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# The chemical industry and the health of the community

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**Before the discussion of Dr Paulson's paper, the following statement prepared by Dr F. J. C. Roe, was agreed by those attending the Conference:**

## Priorities for research into the role of environmental factors on cancer risks in man

**Non-genotoxic rather than genotoxic mechanisms are responsible for the majority of human cancers**

Available information from both laboratory and epidemiological studies suggests that non-genotoxic mechanisms, as distinct from genotoxic mechanisms, are heavily, if not predominantly, implicated in the causation of cancers in man. For some body sites, for example, breast, corpus uteri, prostate and various endocrine glands, there is a particularly strong likelihood that non-genotoxic mechanisms are principally to blame. It is clear that there are many different and varied non-genotoxic mechanisms and, at present, there is no reliable battery of laboratory tests which, between them, can reliably predict the presence or absence of such activity in man.

**Understanding of cancer could best be advanced by research into mechanisms of homoeostasis and consequences of its disturbance**

This unsatisfactory situation could be, at least partly, rectified by systemic and thoughtfully planned research on mechanisms in two related areas:

1. Research into the nature of physiological homoeostatic mechanisms, with special reference to classical and recently discovered hormones and regulatory peptides.

2. Research into the ways in which homoeostatis can be disturbed, and the long-term consequences of such disturbance.

**The conference urges shift from testing to research on mechanisms**

In the light of this position, the member scientists attending this conference urged a move away from research based on the tacit assumption that all or most human cancer is due to exposure to genotoxic carcinogens, and from the regulatory witch-hunt for vanishingly small amounts of genotoxins. Instead, they urged a major shift of resources from the testing of chemicals to research on cancer mechanisms.

**The evidence supports this proposal**

In support of this view, it is no longer possible to ignore the evidence that in laboratory rats and mice, not deliberately exposed to any chemical agent, overfeeding has been shown to increase overall cancer incidence by factors that are far greater than those used as a basis for banning a chemical agent from general use. Not only does this evidence establish the importance of non-genotoxic mechanisms, but it also undermines the confidence that is currently placed by regulatory agencies in the predictive value of laboratory animal tests for carcinogenicity.

**Laboratory test systems of carcinogenic risk must be developed**

In this context, the emphasis of research into mechanisms which is now proposed should include efforts to develop laboratory test systems in which a treatment-related carcinogenic risk can be seen clearly against a background of low tumour risk in untreated control animals that are essentially free from laboratory-induced endocrine and other disorders.

## Summary of discussion

**Support is given to Dr Roe's statement**

Dr Paulson thought that Dr Roe had made some very valid points. He had not discussed diet-tumour incidence in experimental animals in his paper (mainly through lack of space).

Dr Roe added that if he were in charge of a regulatory authority, for every dollar put into testing chemicals he would require a dollar to be put into studying mechanisms of cancer research (Dr Lieberman considered that the ratio should be 2:1).

**Can habits be changed?**

Habits, whether of diet or lifestyle, cannot be changed quickly so, in Dr Lieberman's view, regulation has to start from where people are *now* and in the context of the way they presently live. Professor Kletz reminded the meeting that diet *can* be changed, as evidenced by the changed dietary habits of Americans over the past two decades. They now tend to eat less fat and more fibre. The result is a lower incidence of heart disease in the USA. Why cannot the same be done in the UK? If we could only be *sure* of what we should and should not eat, perhaps the incidence of cancers related to diet could also be reduced.

**What to advise people to eat to reduce cancer risk**

Dr Lieberman responded that although the change in incidence of myocardial infarction in the USA is seemingly linked causatively with changes in diet, definitive proof is lacking. In any case, it may not be easy to advise people how they could reduce the present 35 or 40 per

cent of cancer associated with diet. If we want to lower cholesterol, that is easy, but diet and cancer is a much more difficult problem to sort out. Caloric intake has been stressed, also the difference between saturated and unsaturated fats, trace elements, protein ratio, etc. It is extraordinarily difficult to know what to do.

**The evidence in favour of high-fibre diet is not proven**

That is really the problem. For example, it is said that a high-fibre diet, resulting in faster intestinal transit time, reduces the incidence of cancer, particularly gastrointestinal—but the relationship is not compelling. Certainly, as Dr Roe said, Africans who eat a 'rush-through' diet containing a lot of fibre do not get appendicitis, chronic diverticulitis or colon cancer, but it is an association only.

