Reprinted from

FOOD AND COSMETICS TOXICOLOGY

PERGAMON PRESS

NEW YORK · OXFORD · LONDON · PARIS

1965

Fd Cosmet. Toxicol. Vol. 3, pp. 311–324. Pergamon Press 1965. Printed in Great Britain

Review Section

Chronic Toxicity of Essential Oils and Certain Other Products of Natural Origin*

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(*Received* 13 *February* 1965)

ESSENTIAL OILS

Definition of essential oils (ethereal oils, aetherolea)

The essential oils are a group of odorous principles which are soluble in ethanol but only to a limited extent in water. Chemically they are mixtures of esters, aldehydes, alcohols, ketones, and terpenes. If exposed to the air, oxidation occurs and it is normal practice to add antioxidants, usually either (1) propyl, octyl or dodecyl gallates, or (2) butylated hydroxyanisole, to them at a concentration of 0·1%.

Chemistry of essential oils

The major and more important minor constituents of the essential oils have been known for many years, but following the introduction of vapour phase chromatography the list of substances known to be present in small or trace amounts has increased and is still increasing. The same constituent, such as α-pinene, may be present in a great variety of oils either as a major or minor constituent. Similarly, there may be distinct differences between oils derived from different species within the same genus (e.g. Eucalyptus).

Terpenes and terpene derivatives—alcohols, aldehydes, ketones and esters—are the chief constituents of all essential oils. It is generally agreed that isoprene is the 5-carbon molecule from which the several types of the terpene molecule are built (Fig. 1). Under warm

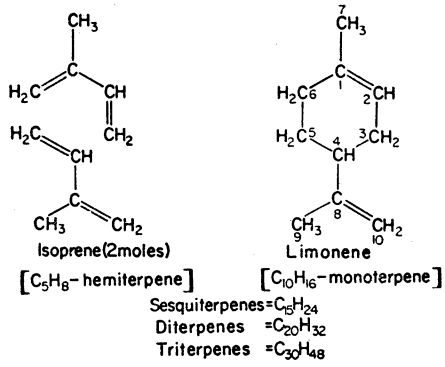


FIG. 1. Isoprene as a building block of terpenes.

*This paper was delivered to the Seventh Meeting of the European Committee on Chronic Toxic Hazards (Eurotox) held in Brussels, 3–6 June 1964. The proceedings of this meeting was published in this Journal (1964, **2**, 655).

conditions in the presence of oxygen, oxidation may occur in the laboratory. In the natural state either oxidation or reduction may proceed. Thus the variety of alcohols, aldehydes, ketones and esters emerge (Figs. 2, 3 and 4). The terpene hydrocarbons are not

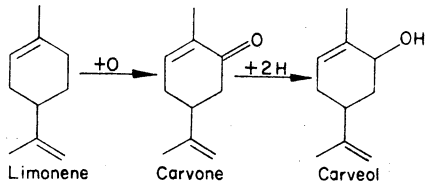


FIG. 2. Oxido-reduction from limonene to carvone and carveol.

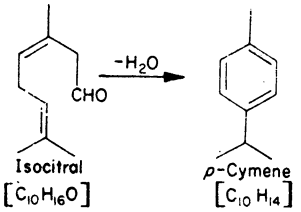


FIG. 3. Oxidation of isocitral in lemon oil to *p*-cymene.

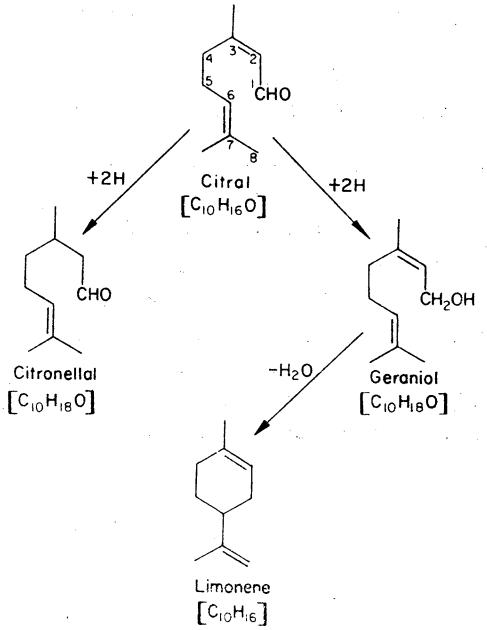


FIG. 4. Relationship of various constituents of essential oils to each other.

devoid of odour, but in most oils it is the other constituents, usually minor constituents, which are responsible for their characteristic scents.

Pharmacology and uses of essential oils

Taken internally it is a general property of essential oils that they are mildly irritant to the mucous membrane of the mouth and digestive tract. Their ingestion gives rise to a sensation of warmth and increased salivation. Because of this property they are used as aids to appetite and digestion. Following ingestion the main constituents are secreted via the lungs, kidneys and skin. In the lungs they are slightly antiseptic and act to stimulate respiration and cardiac activity. Their administration gives rise to a transient rise in blood pressure, and because of this they have been used in conjunction with more powerful stimulants in the treatment of syncope. Taken after meals they have a carminative action, and certain essential oils (e.g. oil of dill) are used to counteract the griping pains of colic.

