Conference Transcript

RECLAMATION AND REDEVELOPMENT OF CONTAMINATED LAND

The Industrial, Economic and Social Issues

In recent years substantial areas of land have been contaminated. This has occurred in a variety of ways and been caused by a variety of substances, some of which were, and remain, of a hazardous nature. Much of the contaminated land continues to be derelict and sometimes potentially dangerous.

Recent incidents both in the USA and in this country have focused attention on the risks to human health and on the problems with the integrity of buildings and underground services associated with the redevelopment of contaminated land.

The need for careful site investigations and planning prior to the redevelopment of contaminated land is now being recognised and appropriate precautions are being taken to minimise the risks involved.

The conference held last December brought together a wide range of bodies and disciplines concerned with these problems. It was of particular use to local and central government officers concerned with environmental control and planning; to industrialists involved with waste disposal especially those producing wastes of a hazardous nature; and to research bodies and architects and consulting engineers dealing with the design and redevelopment.

£20.00 165 pages ISBN 0 9505774 2 1

CONFERENCE TRANSCRIPT

Identification and Control of Chemical Carcinogens in the Workplace

London – July 1981

Published by Scientific and Technical Studies

IDENTIFICATION AND CONTROL OF CHEMICAL CARCINOGENS IN THE WORKPLACE

Conference Transcript

There is a widespread belief that we are in the midst of a cancer epidemic. While as many as one in five deaths is caused by cancer, only a small proportion of these is due to occupational carcinogens. Yet the nature of the disease demands that all avoidable causes of cancer be removed, and while chemical carcinogens cannot all be banned, a system for the identification and control of these substances which can be adopted by industry is now emerging.

*What are the tests for potential carcinogens? Are they reliable?

*How can you isolate and assess an occupational cancer hazard?

*What efforts, both national and international, are being employed to control the presence of carcinogens?

*How do labour representatives view the problem?

The conference, which took place in July 1981, was chaired by Professor Sir Richard Doll, and included eminent speakers who provided answers to these and other questions, and provoked debate on this important and disturbing subject. The transcript reproduces the papers given at the conference and presents an edited version of the discussions that took place during the meeting, which brought together a wide range of people associated with the problem of chemical carcinogens in the workplace, including occupational hygienists, plant managers, safety officers, health and safety advisers, medical officers, toxicologists, epidemiologists, scientists and employers' and workers' organisations.

£35.00 150 pages approx ISBN 0 9505774 7 2

Contents

Contributors

Professor Sir Richard Doll, Warden, Green College, Oxford and Honorary Director of the ICRF Cancer Epidemiology Unit

Dr R Murray, OBE, Occupational Health Consultant

Dr F J C Roe, Consultant in Toxicology and Cancer Research

Dr B Phillips, Genetic Toxicology Department, British Industrial Biological Research Association

Professor J M Harrington, Institute of Occupational Health, University of Birmingham

Dr J P Tassignon, Counsellor in Industrial Medicine and Toxicology, Solvay & Cie, Brussels

Dr Alexander Munn, Director, Medicine & Environmental Health, Monsanto Europe SA, Brussels

Dr R Owen, Medical Adviser, Trades Union Congress

Dr Eula Bingham, Professor of Environmental Health, University of Cincinnati Medical Center and formerly Assistant Secretary of Labor of Occupational Safety and Health, USA

H J Dunster, Deputy Director General, Health and Safety Executive, and Chairman of the Advisory Committee on Toxic Substances

Dr A David, Medical Officer, Office of Occupational Health, WHO, Geneva

Scientific and Technical Studies, Norwich House, 11-13 Norwich Street, London EC4A 1AB.

See over for details of another important publication ⟶

PANEL DISCUSSION

DAY 1

Unidentified contributor:

I have one question which I think should be directed at Dr. Roe. I don't think the topic has been mentioned. What are his views about the difference in incidence of spontaneous tumours in a carcinogenicity study where two control groups are being used?