**Intestinal flora are affected by food**

The spectrum of intestinal flora is affected by diet. Microorganisms in the gut play an important role in metabolically altering compounds. Big differences in gut flora are associated with inanition, as distinct from large intakes of food, but the relevance of these differences to cancer risk is not known.

**Stomach and oesophageal cancers in Japan probably due to genotoxins originating in food. Otherwise traditional Japanese diet carries lower cancer risks**

Some diets certainly appear safer in terms of cancer incidence. For example, the Japanese diet, with which less cancer is associated—except cancer of the stomach and oesophagus. Dr Roe considers it likely that these two particular cancers have a rather direct genotoxic mechanism, perhaps involving nitrosamide formation, whereas most of the diet-associated cancer in the West is probably non-genotoxic. On the whole, the Japanese eat less than Westerners and are slimmer, but it is interesting that, as they and their diet become westernized, their cancer incidence rises. He added that research concentrating on these very striking differences should provide much needed information.

**Epidemiological studies identify problems to be researched**

There was agreement on the need for epidemiology, as shown by the differences recorded. For example, liver cancer is a minor problem in the USA (3000–4000 cases a year), but it is the commonest cause of death from cancer in South-East Asia. Similarly, whereas lung cancer is the commonest form of cancer in males in the USA (100 000 cases a year), in Japan stomach cancer is commonest. Again, while the incidences of breast and intestinal cancer are low in Japan, high incidences of both are found in the USA. The reasons for these cancer patterns, as revealed by epidemiological studies, genotoxic or non-genotoxic, need to be determined.

**Voluntary vs involuntary carcinogens**

Dr Lieberman again reminded the meeting of the need to distinguish between voluntary exposure to carcinogens (via diet and personal habits, such as smoking) and involuntary exposure. This same distinction had been discussed earlier with regard to voluntary and involuntary risks. As far as possible, individuals should be able to exercise choice over whether or not they are exposed to situations which carry a cancer risk.

**Despite heavy pollution, cancer rates remain stable overall. This suggests no close association between pollution and cancer**

It is interesting that, in general, cancer rates have remained relatively constant over the last 30 years, despite the vast increase in environmental pollution. The exceptions are a marked rise in lung cancer, a slight increase in pancreatic cancer and a slight decrease in stomach cancer. Despite the many major changes that have occurred in the nature and levels of pollution in the USA and Japan during the last 50 years, for instance, patterns of cancer incidence (adjusted for age) have not changed much in these countries. They have also retained their national patterns. That must focus our attention back on to diet and lifestyle, and away from environmental pollution (except in the workplace).

**Nature also produces poisons that enter the food chain**

Dr Murray pointed out that nature, as well as the chemical industry, produces poisons that find their way into the food chain. The list of naturally occurring chemical poisons includes toxic and carcinogenic mycotoxins. Is it possible to assess the relative contributions of the chemical industry and nature? Also, what is known concerning the

bioaccumulation in animals and plants of toxic materials other than heavy metals?

**Effects of the bioaccumulation of chemicals in oysters**

There would seem to be some quite surprising inconsistencies. For example, some oysters have disappeared following the use of an anti-fouling paint, whereas other oysters in the Thames estuary accumulate radioactive zinc from Bradwell power station with no apparent damage.

**Nature's toll is soon destroyed, so that causes are difficult to investigate**

Dr Paulson replied that data are meagre, for which two reasons may be cited. First, the evidence is quickly decomposed in the wild. It is pure luck to find (as his organization had recently) the body of a whooping crane which had died from chronic lead poisoning after ingesting a spent bullet shell. Sir Frederick Warner supported the belief that there is undoubtedly a high toll of water-fowl from eating spent lead shot from anglers—but the evidence has gone before it can be found.

**There has been little controlled work on the effect of pollutants on wildlife**

Secondly, minimal work has been done in a scientifically controlled way to investigate pollutants which may take a toll of wildlife, whether in terms of acute or chronic toxicity or (as with mercury) behavioural changes that would make an exposed population less able to resist predation.

