information, however, is available concerning the quantitative importance of the individual metabolic pathways.

TABLE III. Estimated Intake of Myristicin From Essential Oils*

Essential oil from	Food	Level of use of essential oil (mg/kg)[a]	Myristicin (mg/kg food)[b,c,d]	Intake of food (g)[e]		Myristicin intake (mg/day)	
				Mean	Extreme[f]	Mean	Extreme
Dill	Condiments	150	10	12	32	0.1	0.3
	Meats (fish)	51	3.6	24	78	0.09	0.3
	Pickles (processed vegetables)	140	9.8	5.7	24	0.06	0.2
Mace	Nonalcoholic beverages	44	7.9	130	530	!.0	4.2
	Baked goods	77	14	52	154	0.7	2.2
	Candy (sugar confectionary)	260	47	7.2	33	0.3	1.6
	Ice cream	79	14	18	62	0.3	0.9
	Meats	80	14	25	86	0.4	1.2
Nutmeg	Nonalcoholic beverages	14	1.1	130	530	0.1	0.6
	Baked goods	75	6.0	52	154	0.3	0.9
	Candy (sugar confectionary)	19	1.5	7.2	33	0.01	0.05
	Ice cream	13	1.0	18	62	0.02	0.06
	Meats	150	12	25	86	0.3	1.0

*The following assumptions were made in the estimations of the myristicin intake: All foods in the food groups listed contain myristicin. This will obviously result in an overestimate. Intake data for "Condiments" refers to intake of white sauce. Intake data for "Meats (fish)" refers to intake of white fish. Intake data for "Meats" containing mace and nutmeg refers to intake of sausages, meat spreads, pates, bolognaise sauce, and curry sauce. "Nonalcholic beverages" exclude fruit juice, tea, and coffee. "Baked goods" are biscuits, fruit pies, buns, cakes, and pastries.
[a]According to Burdock [1995].
[b]Assuming 7% myritistcin in dill essential oil.
[c]Assuing 18% myristicin in mace essential oil.
[d]Assuming 8% myristicin in nutmeg essential oil.
[e]Intake data were obtained from the British Adult Study [Gregory et al., 1990].
[f]Extreme intake refers to the 97.5%th percentile consumer.

TOXICITY DATA AND TOXICITY EVALUATION
Studies in Experimental Animals
Acute toxicity

An experiment was carried out with 25 white male rats (strain not mentioned). Myristicin was given at dosage levels from 200–1000 mg/kg b.w. Large doses elicited hyperexcitability followed by central nervous system depression. It was concluded that i.p. $LD_{50} > 1.000$ mg/kg in rats [Truitt et al., 1960].

Subacute/subchronic toxicity

Twelve white rats (strain not mentioned) were administered 10 mg/kg b.w. of myristicin daily in the food for 26 days. There were no differences in body weights between the animals receiving myristicin and a control goup. Histological studies of livers/kidneys showed no abnormalities that could be attributed to myristicin.

Chronic toxicity

No studies available.

Reproductive and teratogenicity studies

No studies available.

Carcinogenicity

No carcinogenicity studies with lifelong adminstration of myristicin have been carried out. In the referred short-term studies, special assays have been used, which are not regarded as conclusive but could be used as indicators of carcinogenic activity.

Male $B6C3F_1$-mice were given myristicin i.p. during the preweaning period in 2 separate experiments. This experimental design has, according to the authors, proved to be a sensitive assay for induction of hepatic tumours. A short description of the experiments is given below.

Experiment 1. Myristicin was injected i.p. on days 1, 8, 15, and 22 post partum to male $B6C3F_1$-mice. A total dose of 3.75 µmoles was given during the experiment. The study was carried out with 33 mice/group, all of which were examined 12 months after the start of the experiment. In 21% of the mice, hepatomas were observed in comparison with 15% of the control mice only receiving vehicle (trioctanoin). The average number of hepatomas/mouse was 0.2 in mice treated with myristicin, in comparison with 0.1 in control mice. This result was not statistically significant [Miller et al., 1983].