Dr. Roe

I went through a phase in my life when I recommended that companies testing chemicals in fond hope that they were going to get a negative result would be advised to set up two control groups rather than just one, because this would provide extra assurance against a spuriously positive result, i.e. a spuriously low incidence of tumours in one control group. However, I have subsequently been involved in many discussions on this subject and I am now wholly persuaded that this is a pointless thing to do. If the incidence of tumours is much higher in one control group than the other, you are not free to choose that one because it suits your purposes. The Regulators are not going to permit you to choose the high tumour incidence control group and you would be foolish to choose the low one and so you end up by having to combine the two together. Not only have you gained nothing, but you might have made matters worse by casting aspersions on the validity of the study as a whole because other people looking at your data say, "If there is this big difference between two supposedly similar groups, what reliance can we put on the whole study?" Thus I am now convinced that the best procedure is the one that most statisticians advise, namely, that you have a control group of larger size than the treated groups, according to the formula:-

$$N_C = Nt\sqrt{x}$$

where N_C is the number of control animals, Nt is the number of animals in each treated group and x is the number of treated groups.

Dr. el-Mofty

About the non-treated controls of Dr. Roe, he said that they developed mammary tumours, and you said that it might be due to captivity, don't you think that captivity induces adrenalin, that this, in turn, induces the release

of steroid hormones from the adrenal cortex of the rat, and that it is the release of these hormones that enhances mammary tumour incidence?

Dr. Roe

No, I don't think that is the position. I think if you took an animal from the wild, which had lived a free life, and you put it in a cage then it would be very stressed and have an adrenalin reaction for some time, but that isn't what happens with laboratory animals. Such animals are bred in captivity they are used to it and wholly relaxed. They would only get a release of adrenalin if they were actually set free and faced with dangers that they are protected from. In any case, I doubt whether captivity per se is the factor that increases mammary tumours. It is the whole way in which we keep animals which is in some way associated with abnormal hormonal status. We have one index of this abnormal status already. In laboratory rats from about the age of 6 months onwards the serum prolactin levels begin to rise from the normal levels of about 20 to 40 nanograms per ml to levels of several 100's of nanograms per ml. Diet restriction would to some extent prevent this abnormal rise, but I am sure that other aspects of the artificial way in which we keep laboratory animals also need to be corrected.

Dr. Munn

Q. Chairman, in your introductory remarks this morning you referred to the hormone suggestion that we are experiencing an epidemic of cancer in the United Kingdom and if I understood you right you suggested that this was not the case, nevertheless similar suggestions of a current epidemic of cancer continue to appear from that great land across the Atlantic ocean and I wonder if you are in a position to comment on what exactly is the position in the United States?

Chairman. A. Yes I have examined the data in some detail recently on the claim that there is an epidemic of cancer in the United States and this is based on comparison of cancer incidence as recorded, the number of national cancer surveys and the continuing seer programmes of

epidemiology and end results programme which is trying to record the incidence of cancer in about 10% of the population of the United States each year and the figures obtained from the surveys do undoubtedly show a substantial increase over the last ten years of something of the order of 2% per year. The difficulty in accepting this, this is age standardised rates of course, the difficulty of accepting this is that this is in no way parallelled with the mortality rate which for many cancers other than cancer of the lung and the other tobacco and alcohol related cancers are going down whilst this increase, particularly in cancer of the breast , cancer of the intestine, cancer of the prostate is going up dramatically so you have to explain this difference. Now either you have to say that treatment is improving , that the incidence is going up, the treatment is improving so rapidly that the mortality despite the increase in incidence going down or you have to say that the increase in incidences is an artefact. Now there is of course an improvement in treatment in some cancers dramatic in the case of Hodgkins disease but not I believe any significance in relation to most fatal cancers and there is a much simpler explanation namely that the screening programmes which are being extensively developed in the United States are resulting in the increased diagnoses of pathalogical cancers but not clinical cancers. There is a lot of evidence to support this and you will all know that if anyone, if I were sufficiently misguided as to allow anyone to do a biopsy of my prostate there would be a 25% chance that it would be diagnosed as showing cancer but I am certainly not going to allow that to happen unless I have some significant clinical symptoms. If a woman has cancer of the breast and unfortunately falls into the hands of the surgeons who believe that the treatment for cancer of the breast is bilateral mymectomy which a number of surgeons do believe in the United States and the "normal breast" is sent to the pathologist, cancer will be found in the other breast in 20% of cases. He she goes to another surgeon who doesn't believe in bilateral mymectomy her chance of developing cancer in the other breast is about 0.5% a year of developing clinical cancer and I can give you some examples on large bowel and adenoma which