**Fluorosis in cattle is an example of fatal bioaccumulation**

Sir Frederick cited an example of bioaccumulation of the fluoride ion in the food chain. If aluminium smelters discharge fluoride ions at a ground-level concentration of slightly more than 1 $\mu g/m^3$, there will eventually accumulate 30 mg/kg dry weight fluoride in the herbage, the cattle will develop fluorosis and die. This brings us back to the qualitative aspects of diet. Since humans do not eat grass, they would not die from excess fluoride ion in herbage. This illustrates the point made earlier, that we should not rely on human health effects as an index of environmental pollution.

**Is it useful to distinguish between toxins of natural and unnatural origin?**

A question was raised about the classification of substances in the environment as being of natural or unnatural origin. Is this a useful distinction? Surely the body does not make the distinction. Dr Paulson said that even though the body cannot do that, it is useful so to subdivide substances, not because the biological consequences are different, but because knowledge of the source of toxins helps to determine how to deal with problems if action is considered necessary. If it is a naturally occurring contaminant, for example, in foodstuffs, the technique used to reduce human exposure would primarily be educational rather than regulatory.

**The body is limited in the number of ways it can respond to toxins**

Parenthetically, it is surprising how few responses the body can make to a bewildering array of insults, particularly in high doses. Although our understanding of mechanisms of carcinogenesis is still very limited, a wide variety of chemicals has been shown to be directly or indirectly genotoxic.

**The reasoning behind EPA's approval of a compound leading to bladder cancer in rats**

On a more specific point, an explanation was provided by Professor Golberg why the Environmental Protection Agency (EPA) in the USA allows the use of a product for the prevention of flies breeding on chicken droppings. This product contains a compound which was shown to be completely non-genotoxic when studied in the National Toxicology Program. However, it promptly forms bladder stones in rats, leading to bladder cancer in those animals at the very high levels used and under conditions of maximum tolerated dose. In man there is little association between bladder stones and bladder cancer, probably because stones are removed as soon as they cause symptoms. It is therefore an artefactual situation. True, it is never possible to be absolutely certain that something is not acting as a carcinogen but, on the whole, EPA (possibly on the advice of the FDA) seems to be showing good sense in this instance. Dr Paulson added that the risk of cancer deaths would

be of the order of $10^{-6}$, an acceptably low risk for a carcinogen, and one which has been used as a sort of benchmark by the EPA for carcinogens for some time.

**The term 'carcinogen' should not be loosely used**

Finally, there were two semantic pleas from Dr Goulding. First, that we should not use the term 'carcinogen' loosely and without qualification. A more scientific position would be to state that a substance demonstrates carcinogenic properties in defined circumstances.

**Let us not refer to techniques as 'sophisticated'**

Secondly, cannot the unfortunate term 'sophisticated analytical techniques' also be discarded? The sophists were people who told false stories plausibly—which is not an attribute with which analysts would wish to be associated.

to know what questions to ask, to be able to force good science, and to have the data to give to the Administrator who would be making essentially political decisions in an exacerbated political atmosphere. The Science Advisor was against that argument, which was lost. The research basis that was put in was theoretically sufficient to enable EPA to know where to get the relevant information outside. We have paid the price of that lost argument.

**There were great political pressures from the outset . . .**

There were also extreme political pressures on William Ruckelshaus, EPA's first Administrator, and heightened public expectations. Trying to set up and run it in that atmosphere, he felt, was like trying to perform an appendicectomy while running a 100-yard sprint—a very difficult exercise.

**also, staff warfare – the old and the new had their biases**

Yet another problem in EPA was that of professional staff. On the pesticides programme, most of the personnel came from the Department of Agriculture, with a perceived role of worrying more about pesticides' efficacy than health and environmental effects. They were immediately distrusted by the people running EPA—who promptly hired people of the opposite bias, the result being open warfare.

**The problems of EPA summarized**

Summing up the problems, Mr Costle said that there were insufficient laboratories, warfare on the aim of pesticides' regulation, whether it was to be related to efficacy, or health and safety, and the old versus the new bureaucrats.

**EPA's low ranking in the scientific community adds to its difficulties**

As a working scientist, Dr Lieberman supported both Professor Golberg and Mr Costle, but added a further dimension to EPA's problems. Because EPA has such low standing and credibility in the scientific community, the best university students are discouraged from seeking posts there. This has led to a real estrangement between EPA and scientists of quality.