When large amounts of some of the essential oils are ingested and there is increased excretion of constituents via the kidneys, irritation of the kidneys, bladder and urethra may occur. It is recognized that, where pre-existing inflammatory conditions of the urinary tract are present, they may be aggravated by small doses of ingested oils.

An irritant and rubefacient effect is observed following the application of many of the essential oils to the skin. Typically there is a smarting sensation followed by mild anaesthesia. They have therefore been used medicinally as counter-irritants, although a danger of blistering is recognized.

Inhalation of the oils is followed by the arrest of profuse secretion within the respiratory tract. Thus they have been used to relieve bronchiolar congestion in chronic bronchitis.

It is as pleasing odorous principles that the essential oils are best known to us. We encounter them as flavouring agents and as scents in soaps and cosmetics of all kinds, and in insect repellents. For these purposes they are present in low concentrations and are for the main part applied externally only.

Finally, large quantities of essential oils and products derived from them are used by industry, especially as constituents of paints and varnishes, as disinfectants, in mineral flotation and as solvents. There is a growing tendency for synthetic chemicals to be used in the place of crude or more or less refined essential oils as used in the past. However, it is the essential oils themselves which usually provide the starting materials for the syntheses involved.

Chronic toxicity of essential oils

As we have seen, irritation of the skin, respiratory and urinary tracts may all be attributable to excessive exposure to essential oils.

The questions which faced us in 1959 were: could these irritant effects under certain circumstances lead to cancer induction, or could the oils act as co-carcinogens or tumour-promoting agents?

The substances studied by us were the following:

Oils. Orange, lemon, lime, grapefruit, bergamot, eucalyptus, peppermint, clove, cinnamon, cedarwood, turpentine.

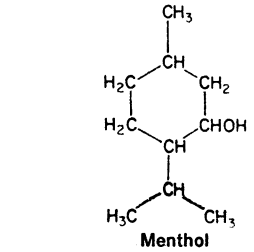
Constituents. α-Pinene, phellandrene, *l*-decene, linalool, terpeneless fraction of orange oil, terpene fraction of orange oil, *d*-limonene, *n*-decyl aldehyde, *d*-carvone, eugenol, terpineol, linalyl acetate, terpinyl acetate, citral.

Preliminary tests

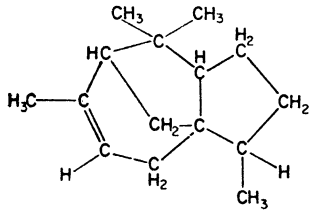
As a preliminary to the main experiments we examined the early effects of these substances on mouse skin. Mice of the '101' inbred strain and approximately 8–10 weeks of age were used for this purpose. The dorsal hair was removed by electric clippers and the substances applied either in undiluted form or at various concentrations in acetone. Two applications of the test material were made 7 days apart. A specimen of dorsal skin was obtained by biopsy 3 days after each application.

In these preliminary tests most of the substances mentioned above gave rise to moderate or marked epidermal hyperplasia. In some cases areas of necrosis with ulceration, weeping and crusting were seen. High concentrations of the oils in acetone were often more irritant to mouse skin than the undiluted oils.

In general, the terpene hydrocarbons proved to be irritant to mouse skin, whereas the alcohols, aldehydes, ketones and esters were systemically toxic and could only be applied as dilutions in acetone. Similarly, oils wherein the main constituents are alcohols or esters (e.g. clove oil, which contains more than 70% eugenol) were particularly toxic to mice when applied to the skin. An exception to this generalization was seen in the case of peppermint oil, which contains approximately 60% of menthol (Fig. 5) and was neither systemically toxic nor locally irritant. Similarly, cedar-wood oil, the chief components of which are cedrene (80%) (Fig. 5) and cedrol (3–14%), was also without either systemic or local effect.



Menthol
(Main constituent of peppermint oil)



Cedrene
(Main constituent of cedar-wood oil)

FIG. 5. Examples of essential oils lacking systemic or local effects.

Skin tumour-promotion by citrus oils

A full report of the experiments in which we observed the promotion of benign and malignant skin tumours by the repeated application of different citrus oils has been presented elsewhere (Roe & Peirce, 1960). Here we give a brief resumé of our findings.