are diagnosed as cancer if you biopsy them and send them to pathologists are indistinguishable from early cancer and of course these are all being picked up very rapidly now through the increasing use of screening for occult blood. So we have this position that a proportion of people like the animals in your controlled experiments, the proportion of people who if adequately investigated, adequately in quotes, will be shown to have a pathalogical cancer is enormous and if you do sufficiently intensive investigation you will pick up one of these cancers and this, its my belief, that this is the reason for the so called epidemic of cancer which is occurring in the United States, its an epidemic of pathalogical diagnoses and I prefer to base my judgment on whether cancer is increasing or not by looking at the mortality rate especially the mortality rate in young people, and these are almost uniformly going down in both countries. Its not true of all cancers, obviously mesalthelioma is going up, though I am glad to say in this country under the age of 65 that has now ceased, but pancreas, bladder, lung are all going down, stomach, colon, if you look at the mortality rates in the under 65's. So I am afraid its rather a long answer to your question, but its a difficult question and my judgment on this particular point may be wrong, but I am glad to have had the opportunity of explaining why I think there isn't an epidemic, yet you get committees, responsible committees reporting to the President of the United States that they are in the midst of a major epidemic of cancer.

J M Gilks, Shell Internationale Petroleum Maatschappij BV

Are these pathalogical cancers that you are talking about just now, are they as it were cancers inside you that do not develop into cancer subsequently or are they simply diagnosed at an earlier stage and possibly treated and cured?

Dr. Chairman:

I dont think anybody can answer that question. Under the microscope they give the appearance that the pathologists are unable to say they are not cancer, and if he says they are not cancer and the patient subsequently develops secondaries he is in for trouble, but as they have been removed in order to look at it nobody is in a position to say whether or not they

would have progressed. The only sort of evidence you have is the sort of evidence I have given you but whether you do bilateral mammectomy or single mammectomy the clinical experience is that the woman does not develop cancer in the second breast immediately, but over 20 years yes, she does. If you remove it and look she has got the cancer. The same applies to your prostate and mine.

Dr. F.J.C. Roe

If I could make a comment, coming back to the animal data - I have also used the term 'epidemic of tumours' in laboratory animals. To a limited extent this is, in reality, an "epidemic of pathological diagnosis", but only to a limited extent. The organs of the mouse are 2000 times smaller than those of man. A single section through the centre of the adrenal gland of a mouse covers a good proportion of the total adrenal tissue. Hence it is unlikely that tumours are missed by the pathologist who examines one adequate section of a mouse's adrenal. In contrast even the most conscientious pathologist undertaking a post mortem examination on a human is unlikely to slice through, say, the liver at intervals of less than one centimetre. Hence he would be at considerable risk of missing lesions that are much bigger than the whole adrenal gland of the mouse. For this reason alone one must be cautious in extrapolating from mouse to man. However, I would not wish to give the impression that most of the tumours that constitute the epidemic that is presently occurring in laboratory animals are small and of no consequence to health. On the contrary many are large and obvious. Humane and other considerations lead one to sacrifice animals which are sick because of neoplasia. For this reason cancer is not literally the cause of death in most animals which develop tumours. For this and several other reasons data for tumour incidence in laboratory animals is not comparable with human cancer mortality data.

Dr. R. Murray.

