Table VI. Estimated Odor Contribution of Components of *Pimenta racemosa* (West Indian Bay Formally Called *Myrcia acris*) Leaf Oil

Compound	Odor units ($C/T \times 10^{-6}$)	% of odor units of whole oil
Whole oil (T = 3.5 ppb)	286	100
α-Pinene	3.1	1.1
β-Pinene	0.02	0.1
Myrcene	16	5.7
Limonene	6.0	2.2
1,8-Cineole	75	26
Linalool	5.3	1.9
Terpinen-4-ol	0.03	0.1
α-Terpineol	0.06	0.2
Eugenol	56	20
Oct-1-en-3-ol (T = 1.4 ppb)	12	4.2
Total for constituents		61.5

California bay oil. A number of panelists familiar with the odor of California bay leaves also indicated that dilute solutions of 1,8-cineole had an odor very similar to that of California bay leaves. Although it comprises 39% of the California bay oil by weight, umbellulone only contributes 0.3% of the "odor units" near threshold concentrations.

With a contribution of 58% of the odor units, 1,8-cineole also is the major aroma component of Mediterranean bay oil. This is probably one of the reasons California bay leaves have been used as a spice in a similar way to the Mediterranean bay leaves. However, the high concentration of linalool in Mediterranean bay oil and its reasonable (4.5%) contribution to the "odor units" probably tends to soften the aroma impact of the 1,8-cineole somewhat. Approximately 30-40% of the odor of the Mediterranean and West Indian bay oils is still unaccounted for and may be due to some relatively minor components which have not been characterized.

The concentration of 1,8-cineole in West Indian bay is much smaller than the other oils at only 10%, but it still contributes substantially (26%) to the total "odor units" near threshold concentrations. Eugenol and myrcene with contributions of 19.6 and 5.7% also contribute considerably, and the odor of West Indian bay is quite different from that of both California and Mediterranean bay oils.

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California Bay Oil. II. Biological Effects of Constituents

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The acute oral toxicity of California bay (*Umbellularia californica*) oil was greater than that of Mediterranean (*Laurus nobilis*) or West Indian (*Pimenta racemosa*) bay oil. The toxicity of California bay oil was due primarily, but not entirely, to umbellulone, a component not present in Mediterranean or West Indian bay oil. 3,4-Dimethoxyallylbenzene (DMAB), a constituent of California and Mediterranean bay oils, produced sedation in mice at low doses and a reversible narcosis at higher doses. A reversible narcosis was also observed in stickleback fish exposed to DMAB. DMAB prevented the death of mice treated with lethal convulsant doses of strychnine. The effects of DMAB suggest it may have some relatively specific central nervous or myoneural effects and indicate a potential clinical utility of this material as a drug.

A knowledge of the biological effects of the constituents of California bay (*Umbellularia californica*) oil is of interest for several reasons. It is known that certain plants produce a variety of chemicals which serve as protectants against insect predators and herbivores (Martin-Smith and Sneader, 1969; Whittaker and Feeny, 1971). Several simple terpenes have been shown to function as insect defensive agents, pheromones, and even as attractants for cats (Martin-Smith and Sneader, 1969; Martin-Smith and Khatoon, 1963). Many mammals, including deer, have highly developed olfactory senses and use chemical signals in social communication (Ralls, 1971). In the Department of Agriculture, investigations of the ability of volatile components present in California bay leaves to repel deer, which are a significant hazard to crops in some areas (Buttery *et al.*, 1974), and to attract insects (USDA Bulletin No. 351) have been initiated. The composition of Cali-

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Table I. Acute Oral Toxicity of Bay Oils and Umbellulone in Mice

	Sex	No. of groups[a]	LD_{50},[b] ml/kg		Slope	
			Mean	SE	Mean	SE
California bay oil	M	5	2.70 (2.13–3.43)	0.21	0.047 (0.037–0.061)	0.0039
California bay oil	F	5	2.77 (2.13–3.60)	0.24	0.049 (0.038–0.066)	0.0049
Mediterranean bay oil	M	6	3.31 (1.86–5.89)	0.77	0.071 (0.038–0.13)	0.018
West Indian bay oil	M	5	4.67 (2.95–7.44)	0.73	0.059 (0.0345–0.10)	0.011
Umbellulone	M	5	1.45 (1.07–1.96)	0.145	0.050 (0.036–0.069)	0.0053