## Statement by Dr Francis J. C. Roe

**The idea of an 'open' society needs careful consideration**

There are a few loose ends that I would like to raise. First, an issue which has not been debated is the open society, about which I am sure most people have views. In theory, I am in favour of open society, but it needs to be thought through carefully, and considered in terms of just how much it costs.

**Openness on committees could destroy the balanced views now arrived at**

The sort of committees on which I sit (government committees, like the Committees on Toxicity and Carcinogenicity) comprise people from very different disciplines. Although each has a reasonable knowledge in his own specific area, he does not come to the committee with a prepared position, but tries to see how his own views dovetail in with other people's knowledge. The idea that such a committee could be 'open', that there could be press or public present, would completely destroy its value. I would not think that is the right way to proceed. It would mean that people would take up a prior position, which would not be a balanced view since it represents only their own knowledge and experience.

**Information cannot be available to all immediately**

So, although I feel that there may be a good case for making our society more open than it is now, immediate availability and freedom of information are nonsensical in the areas in which I work, and would destroy much that is good.

**Nor should committee structure be too broad**

Secondly, related to this, as Professor Golberg said earlier, is the idea that committees should be made up of representatives of all the minority groups. This also does not work in the realm of high science. Even where it seems to work, the reality can make a mockery of the intention. For

example, in the World Health Organization people from a wide range of countries, the undeveloped and the developed, may sit together on committees. However, what happens in practice is that two or three representatives from the USA or Europe do all the talking and make all the decisions, while those from other countries contribute little or nothing.

**Our lives are becoming dominated by paper**

Thirdly, perhaps a slightly (but not entirely) facetious suggestion that a conference of this sort might make is to put a high tax on paper. Paper is beginning to dominate our lives. There was a time when the papers most discussed were the primary scientific papers, the new publications in the scientific journals. Now we find that people have not seen the primary papers. They are interested not in them, but rather in the comments on the primary papers, and then in the lawyers' appreciation of those comments—and, in the end, there are people with piles of paper, who have neither seen nor read (and, if they did read, would not understand) the original documents.

**The primary papers are lost in comments upon them**

This is a very serious matter to which radical thought needs to be given.

**The US tobacco industry fears litigation**

A fourth loose end relates to comments made about the US tobacco industry. In that industry it is the contingency fee-based litigation system and not the serious discussion of scientific issues which dominates the scene. The tobacco industry has only to lose one case in the USA, and the whole of that industry would be turned upside down. Since the industry cannot afford to lose one case, the lawyers have become totally in charge of making all statements. The same 'communication disease' is spreading to Europe because a lot of the tobacco industry, for instance, in the UK, is American owned, and tragically it is also now spreading into other areas, such as the chemical industry. Medico-scientific discussion of complex topics, such as the effects of tobacco smoke and smoking on health, should be free and open and not dominated by voices more concerned with litigation and the law than with science.

**That is why the lawyers have taken it over**

**Nothing must be put in writing for fear of its use in litigation**

We have reached the stage at which people ask for an opinion on something—adding that it should not be put in writing. If anything is put in writing, under the US Freedom of Information Act in no time at all a copy will find its way across the Atlantic, and will prejudice a case in some minor litigation suit in somewhere as remote as Wyoming.

**This power of lawyers over what we do is alarming**

More generally, I see the power of the lawyers, and the legal situation in the USA as worrying. Of course, there are many reputable environmentalists (we have them at this conference), but there are also the disreputable ones who are really an extension of the legal system. They are in the business of making money out of winning cases.

**The lawyers must not be allowed to take over science**

For all these reasons, we see a retreat from science, and a shift towards PR and the lawyers. I think this is bad, and some action is needed to reverse this trend.

**Scientists are afraid to stand up for what they believe to be right**

At the time of the EPA and OSHA hearings, I was called in by industry to give balanced views, which I tried to do. While in the USA, I asked my colleagues at the National Cancer Institute (NCI) why they were not testifying since they agreed with my position. They gave two reasons: first, because they do not want to spend their life doing that; they want to stay on the bench. Secondly, they have their grants to consider; if they are seen to take such a stand, they will be cast as 'industry persons', which may mean that they will not get any more NCI grants.

**The costs of so doing can be too great**

It is said that scientists should stand up and be counted, but it is not so simple. It is not only a question of assembling their thoughts, and then standing up to say what they believe. It is also a question of counting the cost of doing so. This, again, is a very serious situation.