Q. Arising out of something that Malcolm Harrington said I have been thinking about the question of cancer in industry as part of a scapegoat syndrome and I think that to a very large extent cancer is the modern scapegoat. This is the disease which is most feared and you want to get rid of it by throwing it out into the wilderness and the estimates of fraction of cancer paper, this infamous paper that Malcolm Harrington referred to, says that occupation is the main cause of cancer. The villain, the scapegoat is industry and this is particularly the case in one substance, namely chrysidalite asbestos and this point has been raised already and I wanted to focus on it just for a moment. I am of the opinion that chrysidalite asbestos is not necessarily more dangerous than other forms of asbestos. All I would say is that gram for gram chrysidalite is more dusty than other forms of asbestos and that undoubtedly chrysidalite divides into fibres of the critical dimensions for producing mesalthelioma more than other forms of asbestos, but I think that we have taken scapegoat syndrome too far in that chrysidalite is now universally expected to be banned in spite of properties which lend themselves particularly to the manufacture of pressure pipes and the evidence from Canahine and the other evidence that Dr. Goulding and Dr. Roe were talking about earlier indicates that there are other causes of mesalthelioma and I think it behoves us to be rather careful about whatwe cast out into the wilderness because we are not necessarily casting out the disease that offends us so much and I know that Malcolm Harrington raised the point that occupation is something that you can do something about whereas you can't do very much about life style I wanted to raise this question as an issue of debate which we could toss around for a bit.

Malcolm Harrington. A. I would agree with what Bob says. I would point out that I didn't necessarily say that we would do something about it its just that you can, and you can somewhat easier than trying to get people to stop drinking and give up smoking, or stop going to Spain for their holidays. To add to that list whenever anybody mentions vynlchloridemonoma people immediately think of tumours, death,

where in fact the number of people who have actually died of angiocarcoma which is assumed to be related to vnylchloridemonoma on good grounds, is relatively small though to me the reduction levels of exposure at the work place probably having a greater effect in terms ofmorbidityon the decrease in Raynaud's phenomenom that occurs amongst the workers in that area than it does in terms of the number of people's lives it might have saved. I would just throw that in as well. Again we are using cancer as being the immotive issue when in the fact in the wake of that perhaps advantageously, we have decreased a lot of morbidity.

Chairman Q. Do you know what the total number of cases of angiocarcoma related in the world is? 75 now is it. Three in England? Its 4 is it.

D. Palmer, Dista Products Limited

Q. I am not a medical man I am a production director and I would like to touch on a remark Professor Harrington made which got me on the raw a bit. He said you go along to the workers and you say if you keep the level at this rate you probably wont get cancer. Well, you know they are not interested in probabilities, they want a definite answer, what I would like to ask the panel is, there seem to me on the outside to be thousands of people testing hundreds of thousands of compounds using what at best is dubious technology why doesn't somebody invent some much better technology so we can have more faith in the answers?

B. Phillips.

A. We, when I say we I mean people like me who are trying to develop better technology and all we seem to have achieved is more and more confusion. We use the standard methods of breaking down the problem into its component parts and looking at the theory behind cancer causation and all this tends to do is to get us further away from the real situation

and make the interpretation more difficult. I really dont know how you can produce test systems which are that much more liable and certainly when it comes to saying to someone you will or will not get cancer in a particular situation, we need to know a lot about the people as well as the carcinogeresis process. I can't see us being able to say things like that for a very long time.

Professor Harrington

I think there is a certain degree of misinterpretation here. I didn't in fact imply that you should walkalong, as doctors used to do in the old days, and tell the workers what they will and will not do any more than anybody else can do this. I think if you involve them in the process of deciding what an fact will be an acceptable level i.e. tell me is the wood safe I think you then are in a position to begin to try and educate them away from the business of saying we are only interested in a safe environment because there is no such place as a safe environment. They are probably a lot safer going to work than you are staying at home where most of the fatal accidents occur and there is good evidence to suggest being employed is less hazardous than being unemployed. But once you are in the working environment then I think and you are able to produce any sort of figures which put things in some sort of degree of relativity then you may be in a position to say from the evidence we have got and it only occurs for about half a dozen compounds I suppose, it appears that this is the risk associated with this particular level. In a final analysis to turn round and say zero level is the one we go for because there is no threshhold is not a scientific decision its a political decision and its an economic decision.

