

---

---

# ASSESSMENT OF TECHNOLOGIES FOR DETERMINING CANCER RISKS FROM THE ENVIRONMENT

---

---

JUNE 1981

*copy 2  
copy at hand*

*OTA  
H-138*



CONGRESS OF THE UNITED STATES  
Office of Technology Assessment  
Washington, D. C. 20510

life expectancy of a person born in the U.S. in 1950 was 68 years. By 1977 it had risen to 73 years, and 80% of those dying today are over 60 years of age. Cancer, although it kills at all ages, primarily affects the elderly.

Cancer has a major impact on the nation's economy, from the personal costs of treatment and lost income, to public expenditures for screening programs, public education, and cancer research. The costs of cancer are not merely economic, though these are enormous. Social costs have taken on increasing prominence in recent years, and include more than the obvious pain and suffering of the victim. Relatives and friends of victims, and care givers all may suffer direct consequences of the victim's morbidity and mortality. Social isolation, economic dependence, lost personal and business opportunities, and many undesirable and unwanted alterations in lifestyle are inevitable. Serious emotional and psychological problems requiring professional attention are not uncommon among victims and their family members, often producing irreversible changes in family structure and relationships. The costs of these social factors are not directly quantifiable, but some progress has been made in methodologies to measure them. Severity of pain and suffering can be measured, <sup>hardly!</sup> at least in relative terms, by the medication required for relief. Costs of psychiatric care may be used as surrogates for emotional and psychological stress. Other "shadow-pricing" mechanisms have been used, and a number of profiles have been developed to consider many social factors together (Granger and Greer, 1976; Elinson, 1974). There is no question that social costs are enormous, and improved methodologies will paint a more accurate picture of the impact of cancer on its victims and on society as a whole. (For a review of some methodologies for valuation, see OTA, 1980.)

A common measure of disease is the number of years of life lost due to premature mortality. This takes into account both the number of deaths and the age at which people die. The death of a younger person will contribute more

a little like Channay's Stan's  
estimate based on investment in gen for 2-2.  
ignores (1) consumer's surplus  
(2) what can't be bought  
at any price.  
regardless of price?

forces.

All individuals exposed to the same dose of a carcinogen do not develop cancer, indicating the involvement of individual susceptibility or host factors. The genetic contribution may be minimal or may predominate. Certain familial and genetic disorders are known to increase the risk of developing cancer. Daughters of breast cancer patients have a higher breast cancer risk than women without this family history, though many other factors affect the probability of developing the cancer. Individuals with deeply pigmented skin have a lower risk of skin cancer induced by sunlight. Retinoblastoma, a usually fatal malignant disorder of the retinal cells occurring usually before the age of three, has a well-defined hereditary pattern. Individuals with multiple polyposis of the colon, an inherited trait, are at an increased risk of colon cancer. There is also a group of familial disorders manifesting cellular abnormalities that increase the risk of cancer: Bloom's syndrome, Fanconi's anemia, and the immunologic deficiencies (Fraumeni, 1973).

Even in these cases, however, the malignancies are not necessarily completely spontaneous, and actions taken may prevent some of them. A case in point is xeroderma pigmentosum, a genetic disorder predisposing to multiple skin malignancies. Individuals with this defect develop numerous cancers and die at a young age, usually of leukemia or lymphoma, if exposed to even moderate amounts of sunlight. Affected individuals who have been completely sheltered from exposure to sunlight, the precipitating factor, however, have developed no malignancies (ref.).

Table 4-1 lists several cancers that occur as inherited traits or as complications of an inherited precursor state. All of these conditions together are believed to account for not more than an extremely small percentage of all cancer deaths (Knutsen, 19\_\_).

or inherited by single gene mutation.

traits not known to be readily modifiable by env. alterations.

regular cigarette smokers and those among lifetime non-smokers is so extreme that it is not likely to be an artifact of the epidemiologic method. Doll and Peto (1981), calculate that the increase in male and female lung cancer rates can be accounted for almost totally by cigarette smoking.

