

Brief Report

Surface Active Agents as Tumor Promoters

by E. Boyland*

Although physical injury was the first type of tumor promoter to be described (1) and croton oil with its constituents the most investigated, some of the other types of the fourteen listed in Table 1 are certainly involved as causes of human cancer. Some of

Table 1. Tumor promoters.

Type	Promoter
Physical injuries	Wounds, CO ₂ snow
Foreign bodies	Bladder implants, asbestos
Chemical irritants	TPA, iodoacetic acid, SO ₂
Surface active substances	Bile acids, alcohol, sodium stearate, Tweens, saccharin cyclamate
Preparations with high osmotic pressure	Sodium chloride, iron dextran polymers
Metal salts	Lead, possible cadmium
Biological factors	Hepatitis virus, bilharzia
Chelating agents	Catechol, pyrogallol, 8-hydroxyquinoline
Solvents	Dodecane, benzene, chloroform
Drugs	Griseofulvin, valium, phenobarbitone
Hormones	Stilbestrol
Aromatic chloro compounds	DDT, tetrachlorodioxin
Antithyroid compounds	Thiouracil
Overfeeding	Calories or fat

*TUC Centenary Institute of Occupational Health London School of Hygiene and Tropical Medicine, Keppel St., London WC1E-7HT, England.

the types of promoter listed have not been demonstrated as such by animal experiments, but if a substance is a carcinogenic but not mutagenic, then it is most probably a tumor promoter. This assumes that mutagens are initiators and that promoters can induce cancer because initiators are present in the diet or environment. Until recently, the adventitious initiators were considered as contaminants such as aflatoxin or nitrosamines, but the mutagen and carcinogen, quercetin, is present as such or as glycosides in most vegetable matter and in animal foods. Substances which inhibit DNA repair or suppress immune response might also increase cancer incidence and so be considered as carcinogens without being promoters. Some neoplasia including liver tumors in mice, bladder, kidney and thyroid tumors in rats are easily induced by promoters so that their occurrence is almost indicative of tumor promotion.

Tumor promoters are organotropic and can change the site of action of an initiator. Thus tryptophan can change the site of action of 2-acetylaminofluorene from the liver to the bladder and thiouracil from the liver to the thyroid. Some carcinogens, particularly aromatic amines, cause cancer in different organs in different species; this effect could be due to tumour promotion.

Synthetic Surface Active Compounds

The first surface-active compounds shown to be tumor promoters were probably the fatty acid derivatives of polymers such as the commercial products Tweens and Spans. Setala (2) carried out typical tumor promotion experiments with these. Following a single application of 7,12-dimethylbenz(a)anthracene to the skin of mice the surfactants were applied repeatedly. Many, but not all of the Tweens when applied as concentrated solutions in this way caused local skin tumors. Similar results were described by Della Porta et al. (3).

As the effect was seen with concentrated solutions the high osmotic pressure of the applied material could play a role as such solutions, e.g., carboxymethylcellulose and iron dextran seem to be promoters for subcutaneous sarcomas as suggested by Walpole (4). On the other hand, low molecular weight surfactants act as promoters for stomach cancer in rats (5).

Subcutaneous Sarcomas

Many acid dyes and other compounds particularly surfactants induce sarcomas on repeated injection into subcutaneous tissue. The dyes which do this, e.g., Brilliant Blue FCF (C.I. 42090), Light Green SF Yellowish (C.I. 42095), Fast Green FCF (C.I. 42053) and Blue VRS (C.I. 42045), are all surface active, so that the surface tension of 2% solutions is more than 20% less than that of water (5). Injection of more dilute solutions in which the surface tension was reduced by less than 20% did not induce sarcomas. Other surfactants that have induced subcutaneous sarcomas are Tween 60 as 6% solution (7) and calcium cyclamate as 5% solution (8). As these carcinogens are not mutagenic, they are probably tumor promoters and are only active when the concentration is high enough for appreciable surface activity to be exerted.

Measurements of Interfacial Tension

Because of the evidence that some tumour promoters are surfactants, the interfacial tension between water and *n*-octanol of some known and possible tumor promoters was measured (9). Some of the findings are summarized in Table 2.

The compounds investigated fell into three groups with different surface activities. The first group of compounds, which had little surface activity (4% solutions reduced the interfacial tension by less than 10%), include urea, calcium acetate, sodium chloride, glycerol, sodium nitrilotriacetate, phenol and glucose.