J.D. Wilbourn, International Agency for Research on Cancer, Lyon

Q. This morning we put forward a hypothesis between genotoxic agents and promoting agents and I would just like to ask Dr. Murray and perhaps Dr. Roe what sort of possible promoting agents occur in the industrial environment and if there are many promoting agents in the industrial

environement is their control as important as the genotoxic agents?

Dr. Murray (A) I must confess that I have great difficulty in separating out the genotoxic agents from the promoting agents. There are some substances which are initiators and promotors at the same time, like tobacco smoke. I can't think of a situation in industry, and I stand to be corrected by Francis Roe where individuals are exposed only to promoting agents except for this that Eric Boyland was writing just the other day in a magazine called Forum and suggesting that asbestos was a promoting agent and not an initiator but I would like to pass this along the table to see which of my other colleagues can think of an industrial exposure to something which is a promoting agent and not an initiator.

Dr. Roe

Well, most of my answer would be slightly theoretical. The things that would worry me are, first of all, anything which is an irritant in the sense that it causes hyperplasia or prolonged inflammation. I would be concerned about potent enzyme inducers - I mean, specifically, inducers of P450 in the liver - TCDD being a classical example. I would be concerned about an agent which reduces immune competence, particularly one that reduced the numbers of circulating thymus-derived lymphocytes. Finally, I would be concerned about anything which clearly changed hormonal status. For instance, in the early days of the manufacture of the sex hormone , diethylstilboestrol, men exposed to the agent developed a condition known amongst them as "the busters". I will leave it to your imagination what was meant by that! In any event it was indicative of an alteration of hormonal status that might have implications in terms of cancer risk. Incidentally I agree that asbestos is probably not a genotoxic carcinogen but enhances cancer risk by one or more epigenetic mechanisms.

Dr. Munn

Is it not the case, Mr. Chairman, that a number of years ago in the experimental investigation of skin cancer the tweens and spans were widely described as being promoting agents, now these are simply surface active agents They are detergents, and the whole detergent industry, - well the whole workforce of the detergent industry is presumably exposed every day to these promoting agents yet certainly I have never heard of any suggestion of an excess of skin cancer in that particular industry.

Dr. Roe

Historically the spans and tweens were victims of over-zealous laboratory investigation. In high concentrations these agents cause hyperplasia of the naturally very thin epidermis of the mouse and can promote the development of skin tumours in mice previously exposed to a chemical carcinogen. The latter effect was relatively weak. No one has reported that industrial exposure to these agents caused epithelial hyperplasia in humans and in retrospect it would seem that the laboratory research was irrelevant to the assessment of the risks or safety of industrial exposure to these agents.

Dr. Murray. If I can come in, I think there was a great deal more cancer of the scrotum in the days before there were detergents than after the detergent.

Chairman. Perhaps I could end on a note of encouragement that arose out of a comment that was made about sexual activity and cancer of the cervix and cancer of the breast and I think the latest evidence is that sexual activity itself is in no way productive of cancer of the cervix its just a venereal disease, it depen ds how many people have had that sexual activity with whether or not you get an increased risk of cancer of the cervix, so perhaps that will be of some encouragement to some members of the audience.