Experiment 2. In a second experiment carried out in 45 male $B6C3F_1$-mice, myristicin was injected i.p. on days 1, 8, 15, and 22 post partum. A total dose of 4.75 µmoles was given to each animal during the experiment. Hepatomas were observed at 13 months (examination of the livers by laparotomy) and at 13–18 months. The average number of hepatomas/mouse at 13 months was 0.2, and on the later occasion, 0.4. Neither of these numbers was statistically significant in comparison with the control group (0.5 hepatomas/mouse). Thus, myristicin had no detectable activ-

ity for the initiation of hepatic tumours on administration to male mice prior to weaning. It was postulated that the substitution of myristicin in the 2nd and 4th positions may explain the lack of carcinogenic activity of the substance [Miller et al., 1983].

In another study, the inhibition of benzo(a)pyrene (B[a]P)-induced carcinogenicity by myristicin and dihydromyristicin was investigated. Female A/J mice (7 weeks of age at the beginning of the study) were administered perorally (p.o.) (intubation) 1 mg of B[a]P in 0.3 ml cottonseed oil/dose, 2 doses/4 weeks, and/or 10 mg of each test compound (myristicin and dihydromyristicin) in 0.3 ml of cottonseed oil per dose, 3 doses/week for 4 weeks. Before the first dose of B[a]P 3 doses of test compounds were administered. The control mice were given 0.3 ml of cottonseed oil. Eighteen weeks after the first dose of B[a]P, the mice were killed and the lungs and forestomachs were observed and checked histopathologically.

Myristicin treatment resulted in a significant reduction of 65% in the mean number of lung tumours in the tumour-bearing animals. Dihydromyristicin produced a small or insignificant reduction of lung tumour formation. In the forestomach, myristicin treatment resulted in a 31% inhibition of tumour formation, while dihydromyristicin exhibited a 27% inhibition.

These results were in accordance with the fact that myristicin given every 2nd day at 10 mg/dose for a total of 3 doses increased the activity of glutathione S-transferase (GST) to 4.3 and 3.2 times the control values in the liver and the small intestinal mucosa in female A/J mice. In this study, there was no indication of carcinogenicity of myristicin itself [Zheng et al., 1992].

Mutagenicity

Oleoresins prepared from nutmeg fruit were tested in vitro in 2 streptomycin-dependent Salmonella strains (SM[d]): SD 1018 and SD 7823 (which were isolated from S. typhimurium TA 100 and TA 98, respectively). These strains were used for the spot test and plate incorporation test. No metabolic activation of the samples was performed in this study. In the spot tests, the oleoresins were found to be mutagenic in both strains. In the plate incorporation test, oleoresins prepared from the raw seeds of the nutmeg kernel showed a dose-response effect, while those from dried and stored seeds did not have any effects [Damhoeri et al., 1985].

The genotoxicity of the alkenylbenzenes α- and β-asarone, myristicin, and elemicin as determined by the unscheduled DNA synthesis assay (UDS) was investigated in cultured rat hepatocytes. α- and β-asarone and elimicin gave positive responses in the UDS assay while myristicin was negative [Hasheminejad and Caldwell, 1994].

DNA-binding capacity

The binding of a series of alkenylbenzenes to liver DNA from adult female CD-1 mice was investigated. The test compounds safrole, estragole, methylengenol, allylbenzene, anethole, myristicin, parsley apiol, dill apiol, eugenol, and elemicin were administered i.p. at 2 or 10 mg/mouse. The known hepatocarcinogens safrol, estragol, and methyl-eugenol exhibited the strongest binding, with 200–300 pmol adduct/mg DNA after a 10 mg dose, while all the other investigated compounds, except for eugenol, showed intermediate to low binding levels in this ^{32}P-postlabelling assay. The DNA-binding of myristicin was estimated to approximately 50 pmol adduct/mg DNA [Randererath et al., 1984].