Mice of two different strains were used, '101' strain (inbred) and stock albino (random-bred) and experiments were started when mice were approximately 8 weeks of age. In the case of the test groups, treatment began with a single application of 3,4-benzopyrene (BP), 9,10-dimethyl-1,2-benzanthracene (DMBA), or urethane to the whole of the dorsal skin after removal of the hair by electric clippers. These substances were applied to the skin in acetone solution, the dose being sufficient to initiate skin tumour formation but, generally speaking, inadequate for complete carcinogenesis (Berenblum & Shubik, 1947 a,b 1949; Salaman & Roe, 1953). No further treatment was given for a period of 3 weeks, after which the test substance was applied once weekly, either in undiluted form or diluted with acetone. Control groups received either the initial treatment alone, or treatment with the test substance following an initial application of acetone only. Dorsal hair was removed repeatedly as necessary throughout the experiment. Benign warts (papillomata) and malignant skin tumours (epitheliomata) appeared in some of the groups which received both pretreatment

with a subcarcinogenic dose of BP, DMBA, or urethane and repeated treatments with one of the test substances. Occasional tumours only, all of them benign, were seen in the control groups. The results are depicted in Tables 1, 2 and 3.

Table 1. *Tests for tumour-promotion by citrus oils*

Primary treatment with DMBA* (given as single application in 0·2 ml acetone) (μg)	Secondary treatment (0·25 ml once weekly, starting 3 weeks after primary treatment)	Skin tumour incidence (33 weeks after start of secondary treatment)	
		No. of surviving mice with papillomas	Total no. of papillomas
300	Orange oil (either undiluted or at 80% or 40% concentration in acetone)	28/43	83
None	Do.	1/48	1†
300	None	5/38	6†
225	Lime oil (undiluted)	8/14	47
None	40% Lime oil in acetone	0/15	0
225	Bergamot oil (undiluted)	0/10	0
None	Do.	0/8	0
300	Lemon oil (undiluted)	10/15	38
300	Grapefruit oil (undiluted)	13/15	37

*9,10-Dimethyl-1,2-benzanthracene.

†Tumours on skin, outside treated area.

Table 2. *Tests for tumour-promotion by the two main fractions of orange oil*

Primary treatment with DMBA (given as single application in 0·2 ml acetone) (μg)	Secondary treatment (0·25 ml once weekly, starting 3 weeks after primary treatment)	Skin tumour incidence (33 weeks after start of secondary treatment)	
		No. of surviving mice with papillomas	Total no. of papillomas
300	None	1/16	1
300	80% Terpene fraction* of orange oil	8/15	29
300	20% Non-terpene fraction* of orange oil	1/13	1
None	Do.	0/34†	0

*Approximately 95% of orange oil finds its way into the terpene fraction and 5% into the non-terpene fraction. Hence, if the tumour-promoting activity of the oil were due to the activity of the non-terpene fraction a strong positive result should have been obtained in the third group.

†One animal had a melanotic tumour (naevus-type) in subcutaneous tissues of treated area; and another had a small haemangioma in the same region.

Table 3. *Tumour-promotion by eucalyptus and turpentine oils and certain constituents of essential oils*

Group*	Primary treatment with DMBA (given as single application in 0·2 ml acetone) (μg)	Secondary treatment (0·25 ml once weekly, starting 3 weeks after primary treatment)	Skin tumour incidence (33 weeks after start of secondary treatment	
			No of surviving mice with papillomas	Total no. of papillomas
1	300	Undiluted oil of turpentine	8/19†	10†
2	300	None	1/16‡	1‡
3	225	Undiluted oil of eucalyptus	4/14	5
4	225	None	0/13	0
5	150	40% α-Pinene	3/15	4
6	150	40% Phellandrene	2/17	2
7	150	40% 1-Decene	7/17	13

*Groups 1 and 2 were contemporaneous, so also were groups 3 and 4. No control group treated with 150 μg DMBA only was set up in parallel with groups 5, 6 and 7. However, it is extremely unlikely that tumours would have arisen in response to this treatment only.
†One mouse had a single papilloma outside the treated area.
‡Single papilloma outside the treated area.

Tumours at the urethral orifice of female mice treated with orange oil

In our earlier report (Roe & Peirce, 1960) we described the induction and appearance of tumours at the urethral orifice of female mice during treatment with orange oil with or without DMBA pretreatment, or with the terpeneless fraction of orange oil (Table 4).

Table 4. *Incidence of tumours of the urethral orifice of female '101' strain mice treated with orange oil*

Treatment		Incidence of tumours of the urethral orifice in female survivors
FIRST SET OF EXPERIMENTS		
DMBA+Orange oil to dorsal skin		4/40
Orange oil only to dorsal skin		2/40
DMBA only to dorsal skin		0/38
DMBA+terpene fraction of orange oil to dorsal skin		0/10
DMBA+terpeneless fraction of orange oil to dorsal skin		1/10
	Total.....	7/138
SECOND SET OF EXPERIMENTS		
Terpeneless fraction of orange oil only to dorsal skin		0/34
Terpeneless fraction of orange oil applied directly to urethral orifice		0/16
225 μg DMBA applied to dorsal skin, then terpeneless fraction of orange oil (0·05 ml by stomach tube) once weekly		0/20

Altogether we saw 7 of these tumours, all in mice of the '101' strain and all in mice treated with a particular batch of orange oil. No such tumours arose in subsequent experiments where other batches of orange oil were used, nor in experiments with other citrus oils or citrus oil constituents. Deliberate painting of the urethral orifice of female '101' strain mice with the terpeneless fraction of orange oil did not elicit any tumours (Table 4: second set of experiments). Similarly, no urethral tumours arose in female mice painted with the terpeneless fraction repeatedly without DMBA pretreatment, nor in mice given a

single application of DMBA to the skin followed by the terpeneless fraction repeatedly by stomach tube.