LABORATORY APPROACHES TO THE ASSESSMENT OF POSSIBLE OCCUPATIONAL CANCER HAZARD

Dr. F.J.C. Roe

Dr. Glover, Burmah Oil

Returning to one of your slides where you listed the unnatural aspects of the life of a laboratory rat. If you read down the rest you see that they closely describe the life of modern, civilised man today. In fact all the features you list are true, for instance, for an operator on a production platform in the North Sea. First, there is the canteen where you are invited to go round twice. The food is rich and excessively nutritious. You don't have to fight for it or search for it. Next, you suffer from enforced celibacy, despite sexual stimulation, continuously for a fortnight at a time. Thirdly, general boredom is the order of the day. I am wondering whether, if Dr. Roe does pursue this and we put rats back to the conditions they were in in the wild, whether we would not then be comparing them with say stone age man rather than with modern civilised man. On the two occasions when I was on a fairly strict diet I found I could, in my hunt for food, distinguish between a Wimpey bar and a dry cleaners at about 400 yards. Surely the affluent laboratory rat is much more appropriate as a model for modern man than like wild rat?

Dr. F.J.C. Roe

In the light of what you say I shall await with interest the results of epidemiological studies on men who spend much of their life on oil rigs. But more seriously, I believe you are, to some extent at least, making an important and valid point. It is possible that overnutrition, in particular, is enhancing cancer risk in man. However, there are in my opinion important differences between the life-style of the laboratory rat and the man on the oil rig. Firstly life on the rig is not without stress other than that associated with the need to forage for food or fight off preditors. Secondly, periods of 2 weeks enforced frustrated celibacy are not really comparable with a complete life-time of it. Thirdly, we are not seeing in humans the spectrum of evidence of hormonal disturbance that is now such a feature of the ageing laboratory rat. To my mind the first thing to do is to find out how to maintain rats into old age without endocrine disease and the high cancer rates associated with endocrine disease. Armed with this knowledge, we might then be able to identify life-style factors which are important to man.

M. Robinson, ICI Limited

Q. Are you suggesting, Dr. Roe, that in animal experiments stress reduces the incidence of tumours? Might not stress increase cancer incidence?

F.J.C. Roe

I am glad that you asked that question. Stress is a much abused word and has clearly many meanings. There have recently been two semi-popular books published about stress, according to which stress falls broadly into two types. One comprises the ordinary cares of everyday life, for example, the stress I am experiencing in addressing this gathering, the stress of meeting deadlines, of catching trains etc. These may be classed as "desirable" kinds of stress. This is the sort of stress which is removed from a man's life when he retires and his loss of it may well contribute to his going downhill shortly after he retires. The other type of stress, which is deleterious in its effects is epitomized by the stress associated with bereavement. It is something you can't do anything about. There is no action you can take. You just have to sit and suffer it. This latter type of stress might well predispose to cancer development in some circumstances. Obviously, both in the case of animal experiments and studies in humans, it is important to identify whether one is concerned with "desirable" or "undesirable" stress. My thesis is that by overfeeding animals we in some way deprive them of a form of stress that they need for the maintenance of their health.

The lack of "desirable" stress leads to a disturbance of hormonal status and an increase in hormonally-determined tumours. Unfortunately, the subject has been unnecessarily confused by experiments using transplantable tumours. Vernon Riley in the USA has shown that stress of either kind enhances the growth of transplantable tumours in mice. However, his experiments are not a model for spontaneous cancer. In order to grow, transplantable tumours need to overcome immunological defence mechanisms in the new host. This they can do more easily in stressed animals in which corticosteroid levels are high and the production of immune-competent thymus-derived lymphocytes is reduced.

Dr. A. David, World Health Organisation :

Q. You defined here the employer's duty as not increasing the chance of increasing the cancer incidence during the working life or subsequent ly. There are countries however, who even go further in their requests and they define for example the occupational exposure limits, the permissable concentration in the air, not only to the worker but also for subsequent generations. What I would ask you, if you are aware of the existence of any substances which could change the incidence of tumours in the progeny of parents, of animal parents exposed to this substance even if the exposure doesn't continue in the progeny.