The binding of a series of alkenylbenzenes to mouse liver DNA (from male C57B1 × C3H/HeF$_1$-mice) was investigated. The mice were administered i.p. with the compounds on days 1, 8, 15, and 22 after birth. A total dose of 4.75 μmoles was given to each animal. The highest levels of adducts were detected with methyleugenol, estragol, and safrole (30–17.5 p moles/mg DNA). The DNA-binding of myristicin was found to be 7–8 pmol/mg DNA. In comparison with the 3 first-mentioned (carcinogenic) compounds, the adducts of myristicin were less persistent, which has turned out to be of importance in the process of tumour initiation [Phillips et al., 1984].

A series of experiments was carried out with mice given cola drinks instead of water [Randerath et al., 1993]. The development of significant levels of covalent liver DNA adducts in mice consuming cola drinks up to 8 weeks and in fetal liver when pregnant mice were administrated myristicin was investigated. Myristicin adducts were found to be the main type of adduct, amounting to about 80% in these experiments. The liver adduct levels increased in a time-dependent manner in mice chronically exposed to cola beverages. These results strongly suggest that the cola drinks contained myristicin. Myristicin was also found to induce transplacental liver DNA damage in this report. It was also found that pregnancy caused an increase in the binding of myristicin to mouse liver. Induction of transplacental DNA damage in mouse liver and increased binding in the liver of pregnant mice have previously been reported for safrol [Lu et al., 1986].

Special studies

The effects of myristicin on sleeping time in rats treated with phenobarbital were studied. In an experiment with 10 rats treated with myristicin (100 mg/kg i.p.), the sleeping time was significantly reduced in comparison with rats treated with phenobarbital only [Truitt et al., 1960]. These observations might indicate that myrisiticin could act as an inducer of the cytochrome P-450 system.

Myristicin was isolated from the seed of *Myristica fragrans* by column chromatography of the hexane fraction over silica gel [Shin et al., 1988]. In contrast to the previously described experiment, a single treatment of mice i.p. with myristicin at a dose of 300 mg/kg caused a significant prolongation of hexobarbital-induced sleeping time. In addition to this effect, an inhibition of aminopyrine N-demetylase and hexobarbital hydroxylase activities was shown. Furthermore, myristicin was also shown to cause

sleeping episodes even at a subhypnotic dose of hexobarbital. These results suggest that myristicin exerts CNS depressant activity.

The effects of myristicin on the expression of liver cytochrome P450s and its mRNA levels were examined in rats. Male Sprague-Dawley rats were treated i.p. with myristicin at 500 μmol/kg b.w. [Jeong and Yun, 1995]. The effect of myristicin on the expression of inducible liver P450 enzymes (P450: 1A1/2, 2B1/2, and 2E1) was investigated using specific enzymatic activity assays, immunoblot analysis, and Northern blot analysis. It was concluded that myristicin is an inducer of all the examined rat liver P450s and that the induction involves increases in mRNA levels except in the case of P450 2E1.

The effect of myristicin on lipid peroxidation was investigated [Hattori et al., 1993]. Mice were given myristicin p.o. at doses of 25, 50, and 100 mg/kg b.w., respectively, for 3 successive days. As a positive control, DL-α-tocopherol was given at a dose of 50 mg/kg b.w. Control groups administered vehicle-only were also included in the experiment. Lipid peroxidation was induced by repeated injections of $FeCl_2$-ascorbic acid-ADP. The formation of thiobarbituric acid in the liver tissues was measured as an indicator of lipid peroxidation. It was shown that myristicin significantly inhibited the lipid peroxidation. Since myristicin did not appreciably alter the superoxide dismutase level in the liver it was thought that the antilipid peroxidative action may be be attributed to the free radical-scavenging property of myristicin.