The tumours were benign squamous papillomas, often mitotically active but never invasive. Some grew to a size of almost 1 cm in diameter. All were heavily infiltrated by polymorphonuclear leucocytes. Figs. 6 and 7 illustrate the macroscopic and microscopic appearances of these tumours, respectively.

Looking back it would seem likely that a second factor was involved in the genesis of the urethral tumours; perhaps an intercurrent genito-urinary infection in the mice used in the earlier experiments; perhaps a slight dietary difference. Alternatively, one must suppose that the earlier and later batches of orange oil differed in some material way. It is perhaps relevant that '101' strain mice are especially susceptible to papillonephritis, a disease of unknown aetiology which initially causes necrosis and calcification of the renal papilla (there is only one papilla in the mouse kidney) and subsequently retrograde changes in the renal cortex leading eventually to renal failure. However, this disease was seen in both the earlier and later experiments with orange oil. A second possibly relevant fact is that in the earlier, but not the later, experiments referred to above, intussusception and anal prolapse were common causes of intercurrent deaths. We have no idea why this should have been. The fact is that, though we wished to study the mechanism of induction of these urethral tumours further, we could not do so because we had altogether lost the knack of inducing them.

Experiments on other essential oils

Weak tumour promotion was observed with turpentine oil and with α-pinene, one of its principle constituents (Table 3, Fig. 8). Previously, Mackenzie & Rous (1941) reported that

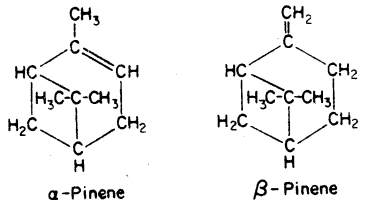


FIG. 8. Main constituents of turpentine oil (average for several varieties of oil). α-Pinene 62%; β-pinene 33%; alcohols, aldehydes, esters, etc. 5%.

turpentine oil promoted skin tumour development in rabbit skin, but Berenblum (1941) and Shubik (1950) found it to be more or less ineffective in the mouse. It is likely that the composition of the oils used in the various experiments was different, and this may explain the disagreement between our findings and those of Berenblum (1941) and Shubik (1950).

The eucalyptus oil tested by us appeared to have weak promoting activity for mouse skin (Table 3). Four out of 14 mice which survived 33 weeks or more developed skin tumours in response to a single application of 225 μg DMBA followed by once-weekly applications of undiluted eucalyptus oil. Malignant skin tumours were seen in 3 of these 4 mice, the first after only 14 weeks of secondary treatment. Mice treated alone with 225 μg DMBA developed no skin tumours during a comparable period of observation. Phellandrene, one of the major constituents of eucalyptus oil, applied at a concentration of 40% in acetone, also had a weak promoting effect.

Bergamot oil was less irritant than the other citrus oils in the preliminary skin tests and proved inactive as a tumour-promoting agent. In fact, this result fits in with the general thesis that the terpene hydrocarbons are responsible for both the irritant and tumour-promoting effects. Whereas the other citrus oils mentioned above, orange, lemon, grapefruit, etc. contain approximately 90% terpene, 60–70% of bergamot oil consists of alcohols and esters. On the other hand, in another test, linalool as a 20% solution in acetone elicited a weak tumour-promoting response. Linalool is one of the principle alcohols in bergamot.

Tumour-promotion and tumour-induction by citrus oils in the forestomach epithelium of mice

A preliminary report has been made of results of the first tests of the activity of lime oil on the forestomach epithelium of mice (Peirce, 1961) and a full report of all the experiments has been submitted for publication elsewhere (Field (née Peirce) & Roe, 1965). Here we will communicate only a brief summary of the findings.

The object of our experiments was twofold. Firstly to see whether two-stage carcinogenesis could be demonstrated in tissues other than the skin and secondly, to see whether citrus oils act as tumour promoters in the gastro-intestinal tract.