These findings on the effects of tobacco on cancer are derived from studies in which large numbers of people have been asked what they normally smoke and they are then followed for several years to determine the causes of any deaths that may occur. Table 7-1 presents data from the first 13 years of the largest of these studies, in which the smoking habits of one million Americans were ascertained in 1959 by Dr. E.C. Hammond on behalf of the American Cancer Society (ACS) (unpublished). The data show that deaths from lung cancer occurred almost 12 times as frequently in male one-pack-a-day smokers as compared to male non-smokers. Deaths from oral cavity, bladder and pancreatic tumors occurred in the smoking population 6, 3 and 2 times as frequently, respectively, as in the non-smokers. It should be borne in mind that these elevated risks would probably have been even higher if the people who had quit smoking during the course of the study were eliminated from the analysis. Many who reported a history of smoking regularly had quit by 1967, and others quit years later but this was not accounted for in the data (Hammond, 1980, Prev. Med.). Deaths from cancers at other sites were not found to be significantly affected by smoking.

*Do you want to footnote something about even greater non cancer*  
The excess cancer rates seen in the ACS study are almost exactly mirrored in a comparison of veterans who were cigarette smokers in 1954 or 1957 and veterans who said they had never smoked regularly. Rogot and Murray (1980) found lung cancer deaths occurred 11.3 times as frequently among smokers; oral cavity cancer deaths, 7 times; bladder cancer deaths, 2 times; pancreatic cancer deaths, 2 times; and deaths from cancers at other sites, 1.3 times. Other studies from Great Britain (Doll and Peto, 1976) and other countries (Surgeon General, 1979; 1980) show similar elevated cancer death rates among smokers.

*P.S. Smoking-induced cardiovascular mortality may even mitigate the apparent cancer effects of heavy smoking*

*Handwritten scribbles and lines, possibly a signature or initials.*

*Health impact of smoking?*

see Hansen, Obe  
reference, Obe  
attached

consumed as spirits (ref.). The apple-based drinks that are consumed in Northwest France are believed particularly harmful (ref.).

Pure alcohol is not by itself mutagenic or carcinogenic by any of the laboratory tests thus far devised, although many alcoholic drinks are found to be positive in short-term tests for mutagenicity. Given the good correlation

*Mutation Research*, 65 (1979) 229-259  
© Elsevier/North-Holland Biomedical Press

### MUTAGENIC, CANCEROGENIC AND TERATOGENIC EFFECTS OF ALCOHOL

GÜNTER OBE and HANSJÜRGEN RISTOW

*Institut für Genetik, Arnimallee 5-7, D-1000 Berlin 33 (Germany)*

(Received 12 January 1979)  
(Revision received 29 March 1979)  
(Accepted 5 April 1979)

#### Summary

Alcohol is mutagenic, cancerogenic and teratogenic in man. Ethanol is mutagenic via its first metabolite, acetaldehyde. This is substantiated by the findings that acetaldehyde induces chromosomal aberrations, sister-chromatid exchanges and cross-links between DNA strands. Methanol, a contaminant of many alcoholic beverages, is also mutagenic via its metabolite, formaldehyde. In addition, different indirect pathways may lead to mutations by alcohol. The cancerogenic activity of alcohol remains unverified by modern standard carcinogenicity tests. Ethanol and other alcohols, as well as aldehydes, inhibit RNA synthesis in cells and in cell-free transcriptional systems. A reduction of cellular RNA synthesis may play an important role in the mutagenic, cancerogenic and teratogenic activity of alcohol.

ments of alcoholic  
cancer risk. Alcohol  
between extrinsic  
it are responsible  
and larynx.  
sive alcohol  
mouth (excluding  
and perhaps even  
f the upper  
Jensen, 1977).  
e esophagus in  
ective study of male  
effects for smoking  
the mouth and  
ould be eliminated if  
imate was made by

exposures to alcohol and tobacco sites (76%). These sites combined represent approximately 36% of cancer deaths for all sites. Feldman, et al. (1975) found that the risk of head and neck cancer was 6 to 15 times greater in heavy drinkers who smoked than for nondrinkers and nonsmokers. Nonsmoking drinkers had a "slightly" higher risk (around 1.5) than total abstainers while nondrinking or light-drinking smokers had 2 to 4 times the risk.

Breslow and Enstrom (1974) correlated average annual age-adjusted cancer

the United States (Cole, 11—) In animals, caffeine is shown to potentiate the effect of carcinogenic substances (Donovan, 11—) and whether it has similar properties for humans is not yet known.

Whether other naturally occurring carcinogens exist in food is left to speculation, but on present evidence, naturally occurring carcinogens are not regarded as an important cause of cancer in the United States.