F.J.C. Roe

As far as I am aware there is no epidemiological evidence that suggests a hazard of this kind from exposure to a chemical at work (as opposed to exposure to contaminants ~~drug~~). There are a host of theoretical possibilities and there are some positive animal data from studies involving unrealistic exposure. The morphology of sperm may be altered in men occupationally exposed to certain chemicals but the significance of this in terms of their children is not clear. Obviously, if altered sperm morphology reflects altered nucleic acid content then there is some cause for concern. I know of no real life situation in which there has arisen a cause for concern for the safety of the children as a consequence of a man's occupation. Perhaps the chairman would like to address this point also.

Chairman. The only suggestive evidence I know of was from our attempt to prevent poliomylitis and when pregnant women were immunised with the first batches of polio vaccine which was contaminated with SV 40 virus and their children did have somewhat higher incidence of ~~neoplasms to~~ neoplasms of the central nervous system. I think it was 7 observed against 1 expected, but of course current vaccines are very carefully prepared not to have the SV 40 virus. That's the only evidence I know, a number of claims have been reported of workers exposed , particularly to polycyclhydrocarbons. When these have been checked, as far as I know, they have never produced consistently positive results in the children. I dont believe that there is any evidence that parental exposure will produce cancer in children. On the other hand cancers do occur in children and we dont know what the causes of them are and it behoves us to look for them.

Dr. M.M. el-Mofty, University of Alexandria

Q. I use toads as biological test animals for screening chemicals for carcinogenicity. The toads are fed three times per week on earth worms. Toads are seasonal breeders. In the spring, which is the breeding season for toads, and at another time outside the breeding season we force-fed them with known chemical carcinogens. They were highly responsive in terms of tumour development during the breeding season but in the non-breeding season they were rarely responsive. In untreated controls we never saw any tumours. Do you have any comment on this?

Dr. F.J.C. Roe

I would be very interested to see the information. Without more information I really cannot offer any comment.

Dr. M.M. el-Mofty

We have published our work on these toads. We succeeded in inducing tumours with carcinogenic polycyclic hydrocarbons, with bracken-fern and with the insecticides, DDT, Aldrin and Dieldrin.

Dr. F.J.C. Roe

Your research is obviously very relevant to ecology. I would be very interested to see the data and to see if it has implications in the field of occupational medicine.

B. Phillips, British Industrial Biological Research Association:

Q. I quite agreed with Dr. Roe's distinction between the genetic or genotoxic carcinogens and compounds which may increase cancer by epigenetic mechanisms and I also agree that the animal studies cannot distinguish between those two mechanisms but I did get the impression, perhaps mistakenly that you might have been saying the epigenetic type of compound was not a carcinogen and therefore of no importance. Could you enlarge upon that point. If the compound is increasing the incidence of cancer by a mechanism other than a genetic mechanism is it not still a carcinogen to be worried about?

Dr. F.J.C. Roe

Yes, that is obviously a very important question. The worker at increased risk of cancer may understandably not be terribly concerned as to whether it is a genetic agent or an epigenetic agent which is involved. So, yes, of course, we have to be equally concerned. However, there are two points I would like to make. Firstly, whereas genetic mechanisms cross species barriers rather well, epigenetic mechanisms are apt not to do so. Secondly, with many epigenetic mechanisms it is reasonable to postulate a threshold or a dose which is, for practical purposes anyway, 'safe'. It is not so easy to do this for genotoxic carcinogens, unless one can identify a reason why there should be a threshold. Thus I believe it is both worthwhile and very important to make the distinction. At the start of my lecture, I said that opinion is divided as to whether exposure to genotoxic agents of epigenetically acting agents is the more important determinant of human cancer risk. Personally I suspect that epigenetic mechanisms are the more important and for this reason I am highly cirtical that the pre-occupation of the theoretical oncologists is presently with genotoxic agents. This pre-occupation is leading them to recommend extremely stringent precautions against exposure to minute doses of genotoxic agents when, in all probability, the epigenetic mechanisms which, because they don't understand them, they ignore, are possibly orders of magnitude more important.