The second group of compounds with moderate surface activity (4% solutions reduced the inter-

facial tension by 20%) included ethanol and the known tumor promoters sodium saccharin, sodium cyclamate and sodium phenobarbitone. The doses of saccharin and cyclamate which act as tumor promoters being at least 5% of the diet, are such that the concentration in the bladder shortly after feeding would be sufficient to reduce interfacial tension by 20%. Although sodium cyclamate and saccharin have about the same surface activity and promoting action, cyclohexylamine, a metabolite of cyclamate by bacterial action, was twice as active in reducing interfacial tension. Saccharin is not metabolized so the effect is probably due to the compound itself. Saccharin is used in the electroplating industry presumably because of its surfactant activity. Tryptophan is also a promoter for bladder cancer, but this is probably due to some metabolite such as indoxyl sulfate. The concentration of alcohol in the mouth and esophagus causing cancer is probably sufficient to have about the same effect on interfacial tension. The doses of phenobarbitone that promote liver tumors (0.25% of the diet) are such that the reduction of tension would be small. Thus although saccharin, cyclamate and ethanol could act as promoters because they are surfactants, it is unlikely that phenobarbitone acts by virtue of this activity. It seems possible that enzyme inducers could be tumor promoters.

Sodium nitrilotriacetate induces bladder tumors but the reduction in interfacial tension observed would indicate that it operated by some other mechanism. It is a chelating agent, and, like catechol, could be a promoter because of this property.

Of the substances with higher surface activity sodium lithocholate is a known promoter of cancer of the colon in rats (10). Other salts of the bile acids, desoxycholic and taurocholic acids are also potent surfactants and presumably tumour promoters. That the salts of the fatty acids, sodium stearate and sodium oleate, had similar activity is known (11). The incidence of cancer of the colon in different countries varies with the fat intake (12). Oleic acid, lauric acid and known promoters including saccharin and phenobarbital were active in the transformation of Rauscher virus infected cells after initiation with 3-methylcholantrene (13). If the proposed hypothesis is correct then the fatty acids as well as bile acids in feces could be promoters for cancer of the colon. Long-chain fatty acids are weak promoters for mouse skin (14). An extension of the hypothesis would indicate that those laxatives such as diocetyl sodium sulfosuccinate (Aerosol OT) which are surface active compounds could also be colon tumor promoters.

The effect of dietary fiber in reducing the incidence of cancer of the colon could be due to the

Table 2. Concentrations of surface-active agents which reduce interfacial tension between water and octanol by 20%.

Concn = 0.1%	Concn = 3%
Sodium lithocholate	Sodium saccharin
Sodium taurocholate	Sodium cyclamate
Sodium oleate	Sodium <i>o</i> -toluenesulfonamide
Sodium stearate	Ethanol
Sodium dioctylsulfosuccinate	Sodium indoxyl sulfate
	Sodium phenobarbitone

fiber either absorbing the surfactants or holding water and so reducing the concentrations of harmful surface active agents in the feces.

Alcohol as Tumor Promoter

The published data and the experimental findings (Table 2) show that ethanol has surface activity; 5% (v/v) solutions reduced the interfacial tension by 22% and surface tension by 20%. This activity is sufficient for alcohol to promote a tumor if taken in concentrated forms such as spirits. There is abundant evidence that cancers of the mouth, pharynx, larynx and esophagus occur more frequently in men who consume large amounts of alcoholic beverages (15, 16) or use alcoholic mouthwashes (17). These cancers are seen most frequently in men who smoke and drink spirits. Tobacco smoke must provide initiators. The search for carcinogens in spirits has not revealed any potent initiators or carcinogens in significant quantities. The consumption of large quantities of beer increases the incidence of cancer of the esophagus (18, 19) much less or not at all. It seems to increase the risk of cancer of the colon (20). It is thus the concentration of ethanol at any moment that is important rather than the total amount of ethanol imbibed. It is not unusual for threshold levels to be necessary to produce biological effects; oxygen and cyanide are suitable examples. The increased incidence of colon cancer in beer drinkers could be due to these men having less fiber in their diets.

It should be sufficient to add water to spirits to reduce the carcinogenic effect on the mouth and esophagus. Connoisseurs are divided about the addition of water to a good whisky and few seem to add water to a good brandy. There are, however, those that consider that the flavor of a good cognac can be better savored if water is added, but a good spirit deserves good water. Perhaps the best procedure is to appreciate the bouquet and then add water to taste the flavor and reduce the carcinogenic hazard.

Effective Levels of Surfactants

Of the different types of tumor promoters (21), some, including those which are surfactants, probably have safe or threshold levels. The surfactants probably act by changing cell membranes and there must be levels below which the effect on cells is negligible. The safe or threshold level of these compounds is not so much the total dose, but the maximum levels attainable at any time. Thus the same amount of ethanol taken as beer, containing 4% ethanol, has less carcinogenic action on the mouth and esophagus than when consumed as spirits with 40% alcohol.

Table 3. Promoters which are probable causes of human cancer.

Promoter	Cancer/site
Asbestos Smoking	Lungs
Bile acids Fatty acids	Colon
Alcohol	Mouth, esophagus
Salt	Stomach
Fat	Breast
Bilharzia	Bladder
Benzene	Leukemia

Different surface active compounds act as tumor promoters for the bladder, colon, mouth, esophagus, skin and stomach. As the effect of these is physical because it does not involve chemical combination, there are safe levels below which the effect on cell membranes is negligible. Of the many experiments in which saccharin has induced bladder tumors, the doses were high—either 5% of the diet or more than 1 g/kg body weight daily for a year. It is therefore unlikely that the amounts of saccharin taken by humans present a cancer hazard. Although there are safe levels of promoters that act as surfactants and solvents such as benzene (22) it is difficult to postulate that there could be safe levels for those promoters, which, such as asbestos, remain in tissues.