Studies in man

In a study of 10 subjects given a single dose of 400 mg myristicin and placebo in a crossover design, definite reactions to myristicin were experienced by 4 subjects. Two persons experienced generally pleasant reactions such as increased alertness, a feeling of irresponsibility, freedom, and euphoria. The other 2 subjects reported symptoms of an unpleasant character such as nausea, difficulty in concentrating, tremor, tachycardia, anxiety, and fear. The onset was 1–2 hours after ingestion. The duration of the symptoms was 7 hours to "one day" [Truitt et al., 1960].

Several cases of nutmeg intoxication have been reported. Accidental and voluntary (in order to experience hallucinogenic effects) intoxications have generally been reported after the ingestion of 5–15 g of nutmeg. As the myristicin content of nutmeg is approximately 1–3%, the ingested amount of myristicin might be considerably less than in the study on human volunteers above. It is therefore likely that there are several other components of nutmeg that contribute to the adverse effects. The principle effects of nutmeg ingested orally at the dose levels mentioned above are flushing of the skin, tachycardia, salivary inhibition, central excitation, burning epigastric pain with or without vomiting, restlessness, giddiness, and hallucinations. The clinical course of nutmeg intoxication may be shock, coma, and acidosis. The onset of the symptoms is commonly reported to occur 2–6 hours after ingestion. The duration of the symptoms may last for 9 hours–several days, depending on the dose, etc. [Painter et al., 1971].

Toxicity evaluation

The metabolism of myristicin broadly seems to resemble that of safrole. However, most of the studies found are rather old, and no information is available concerning the quantitative importance of the individual metabolic pathways.

The acute toxicity of myristicin appears to be low. No toxic effects were observed after peroral administration of 10 mg/kg b.w. daily for 26 days in rats. Myristicin (100 mg/kg b.w. i.p.) significantly reduced the sleeping time in rats pretreated with phenobarbital. According to one in vitro study of the mutagenicity of nutmeg, it is possible that both nutmeg and myristicin may be weakly mutagenic. Important information concerning the performance of this study is, however, lacking. On the other hand, myristicin was not found to be genotoxic in a UDS assay. In order to examine the mutagenic potential of myristicin, more studies would be required. Myristicin showed no detectable activity for the initiation of hepatic tumours on administration to male mice prior to weaning. In female mice pretreated or simultaneously treated with myristicin before/during exposure to benz(alpha)pyrene, the mean number of lung tumours in tumour-bearing animals was significantly reduced. In ^{32}P-postlabelling assays of some alkylbenzenes the DNA-binding of myristicin was considerably weaker than that of known hepatocarcinogens such as safrole, estragole, and methyleugenol. The adducts of myristicin were also less persistent.

In 400 mg doses (corresponding to 6–7 mg/kg b.w.), myristicin produced "mild cerebral stimulation" in 4 out of 10 human subjects. Several intoxications have, however, been reported after the ingestion of approximately 5 g of nutmeg corresponding to approximately 1–2 mg myristicin/kg b.w. The reason for this may be combined effects between myristicin and other components of nutmeg.

RISK EVALUATION AND CONCLUSIONS

Human studies indicate that myristicin at a dose level of 6–7 mg/kg b.w. may cause psychopharmacological effects in man. Although a lowest observable effect level (LOEL) of myristicin in humans has not been defined, it seems unlikely that the intake from essential oils and spices that contain myristicin, estimated to a few mg per person and day, would cause acute adverse effects in humans.

As regards long-term effects, data are at present not sufficient to estimate a tolerable daily intake (TDI) for myristicin. A weak DNA-binding capacity has been demonstrated, but there are no indications that myristicin may exert carcinogenic activity in short-term assays using mice. Clearly, further studies are needed to evaluate the genotoxic/ carcinogenic potential of myristicin. Until studies of genotoxicity and chronic toxicity, including reproduction and carci-

nogenicity, have been performed, it is not possible to assess if the present intake of myristicin may represent a long-term health risk.

Intakes of several grams of nutmeg should be avoided as there is a substantial risk for severe and harmful intoxication. It is, however, still not known to what extent myristicin may contribute to the development of the intoxication.

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