### C. Carcinogens or Precursors Produced by Cooking

Another possible source of carcinogens is their production in cooking. Humans are the only animals which cook their food, and it has been known for many years that carcinogenic chemicals such as benzo(a)pyrene and other polycyclic hydrocarbons are produced by pyrolysis when meat or fish is broiled or smoked or when food is fried in fat which has been used repeatedly. Sugimura (1977) demonstrated that broiling also produces powerful mutagens that cannot be accounted for by the production of benzo(a)pyrene alone. Commoner (11—) and SRI (11—) have shown that mutagens are produced by cooking to relatively low temperatures between 100-200 C.

*carcinogens  
man*

*This is so important I will expand on the observation of the*

Many epidemiologists have sought to relate the consumption of various cooked foods to the development of gastric cancer, but none has succeeded in doing so convincingly. Few people eat more broiled foods than Americans (ref.), and with gastric cancer rapidly diminishing in incidence in the U.S., it is unlikely that this source is important. While the method of cooking might be important, its effect is not subject to quantification.

*chemists  
of it.*

*for gastric ca. ? increasing last 20 years?*

*maybe  
systemic*

### D. Adventitious Carcinogens

A less obvious source and one that was overlooked altogether until the early 1960's, is the production of carcinogens by microorganisms in stored food. There is now good evidence for believing that aflatoxin, a product of the fungus

epidemiologic data. Many of these studies were reviewed by the National Academy of Sciences (NAS) Safe Drinking Water Committee (NAS, 1977; 1978; 1979, 1980) as mandated by the Congress. These reports serve as references for many issues concerning the health effects of drinking water contaminants.

Crump and Guess (1980), in a draft report for CEQ, review five of the recent case-control epidemiologic studies on cancer risk associated with drinking water in this country. Inadequacies are identified with each of the studies but most suggest an elevated cancer risk when the rates for persons living in areas with chlorinated water are compared to those for persons in areas with unchlorinated water. The most consistent association found is with rectal cancer. None of the studies permitted linking individual risks with individual exposures.

*confounding*

*You touch on this later but I would already here stress problems of confounding, perhaps systematic bias: water that has to be chlorinated even by this many problems.*

ogens and 3  
ng water. Based on  
ancer risks to  
m/liter for each of  
risk estimates for  
P-1.  
or 100-fold  
s are due to the  
interval estimates  
e and 1,2  
ve since been shown

bromodichloromethane and chlorodibromomethane, found in most drinking water systems surveyed by EPA, have not been appropriately tested for carcinogenic properties. They have, however, been shown to be mutagenic in the Ames test (Simmon and Tardiff, 1978). Presumably, additional substances found in drinking water will also be shown to be carcinogenic as more chemicals are tested. NCI

12/80  
draft

Consumer Products

Consumer products such as detergents and other surfactants, hair dyes and other cosmetics, solid or foam plastics, paints, dyes, polishes, solvents, fabrics, and even the processed paper and the printer's ink in the present volume are a class of agents which are so numerous that it is only possible to echo the uncertainty with which pollutants were discussed in the previous section. It is possible that some of these products are already causing, unnoticed, a number of today's cancers, and it is quite possible that, after prolonged exposure to them, some substantial risks will be detected in the future. For example, in mouse skin carcinogenesis experiments, surfactants (e.g., Tween 60) are potent promoting agents; permanent hair dyes contain substances such as 2,4 diaminoanisole which can damage DNA, and some components of hair dyes are carcinogenic to laboratory rodents. Many of the monomers from which plastics are made are carcinogenic in animals, and the monomer inevitably slightly contaminate the finished products. Many of the halogenated solvents in common domestic and office use can cause mouse liver tumours. For many consumer products, the type of laboratory and human evidence is insufficient for determining whether they pose a cancer risk.

*Handwritten notes:*  
Tweens  
detergent  
[unclear]

At this time, it is difficult if not impossible, to assess the contribution of consumer products to the overall cancer rate. Doll and Peto attribute "less than 1%" of all cancer deaths to such products, but they stress that there is too much ignorance for complacency to be justified. Many industrial products have been introduced so recently that even if they do prove hazardous their effects would not yet be apparent.