[a] Five animals per group. [b] LD_{50} (75 hr after administration), slope, standard error (SE), and 95% confidence intervals (in parentheses) calculated by method of Berkson (1957).

fornia, Mediterranean (*Laurus nobilis*) and West Indian (*Pimenta racemosa*) bay oils has been reported in the first paper in the present series (Buttery *et al.*, 1974), and the high content of umbellulone (39%) in California bay oil should be noted. This constituent is not present in Mediterranean or West Indian bay oils.

Further, although monoterpenes derived from the essential oils are components of a variety of spices and flavors (Swaine, 1968), there does not seem to have been a great deal of experimental work on the toxicity of this important class of compounds. California bay leaves are used by many people as a spice.

In 1958 the Food and Drug Administration initiated extensive studies on the safety of flavoring agents (Hall, 1960; Hall and Oser, 1961, 1965), including the essential oils, which occur in many widely used spices and flavorings. Approximately 1100 substances were considered (Hall, 1960). Because it was impossible to conduct immediate, extensive toxicity tests on all the flavors in existence at that time, the initial approach was to classify substances on the basis of toxicity and metabolic data available, occurrence of the substance in natural foods, and the nature, level, and volume of use in foods (Hall and Oser, 1961), and then to proceed with the determination of acute effects of oral administration (Jenner *et al.*, 1964). Subacute and chronic tests were then performed on those substances which had very wide use, which showed toxic effects in the acute studies, or which bore a structural resemblance to known toxic compounds (Hagan *et al.*, 1967). The results of subacute and chronic studies on 48 substances meeting the above criteria were reported in 1967 (Hagan *et al.*, 1967). Of these 48 compounds studied only 14 were subjected to chronic (1 year or longer) studies, illustrating the enormous amount of time required to collect this type of toxicity data. Jenner *et al.* (1964) reported the acute oral toxicity of 107 synthetic and natural flavorings, including eugenol, eucalyptol (1,8-cineole), menthol, thymol, and several essentials oils and Taylor *et al.* (1964) reported the comparative toxicity of a series of allyl compounds including eugenol and safrole. The toxicity of umbellulone, the chief constituent of California bay oil, was investigated by Drake and Stuhr (1935) and umbellulone is listed by Hall (1966) as one of the few naturally occurring flavoring materials which would be regarded as toxic, along with myristicin and safrole, two other toxic terpenes. This classification of umbellulone as a toxic substance by Hall seems to have been based largely on the early work of Drake and Stuhr. Following the Flavoring Extract Manufacturers Association survey conducted as a result of the 1958 food additive amendment to the Food, Drug, and Cosmetic Act, which required the classification of presently used flavors as generally recognized as safe for their intended use (GRAS), or otherwise (Hall, 1960), "Bay" (*Laurus nobilis*) was classed as GRAS. California bay was classed as a food additive, a category reserved for substances for which there was not enough evidence to permit GRAS status. The difference in classification is presumed to be due to the umbellulone content of California bay (Hall, 1960, 1966). The close resemblance of umbellulone to thujone, a major constituent of oil of wormwood which is known to produce convulsions associated with lesions of the cerebral cortex, has been noted by Hall (1966).

The monoterpenes are known to be metabolized by animals (Williams, 1959) and effects of essential oils on the metabolism of other compounds have been reported (Jori *et al.*, 1969; Hohenwallner *et al.*, 1971; Seto and Keup, 1969).

Because there is so little information on the biological effects of California bay oil, we have compared the acute toxicity of California bay oil and umbellulone with that of Mediterranean and West Indian bay oils and have made some observations on the physiological activity of some of the components of California bay oil.