Previous attempts to induce tumours of the stomach in mice by "small" doses of polycyclic hydrocarbons followed by croton oil (Berenblum & Haran, 1955) failed, possibly because the dose of the hydrocarbon was excessive in view of the high susceptibility of the epithelium of the mouse forestomach to tumour-induction (Bock & King, 1959). In her experiments, therefore, Peirce (1961) tested various much lower doses of BP or DMBA, either alone or followed by repeated treatments with lime oil. The technique was as follows: mice, when 6–8 weeks old, were starved overnight and given the requisite dose of BP or DMBA dissolved in 0·05 ml of polyethylene glycol (PEG of average mol wt 400). Three weeks later secondary treatments were begun. These consisted of once-weekly doses of 0·05 ml undiluted lime oil, or no treatment, following overnight starvation. The only tumours observed in the gastro-intestinal tract were in the stomach. Tumours of the

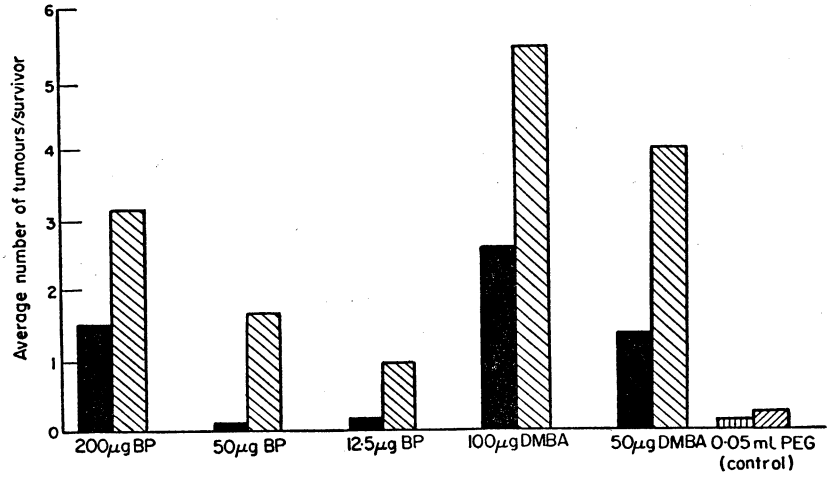


FIG. 9. Tumour-promoting effect of 40 once-weekly treatments with lime oil after various initiating doses of 3,4-benzopyrene (BP) or 9,10-dimethyl-1,2-benzanthracene (DMBA) in the mouse forestomach. ■, initiator alone; ▨, initiator+promoter; ▥, polyethylene glycol solvent control; ▨, control+promoter.

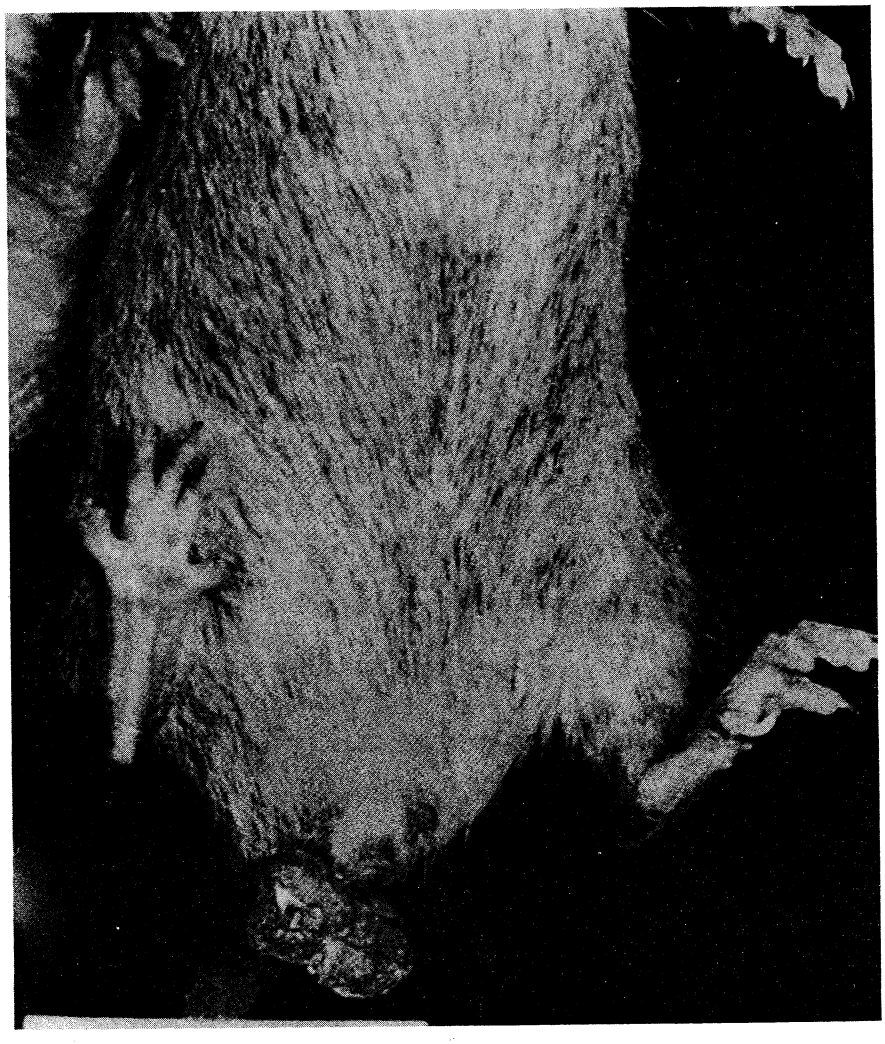


FIG. 6. Papillomatous tumor of urethral orifice in a female mouse of strain 101 treated with a single application of 300 μg. DMBA followed by 15 once weekly applications of 40% orange oil in acetone. (Reprinted by kind permission of the Editors of the *Journal of the National Cancer Institute*).