*reference?  
other surfactants?*

for American women, thought to be attributable to improved nutritional status (Miller and Bulbrook, 1980). The effect of this on future breast cancer rates is uncertain. Early studies in rats correlated body size, more than age, with onset of menarche (Kennedy & Mitra, 1963). Observations in humans, including a recent look at menarche and amenorrhea in ballet dancers (Frisch, et al., 1980), provide additional evidence that lean body mass is related to later menarche.

Later age at menopause brings increased risk. Women with natural menopause after age 55 have about twice the risk of developing breast cancer as do women with natural menopause before age 45 (MacMahon, Cole and Brown, 1973). Although increasing age is an important risk factor for the development of breast cancer,

different populations.

increases throughout

increases until middle

73). This

most cancer may have

and one acting

question,

the breast cancer

evidence examined here

is not to modifying

there is no consensus about

causes.

Breast Ca. genetics

In an exciting new development  
phase see: M C King

Science 208:406

4/25/80

Jack Fishman here and Mark Skolnick  
at Uchicago in hot pursuit related issues:  
204:1089 (1979)

Breast cancer risk has a strong familial component that has not been entirely explained by lifestyle similarities among relatives. Anderson (1971) categorized different types of risks for women with different familial histories of breast cancer. Relatives of women with unilateral disease have a risk of 2 to 3 times that of the general population; and relative of women with bilateral breast cancers have a much higher risk.

Infection

*I would give  
more credit  
to B. Blumberg  
on hepatitis/liver  
cancer.  
Blumberg*

Infection particularly viral, has long been thought a cause of cancer, but Statistical evidence does not support the idea that cancer is a contagious disease. People who come into close contact with cancer patients, such as nurses, doctors, and spouses of patients, are at no higher risk of developing the disease than others. Reports have occasionally been published of the occurrence of an unusually large number of cases of some rare type of cancer in a small community, but such clusters can be expected to occur periodically by chance alone in a population as large as that of the United States. It is more plausible that viruses that are transmitted from one person to another are important in the development of some types of cancer, but they probably they are widespread in the community. A variety of other factors determine whether exposure to the virus leads to the development of disease, which probably happens in only a small proportion of those exposed.

The strongest evidence to implicate a virus in cancer causation concerns two types of cancer that are rare in the United States -- Burkitt's lymphoma and nasopharyngeal carcinoma. In both cases, the causative agent is believed to be the Epstein-Barr virus, a DNA herpesvirus which occurs ubiquitously and is known to be the specific cause of infectious mononucleosis. It is postulated that the viral DNA integrates into the genetic material of a human stem cell and that cell becomes the parent of a malignant clone. Seroepidemiologic data and the detection of Epstein-Barr viral DNA in lymphoma cells supports the association between the virus and these two cancers. Burkitt's lymphoma occurs mainly in children in central Africa and New Guinea. The unusual geographical distribution suggests that the virus may act as a co-carcinogen and that additional factors, such as immunosuppression from malaria may be involved.

Nasopharyngeal carcinoma, found in the Far East, also is associated with the Epstein-Barr virus, but the association is not as strong as with Burlett's

limited. Studies of patients in mental hospitals (Clemmesen and Hjalgrim-Jensen, 197\_ ; Buldwin 1979) are not supportive of an increased risk. Psychological stress does have a recognized importance in causing people to smoke, drink, overeat, and partake in other harmful activities which may indirectly increase their risk of cancer.

#### New Cancer Associations

Hazards exist today which may not have caused any cancers, but which may do so in the future. A timely example are hazardous wastes that have been improperly disposed of in areas commonly termed "dumps." EPA has estimated that there are more than 50,000 dump sites containing hazardous waste that are not being properly operated. Of these, they estimate that 30,000 pose a significant health risk. The carcinogenic potential of the myriad of chemicals in these dumps is unknown at present. (OTA is conducting an assessment of non-nuclear industrial wastes which will look at health risks, among other things, to be completed in late 1982.)

\*

Development of new chemicals has been booming. They are introduced into commerce at the rate of about 400 per year at present. The ability of the EPA to adequately evaluate these additions is limited. Some potential hazards will undoubtedly be identified through the Premanufacturing Notices required by Section 5 of TSCA, but new hazards may well be released. Exposures will most likely be through pollution, occupation, consumer products, foods, or other routes already described.

Sources of carcinogens yet to be imagined are difficult to discuss, except to say that we best be on the lookout.