METHODS

Toxicity studies were conducted on 27–32-g Swiss-Webster mice. Oral doses of the bay oils were administered by stomach tube as a 40 or 80% solution in corn oil. Intraperitoneal (ip) injections of bay oil constituents were delivered from a microliter syringe without solvent. After preliminary range-finding experiments, LD_{50} values were determined using groups of five mice at each dosage level. Animals were observed for 2 weeks and deaths and signs of toxicity were noted. LD_{50} values, standard error (SE), and 95% confidence intervals were calculated using the method of Berkson (1957). Pentobarbital sleeping time and anticonvulsant activity were determined in 30–35-g male, Swiss-Webster mice. Test substances were administered, ip, into the right inguinal region with a microliter syringe without solvent. To determine pentobarbital sleeping time, 10 min after administration of the test substance, 65 mg/kg of pentobarbital was administered ip into the left inguinal region and the time to regain the righting reflex was noted. To determine the effects of the test substances on strychnine convulsions, strychnine sulfate in isotonic saline was administered subcutaneously 10 min after administration of the test substance and the time to develop clonic and tonic extensor convulsions and the time to death were noted.

Studies on fish were conducted on 1.5–2 in. *Gasteresteus aculeatus* (stickelback). Bay oil components were dissolved in 1 ml or less of dimethyl sulfoxide (DMSO) and added to 2 l. of water with stirring. The fish were then introduced (six fish per 2 l. of water) and observed for signs of toxicity or death. DMSO at concentrations of 1000–20,000 ppm elicited no signs of toxicity.

RESULTS AND DISCUSSION

Jenner *et al.* (1964) and Taylor *et al.* (1964) found that most of the volatile oils used as flavoring agents produced depression, ataxia, and finally coma after large oral doses. Our observations are in general agreement with these findings. The three bay oils all produce signs of depression, ataxia, and coma at doses near the LD_{50}. California bay was the most toxic of the three bay oils to mice after a single oral dose. The LD_{50} values for male mice were 2.7, 3.3, and 4.7 ml/kg for California, Mediterranean, and

Table II

Distillation fraction	% umbellulone	Mortality (75 hr) 1.1 ml/kg	1.3 ml/kg	1.7 ml/kg	2.2 ml/kg	3.3 ml/kg
(A) Oral Toxicity of California Bay Oil Distillation Fractions						
Whole oil	39	0/5		0/5	0/5	4/5
1	0.4				0/5	
2	5				0/5	
3	54	1/5			3/5	5/5
4	81	1/5			3/4	
5	2				0/5	
Umbellulone	100	0/5	2/5	4/5	5/5	
Whole oil calcd as dose umbellulone		3/5	4/5	5/5	5/5	

Component	% composition of distillation fraction[a] 1	2	3	4	5
(B) Composition of Distillation Fractions					
α-Pinene	97	13			
β-Pinene		10			
Sabinene	0.8	29			
Myrcene		5			
1,8-Cineole	1	35	11		
Terpinen-4-ol			17	2	3
Umbellulone	0.4	5	54	81	4
α-Terpineol			17	17	3
3,4-Dimethoxyallylbenzene			0.2	1	56
Thymol					26

[a] The percentage yields and boiling ranges (°C, 16 mm) of the distillation fractions were: 1, 12%, 27–72°; 2, 25%, 72–76°; 3, 53%, 76–109°; 4, 5%, 109–115°; 5, 5%, residue.

West Indian bay, respectively (Table I). The LD_{50} of California bay oil for female mice (2.8 ml/kg) did not differ significantly from that for male mice.

These observations are of course limited to acute effects and should not be construed to be relevant to the relative hazards which might be associated with the chronic use of low levels of these materials in foods. Far more extensive toxicity texts would be required before any specific assessment of the relative hazard of using California bay as a spice compared with the other "bay" oils could be made.