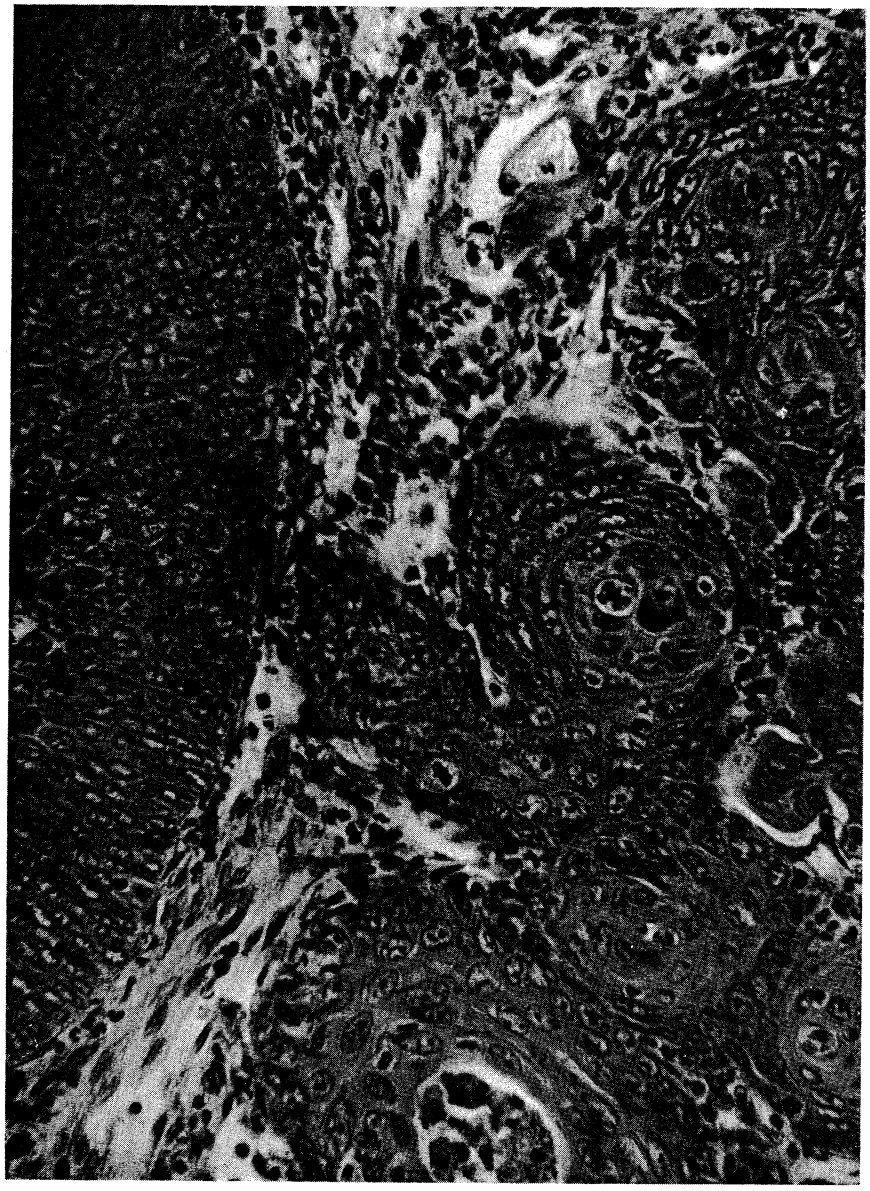


FIG. 7. High-power view of same section. *Note* inflammatory infiltration by polymorphonuclear cells. ×85. (Reprinted by kind permission of the Editors of the *Journal of the National Cancer Institute*).

glandular stomach were infrequent and their occurrence showed no relation to treatment. Forestomach tumours arose in response to treatment with BP alone or DMBA alone, particularly at the higher dose levels. However, secondary treatment with lime oil for periods up to 40 weeks consistently and significantly increased the incidence of forestomach tumours (Fig. 9).

In mice killed at the cessation of 40 weeks of secondary treatment the vast majority of tumours were benign papillomas. However, malignant tumours were seen occasionally before this time and more frequently in animals allowed to live longer. Every one of 12 malignant forestomach tumours, all examined histologically and all showing penetration of the muscular coats of the stomach, arose in animals treated with both hydrocarbon and lime oil: none were seen in comparable mice treated with hydrocarbon only. Transperitoneal spread and distant metastases were observed in some cases.

Occasional benign, but no malignant, tumours were seen in mice treated with PEG and no further treatment, or PEG followed by lime oil (Fig. 9).

Urethane dissolved in water followed by lime oil once weekly gave rise to a few forestomach papillomas, whereas urethane without subsequent treatment was almost ineffective.