Of the many tumor promoters some of which are listed in Table 1 only the few given in Table 3 would appear to increase the risk of human cancer. Cigarette smoke provides a complete carcinogen and acts as initiator for asbestos workers and as promoter for uranium miners.

REFERENCES

1. Deelman, H. T. Die Entstehung des experimentellen Tierkrebses und die Bedeutung der Zellregeneration. *Z. Krebsforsch.* 21: 220-226 (1924).
2. Setala, K. Progress in carcinogenesis, tumour enhancing factors. A bioassay of skin tumour formation. *Proc. Exptl. Tumor Res.* 1: 226-278 (1960).
3. Della Porta, G., Shubik, P., Dammert, K., and Terracini, B. Role of polyoxyethylene sorbitan monostearate in skin carcinogenesis in mice. *J. Natl. Cancer Inst.* 25: 607-625 (1960).
4. Walpole, A. L. In: Proceedings of the International Conference on Morphological Precursors of Cancer, Perugia, 1961 (L. Severi, Ed.), Perugia Univ., 1962, p. 83.
5. Fukushima, S., Tatematsu, M., and Takahashi, M. Combined effects of various surfactants on gastric carcinoma.

- genesis in rats treated with *N*-methyl-*N*-nitro-*N*-nitrosoguanidine. *Gann* 65: 371-376 (1974).
- Gangolli, S. D., Grasso, P., and Goldberg, L. Physical factors determining the early local tissue reactions produced by food colorings and other compounds injected subcutaneously. *Food Cosmet. Toxicol.* 5: 601-621 (1967).
 - Lusky, L. M., and Nelson, A. A. Fibrosarcomas induced by multiple injections of carboxymethyl cellulose (CMC), polyvinylpyrrolidone (PVP) and polyoxyethylene sorbitan monostearate (Tween 60). *Fed. Proc.* 16: 318 (1957).
 - Grasso, P., Gangolli, S. D., Goldberg, L. and Hooson, J. Physicochemical and other factors determining local sarcoma production by food additives. *Food Cosmet. Toxicol.* 8: 617-623 (1971).
 - Boyland, E. and Mohiuddin, J. Surface activity of some tumour promoters. *IRCS Med. Sci.* 9: 753-754 (1981).
 - Reddy, B. S., and Watanabe, K. Effect of cholesterol metabolites and promoting effect of lithocholic acid in colon carcinogenesis in germ-free and conventional F344 rats. *Cancer Res.* 39: 1521-1524 (1979).
 - Peters, R. A. Interfacial tension and hydrogen-ion concentration. *Proc. Roy. Soc. B133:* 140-154 (1931).
 - Wynder, E. C., and Reddy, B. S. Dietary fat and colon cancer. *J. Natl. Cancer. Inst.* 50: 1099-1106 (1973).
 - Traul, K. A., Krik, R. J., Kachevsky, V. and Wolff, J. S. III Two-state carcinogenesis *in vitro*: transformation of 3-methylcholanthrene-initiated Rauscher murine leukemia virus-infected rat embryo cells by diverse tumor promoters. *J. Natl. Cancer Inst.* 66: 171-175 (1981).
 - Rohrschneider, L., and Boutwell, R. Phorbol esters, fatty acids and tumour promotion. *Nature* 243: 212-213 (1973).
 - Tuyns, A. J., Pequignot, G., and Jensen, O. M. Les cancers de l'oesophagee en Ile-en-Villaine en fonction des niveaux de consommation d'alcool et de tabac. *Bull. Cancer (Paris)* 64: 45-60 (1977).
 - Wynder, E. C., and Gori, G. B. Contribution of the environment to cancer incidence. An epidemiologic exercise. *J. Natl. Cancer Inst.* 58: 825-832 (1977).
 - Maclure, K. M., and MacMahon, B. An epidemiological perspective of environmental carcinogenesis. *Epidemiol. Rev.* 2: 20-48 (1980).
 - Kono, S., and Ikeda, M. Correlation between cancer mortality and alcoholic beverage in Japan. *Brit. J. Cancer* 40: 449-455 (1979).
 - Enstrom, J. E. Colorectal cancer and beer drinking. *Brit. J. Cancer* 35: 674-683 (1977).
 - Jensen, O. M. Cancer morbidity and causes of death among Danish brewery workers. *Int. J. Cancer* 23: 454-463 (1979).
 - Boyland, E. Some implications of tumour promotion in carcinogenesis. *IRCS Med. Sci.* 8: 1-4 (1980).
 - Boyland, E. The role of benzene in carcinogenesis. *IRCS Med. Sci.* 9: 560-561 (1981).