The California bay oil was divided into five fractions by distillation using a 10-cm Vigreux column and the relative toxicities of these fractions were compared. After oral doses of 2.2 ml/kg all five fractions affected the mice but only fractions three and four produced fatalities. Fractions one through four all produced an initial period of excitement and ataxia. Fraction three produced the most severe ataxia. Fraction five caused a rapid onset of sedation followed by recovery in about 1 hr. The mortality 75 hr after a single oral dose of the five fractions is summarized in Table II. It is clear from the data in this table that fractions three and four, consisting primarily of umbellulone, were the most toxic fractions. Because of the high content of umbellulone in California bay oil it is probably the primary contributor to the acute toxic effects of the whole oil. It is apparent from the data, however, that it was not quite toxic enough to account entirely for the number of deaths seen from the whole oil. On the basis of the LD_{50} of umbellulone (1.45 ml/kg) and the umbellulone content of the whole oil, the LD_{50} of the whole oil should be 3.7 ± 0.37 (SE) ml/kg if umbellulone is the sole component responsible for the observed toxicity. The observed LD_{50} of the whole oil, 2.7 ± 0.21 (SE) ml/kg, indicates that the other constituents present in the oil also contribute to the toxicity, although it is clear that umbellulone is the major contributor.

It is interesting that ptosis of the eyes was observed after administration of umbellulone. Ptosis is also observed after administration of reserpine, and is considered to be a unique neuropharmacological effect of this compound caused by central depression (Turner, 1965). This is an interesting observation in light of the previously reported CNS activity of umbellulone and thujone (Hall, 1966).

There has been some experience with the human toxicity of essential oils. Acute poisoning by monoterpenes probably occurs most frequently from ingestion of turpentine, which consists primarily of α- and β-pinene and Δ^3-carene. Turpentine is less toxic than most volatile oils. The mean lethal dose for adults probably lies between 120 and 180 ml, but 15 ml has been fatal to a child (Gleason *et al.*, 1969). Eucalyptol (1,8-cineol), however, is rated as very toxic in the acute toxicity classification of Gleason *et al.* (1969) and as little as 1 ml has been reported to cause coma and 3.5 ml to have been fatal, although considerably larger doses have been survived.

Eugenol, the primary constituent of West Indian bay oil, and the whole oil itself are rated as moderately toxic in this rating system (between 30 and 480 ml is the probable lethal human dose). Jenner *et al.* (1964), however, noted little difference between the acute oral LD_{50}'s of eucalyptol and eugenol in rats. We have not found a report of the lethal dose to humans of umbellulone in the literature, but if the LD_{50} we observed in mice is extrapolated to man using the conversion factor for body weight to surface area suggested by Mellett (1969)

$$(km) = 10^2 W^{1/3}/K \qquad (1)$$

where km = conversion factor (body weight to surface area), W = body weight in kilograms, and K = a value characteristic of the species, the lethal dose to a 60-kg man would be roughly 5–10 ml. The probable lethal doses of cineole and eugenol for a comparable sized man have been estimated to be 3–30 and 30–300 g, respectively (Gleason *et al.*, 1969). Jenner's data on rats extrapolated to man in the above manner would predict lethal doses of 24 and 26 g, respectively, for cineole and eugenol.

The sedation produced by fraction five was found to be due to the content (56%) of 3,4-dimethoxyallylbenzene (DMAB), which produced sedation and incoordination at ip doses of 0.14 ml/kg. This same fraction exerted a potent reversible narcotic effect in the tests on fish. Fraction five at 50 ppm immobilized the fish within 2 min, but recovery was complete within 30–45 min if the fish were re-

Table III. Effect of Bay Constituents on Strychnine Convulsions

Test material, ml/kg	Mortality	Time to death, min	Std dev
2.7 mg/kg of strychnine	17/17	7.3	3.3
+ DMAB, 0.17	5/5	31.7	5.6
+ DMAB, 0.33	*5/12*	36.4	26.5
+ eugenol, 0.33	10/10	34.4	19.1
+ umbellulone, 0.33	10/10	16.4	17.6
1.9 mg/kg of strychnine	11/13	8.5	3.0
+ DMAB, 0.31	*0/5*		
+ umbellulone, 0.31	4/5	27.3	4.6
+ toluene, 0.31	4/6	19.3	4.1

moved to fresh water within 10 min of the onset of narcosis. The effect on the fish was also shown to be due to the DMAB present in fraction five. Because of these observations, and because the observations of Seto and Keup (1969) to be discussed below suggested that DMAB might have some relatively specific CNS effects, the effects of DMAB in mice after ip administration were investigated further and these effects were compared with the effects of similar doses of umbellulone and eugenol.