\* But since 1950, Industry + all of us are  
1000x more careful about dissemination of bulk  
chemicals, esp. solvents.

4-79'

*Handwritten signature/initials*

Table 1. General Classification of Tests Available to Determine Properties Related to Carcinogenicity

Method	Organism used	Time required	Basis for test	Result	Conclusion, if result is positive
1. Molecular structure analysis	- <i>hu.</i> <i>exptl.</i>	Short (days) <i>-- weeks</i>	Chemicals with like structures interact similarly with DNA	Structure resembles (positive) or does not resemble (negative) structure of known carcinogen	Chemical may be Hazardous. That determination requires further testing
2. Short-term tests	Bacteria, yeast, cultured cells, intact animals	Generally few weeks (range 1 day to 8 months)	Chemical interaction with DNA can be measured in biological system	Chemical causes (positive) or does not cause (negative) a response known to be caused by carcinogens	Chemical is recognized as a potential carcinogen
3. Bioassay	Intact animals (rats, mice)	Ca. 5 years	Chemicals that cause tumors in animals may cause tumors in humans	Chemical causes (positive) or does not cause (negative) increased incidence of tumors	Chemical is recognized as a carcinogen in that species and as a potential human carcinogen
4. Epidemiologic	Humans	Months to lifetimes	Chemicals that cause cancer can be detected in studies of human populations	Chemical is associated (positive) or is not associated (negative) with an increased incidence of cancer	Chemical is recognized as a human carcinogen

\* divide into paper chemistry (theory)

and elementary reaction studies -  
in lab.

e.g.

alkylation of DNA

or of model substrate

years), which dictate the length of a lifetime exposure experiment, and a large amount of information about the genetics, breeding, housing, and health of these animals. Rats and mice are cheap to buy, feed, and house.

Primates are sometimes used for certain toxicological testing. They are certainly more like humans than rodents but their supply is limited. They are expensive, live up to 25 years, and require large areas for housing. Despite these difficulties, NCI now maintains about 600 monkeys for carcinogenicity testing at a cost of about \$500,000 a year (R. Adamson, personal communication).

Dogs lie between rodents and monkeys in their apparent likeness to humans, but are more like primates in costs.

*what every body says  
but evidence is almost nil!*

Differences in metabolism, bioaccumulation, and excretion between rodents and humans are valid reasons for questioning rodent results; however, these differences should be documented before they are used to negate test results. There is no question that further research in the comparative biochemistry and physiology of man and rodents is necessary, but the comparisons will ultimately be limited by restrictions on what can be determined by experimentation in humans.

General Objection 4. Some test animals or organs of test animals are exquisitely sensitive to carcinogens, and such sensitivity invalidates use of results from such animals.

Griesemer and Cueto (1979) have analyzed the results of testing 190 chemicals in the NCI Bioassay Program (see discussion in "Expert Reviews of Bioassays," below). They identified 35 chemicals which were "strongly carcinogenic" in either the rat or the mouse and non-carcinogenic in the other species. Of the 35, 18 were positive in the mouse and negative in the rat, and 17 were positive in the rat and negative in the mouse, which indicates that neither animal is much more often the sensitive species. However, 12 chemicals caused mouse liver tumors, no other lesion in the mouse and no lesions in rats. Taken by themselves these results suggest that the mouse liver is a sensitive

basis for such estimates, and all of them show that a significant porportion of tested chemicals have been classified as carcinogenic.

A definitive answer to questions about what chemicals are carcinogens depends on testing every chemical, and that is beyond the capacity of the bioassay system. Tomatis (1977) reported that 828 chemicals were under test worldwide in 1975, and that 317 were repeat tests of chemicals for which, in his opinion, adequate data already existed. The 828 chemicals did not include all chemicals under test in private or commercial laboratories; he did not estimate that number.

Finding more and more chemicals to be carcinogenic in bioassays raises important policy questions and may force a decision to place carcinogens in order for possible regulation or voluntary reductions. It is not apparent how to deal with a large number of carcinogens without ordering them as to their riskiness.

You might want to pursue further the eventual consequences of the always prudent approach exemplified by Peter Heett's "life is too short" aphorism. If there is an infinity of alternatives, "prudence" is prudent. But surely I do not have to expand on opportunity costs. You mention, but perhaps might enlarge upon this theme.

Need much  
stronger statement.  
cf. my ASTM  
editorial  
unloaded.