Heating the lime oil under a reflux condenser for 3 hr did not abolish its tumour-promoting activity for the forestomach epithelium.

In other experiments lime oil was incorporated in the diet of mice and comparisons were made between animals receiving 50 μg BP by stomach tube and then fed diets containing various levels of lime oil or no lime oil at all. The presence of lime oil in the diet at all levels (0·5, 2 or 8 ml/kg) increased the incidence of papillomas of the forestomach. In this experiment there was no effect on the incidence of malignant forestomach tumours.

A less clear-cut result was obtained in mice given "orange squash" instead of drinking water following a single dose of 50 μg BP. In this case treatment with squash appeared to increase the incidence of forestomach tumours, but the extent of the increase bore no relation to the concentration of orange oil in the squash. A subsequent experiment with orange squash, using a different strain of mice, gave a negative result.

Carcinogenicity of safrole

Another component of many essential oils but especially of sassafras oil, namely safrole (Fig. 10) has recently come into the news as a possible environmental carcinogen. Safrole is a major constituent of sassafras oil, star anise oil and camphor oil, and a minor con-

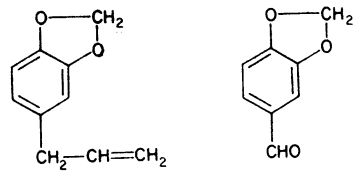


FIG. 10. Possible carcinogenic components of essential oils.

stituent of oil of nutmeg and cinnamon leaf oil. It has been used widely as a flavouring agent in 'root beer' (a beverage consumed in large volumes in North America), in chewing

gum, toothpastes and certain pharmaceutical preparations. Safrole itself, but more frequently heliotropin, a related aldehyde, is used to scent soaps and cosmetics.

Homburger, Kelley & Friedler (1961) reported the induction of hepatic tumours in rats fed safrole at 1% in the diet. Tumour-induction was preceded by cirrhosis and the accumulation of massive deposits of ceroid pigment. Most of the tumours were benign. Occasionally adenomata were seen in the absence of cirrhosis. Tumours were more prominent in animals fed a casein-supplemented than a protein-deficient diet. Long, Nelson, Fitzhugh & Hansen (1963) were able to confirm the findings of Homburger *et al.* (1961) using only a 0·5% dietary level of safrole.

NATURAL PRODUCTS OTHER THAN ESSENTIAL OILS

An investigation of certain euphorbia latices

When we first began our investigation of the biological activity of the euphorbia latices we did not realize that there was a possible relationship between them and the essential oils (*vide infra*).

Dr. J. Fawcett at the London Hospital drew our attention to the fact that some of the euphorbia latices are highly irritant for the human skin and mucous membranes. He thought it might be of interest to test them for tumour-promoting activity since *Croton tiglium*, which provides croton oil, is of the euphorbia family.

Most members of the euphorbia family have it in common that when their stems are cut a thick white latex exudes and eventually coagulates. During the war, when Britain was deprived of its source of natural rubber by the Japanese occupation of Malaya, the latex of *E. ingens* was examined to see if it could act as a substitute. However, it proved too irritant to handle on a large scale.

In 1959, we tested the latex of *E. ingens* on mouse skin (Roe & Peirce, 1961; Peirce & Roe, 1962). It evoked marked hyperplasia and ulceration of the epidermis at concentrations above 1% in acetone. At 1% and lower concentrations it caused hyperplasia without necrosis. A 1% solution in acetone proved to be highly effective as a tumour-promoting agent (Table 5).

Table 5. *Tumour-promotion by latex of* Euphorbia ingens *in* '101' *strain mice*

Initiating treatment (μg DMBA)	Promoting treatment	No. of surviving mice with papillomas	Total no. of papillomas
300	None	0/19	0
300	0·1–2% extract of latex of *Euphorbia ingens*	12/20	54
None	Do.	1/17	1

Subsequently, with the help of the Royal Botanic Gardens, Kew, London, we tested several other euphorbia latices both for irritant and tumour promoting effects on mouse skin. Several were found to be highly or moderately active in both respects. On the whole, the two types of activity went hand in hand. The most effective latex was that of *E. tirucalli* (Table 6).

Table 6. *Tumour promotion by various euphorbia latices for skin of mice*

Promoting treatment (1% acetone extract once weekly)	Hyperplastic changes in epidermis	No. of surviving mice with papillomas	Total no. of papillomas
	DMBA INITIATING TREATMENT (150 μg)		
None	—	0/20	0
E. tirucalli	++++	15/15	358
E. grandidens	+++	13/16	163
E. canariensis	+++	10/17	103
E. wulfenii	++	11/18	69
E. candelabrum	++	15/19	68
E. obovalifolia	++++	7/20	40
E. abyssinica	+	10/19	28
E. cooperi	+	3/18	4
E. triangularis	+	1/20	1
	NO INITIATING TREATMENT		
E. tirucalli	++++	2/20	2
E. grandidens	+++	0/17	0

The complete chemistry of these latices is not known but it is clear that we are once again involved with terpene chemistry. According to Warren & Watling (1958), two of the major constituents of the resin derived from *E.* tirucalli are triterpene alcohols (Fig. 11).