We observed that DMAB at 0.14 ml/kg, ip, produced sedation within 15 min. Although there was initially some ataxia, after 25 min the animals simply sat quietly and appeared asleep, but were easily aroused, quite alert, and apparently normal when prodded. Control animals were considerably more active over this same time period (after dosing, animals were transferred to clear plastic observation cages where they normally are quite active for the first 30–45 min in the new environment). A dose of 0.33 mg/kg produced a marked depression, ataxia, and in some cases loss of righting reflex. Effects persisted 60–90 min and 3–5 hr at the above doses, respectively. A dose of 0.67 ml/kg was lethal for two of six mice tested and a dose of 1.7 ml/kg or greater was invariably lethal. The effects of eugenol were similar but less marked. Umbellulone caused incoordination and ptosis at 0.16 ml/kg, ip, followed by recovery in 30–60 min. Two of five mice given 0.67 ml/kg of umbellulone, ip, died between 3 and 6 hr after administration.

Seto and Keup (1969) investigated the effects of a series of alkylmethoxybenzene and alkylmethylenedioxybenzene derivatives on pentobarbital and ethanol sleeping times in mice. Of a series of 17 compounds (all allylbenzene or propenylbenzene derivatives, with varying degrees and types of substitution in the 2, 3, 4, and 5 positions, the substituents being OCH_3, OH, or a OCH_2O bridge) only elemicin (3,4,5-trimethoxyallylbenzene) produced a greater potentiation than DMAB of the pentobarbital sleeping time. Eugenol, isoeugenol, and isoeugenol methyl ether are all considerably less potent in this respect. At higher doses asarone (2,4,5-trimethoxypropenylbenzene) proved to be the most potent potentiator of ethanol sleeping time while DMAB was the next most potent in this respect. Eugenol had little effect on ethanol sleeping time. We used a dose of 150 μl/kg of DMAB (Seto and Keup used 50 mg/kg) and found that the pentobarbital sleeping time was increased to 277 ± 51% (SE) of control (n = 5). Umbellulone at the same dose increased the sleeping time to 256 ± 22% of control (n = 5). Because these compounds were generally ineffective in potentiating ethanol sleeping time, Seto and Keup have suggested that the effects on the pentobarbital sleeping time are a result of interference with pentobarbital metabolism. Although 50 mg/kg of DMAB did not potentiate ethanol sleeping time, it was one of the few compounds to produce 50% or greater mean ethanol sleeping time than control at 100 mg/kg (Seto and Keup, 1969).

The results from our anticonvulsant experiments also suggest that DMAB may exert some relatively specific CNS effects.

Table III is the summary of these results. A dose of 0.3 ml/kg of DMAB completely prevented death from a LD_{85} dose of strychnine and provided marked but not complete protection from a lethal dosage (2.7 ml/kg); 160–170 μl/kg prolonged the time to death after 2.7 ml/kg of strychnine. Other experiments suggest this dose is probably sufficient to protect completely from a dose of 1.3 ml/kg. Umbellulone in a dose sufficient to cause ataxia and ptosis offered slight protection from a LD_{85} dosage of strychnine but this was probably a very nonspecific effect because a dose of toluene only 60% higher on a molar basis also offered slight protection. Eugenol also offered some protection, but was less effective than DMAB. This is consistent with the findings of Seto and Keup referred to above. It is possible, of course, that the protection is due to a myorelaxant effect of DMAB (Turner, 1965) and this would be consistent with our observation that DMAB seemed to be more effective at preventing tonic extensor convulsions than clonic convulsions.

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