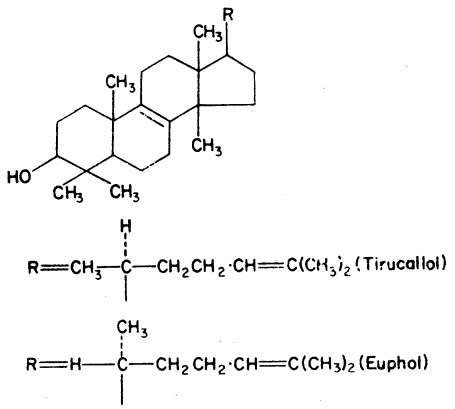


FIG. 11. Major constituents of resin of *Euphorbia tirucalli.*

The discovery of the strong promoting activity of the euphorbia latices is especially interesting because it is the first time that agents of the same order of potency as croton oil have come to light.

Carcinogenicity of tannins

The late Professor Korpassy was the first to draw attention to the fact that hydrolysable tannins may give rise to cirrhosis and liver tumours in rats (Korpassy, 1961). Moreover Kirby (1960), at the Chester Beatty Institute, London, induced both liver tumours and tumours at the site of injection of three different condensed tannins. With three hydrolysable tannins, myrobalans, chestnut and valonea, liver tumours but no local neoplasms were obtained.

Tumour-promotion by cashew-nut shell liquid

The liquid obtained from the shells of cashew nuts contains phenolic substances of value as raw materials in the manufacture of resins, lubricants and plastics. Its main constituents are anacardic acid (90%) and cardol (10%) (Fig. 12).

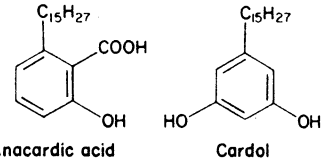


FIG. 12. Main constituents of cashew-nut oil.

The liquid is a cause of occupational dermatitis (Schwartz, Birmingham, Campbell & Mason, 1945), the irritant properties being associated mainly with cardol, which is chemically related to urushiol, the irritant factor in poison ivy.

We tested it in mice to see whether it caused epithelial hyperplasia. On finding that it did so we proceeded to test it for tumour-promoting activity.

Twenty '101' strain mice were given a single application of 150 μg DMBA and then once weekly applications of 3–5% cashew nut oil in acetone. Of 15 mice which survived for 20 or more weeks, 12 developed papillomas. A total of 41 papillomas arose in these 12 mice. We saw no malignant tumours in this particular experiment.

GENERAL DISCUSSION

Taking the essential oils together as a group it is clear that we have relatively little precise knowledge regarding the toxicity of many of their major constituents and next to none regarding the majority of their minor constituents or oxidation products.

The fact that most of the oils have been used through the centuries by man as flavourings, aids to digestion, perfumes and medicines, may be taken by some to be a guarantee of their safety for man. However, this evidence alone is insufficient to warrant the unrestricted use of materials which have not been properly examined in the laboratory. Some chronic toxic effects, including carcinogenesis, are insidious, and detecting cause and effect relationships is no easy matter. The dramatic story of aflatoxin has taught us, or reminded us, of another thing. A knowledge of the toxicology of only the major constituents of a mixture is not enough. Biologically, significant toxicity may be attributable to a substance present in only a trace amount, or to a substance which is present under some, but not other, circumstances. It seems then that if continued use is to be made of essential oils, particularly in food, or as aerosol sprays, sooner or later a systematic study will have to be made of the pharmacology and chronic toxicity of all their constituents. One would not wish to exaggerate the urgency of this need. No doubt there are many other insufficiently investigated environmental factors which merit greater concern. On the other hand, in the event of man suddenly increasing his degree of exposure to a traditional environmental factor, he ceases to be "protected" by the "safety" guarantee provided by the tradition. For this reason we are bound to take a serious view, for example, of the increased use in recent years of safrole in root beer.

In general it is right that we should spend a great deal of energy in making sure that in the course of advancing in the fields of food and cosmetics technology we do not add new

carcinogens or other toxic agents to the environment. However, it should be emphasized that if all our energies are spent in this way, and even if we were 100% successful in these endeavours, we should do nothing to lower the incidence of cancer or other forms of intoxication which are attributable to factors already present in the environment. In other words, if we wish to reduce the present incidence of cancer in man we must examine most carefully all the factors which go to make up his traditional environment. In this connexion a careful and thorough study of the essential oils is long overdue.

Acknowledgements—Most of the experimental work referred to was performed in the Cancer Research Department, London Hospital Medical College, London, E.1, and was supported by a block grant from the British Empire Cancer Campaign.

We are grateful to several members of the technical staff of that department for their help, to the Photographic Department of the Chester Beatty Research Institute for some of the illustrations, and to Mrs. K. Foster for her assistance in preparing this manuscript.

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