D.D. Bryson, ICI

In the general principle you stated that animal tests should be treated as indicative of a hazard in man unless there are good grounds for concluding otherwise. What would you as an experimental toxicologist accept from occupational physicians working in the field as "good grounds". What would be the minimum evidence we would have to present to you to accept that there are good grounds for accepting that a material is not a carcinogen.

F.J.C. Roe

I wouldn't like to answer that question generically because I firmly believe that every situation and every compound has to be looked at separately. Different galaxies of problems relate to different situations and different chemicals. In most instances I would attach considerable importance to occupational hygiene data, monitoring data, and exposure data. I might be happy to discount positive

animal data if it were clear that humans are not exposed by the route of administration used in the laboratory studies. If you could demonstrate a difference in metabolism between the animal species which is coming out with a positive result and man and those data are reliable, this could constitute compelling grounds for rejecting the animal evidence as being relevant for man. I wouldn't like generically to say do this, do that and do the other. There is no magic formula for getting off the hook created by positive results generated by the laboratory.

I believe the only correct way to make assessments is to have people of different disciplines including, if possible, the actual investigator who did the work. Making assessments is hard work that requires people of many disciplines who look in detail at the evidence. It should never be undertaken by people without relevant laboratory experience sitting remotely in isolated places.

It is always very important to look at the animal data to make sure that it is not in some way flawed, or that it is not subject to alternative interpretation It is in fact very difficult to design a perfect and properly controlled animal test.

Dr. Munn, Monsanto

I would like to ask Dr. Roe, in his capacity as an experimental pathologist his views on a trend which has emerged in recent publications on the epidemiology on workers exposed to 2,4,5-T - a trend which identifies an association between exposure to the chemical and increased risk of a group of quite different tumours, namely 'soft-tissue sarcomas'. These are tumours which arise in perhaps 8 or 10 different tissues. Is there any justification in classifying them together under one heading?

Dr. F.J.C. Roe

I am informed, and I believe reliably, that this epidemiology to which you refer, which comes from Sweden, is highly unreliable and poorly controlled so I am not in the first instance persuaded by the human data. I don't know whether Sir Richard would like to say something. I am not sure whether there is anything more to be said, if you really dismiss the human data on the grounds that it has been collected in a bad way and analysed inappropriately, that really is the end

of it. I have incidentally, looked very carefully at the experimental data on 2,4,5-T and there is absolutely no reason for predicting or expecting there to be an increased risk of soft tissue sarcomas in any species. There are, in my opinion, no scientific grounds, in terms of what is known about aetiological factors, for lumping pathologically widely different entities together under the generic title "soft tissue sarcoma".

THE EPIDEMIOLOGICAL APPROACH TO INVESTIGATING OCCUPATIONAL CANCER

Professor J.M.Harrington

G.E. Burrows, ICI

Q. Professor Harrington emphasised the importance of the exposure data in a good epidemiological study and in the Company we are looking to computerised medical reports and environmental data and I am just wondering how much detail we should be going into. Its very easy on a continuous plant to get a pattern of exposure data but in a batch process for instance do you capture it morning and afternoon, once a day, once a week, how important is it over 20 years. Is it... I would just like your views on that point.

J M Harrington:

Ah I think its a good point. I know that ICI have been doing this and there is IBM I think have been doing it as well and I have been peripherally involved in Fisons attempts to do the same sort of thing. I would say that you still need to come down and say what do we consider to be the probable hazardous occupations and we will try and make sure that those are adequately monitored because we may well need to go back and look at that group of people. That in some ways avoids the question of saying "Ah but what we are looking for is the unknown" my thing is that maybe I am cynical about this, I am afraid that some sort of sod's law or whatever is going to apply, in that the one thing you wont have collected because you didn't know about it, is the one thing you need in 20 years" time so that the safer way, perhaps is to be to go "look we will list the number chemicals or processes we deal with and list the ones we think cause (a) the greatest exposure to the workers and (b) the chemicals and materials which we think either are known to be hazardous or suspected to be hazardous and those are the ones we will choose to follow but we wont follow everybody".

Dr. J.R. Glover, Burmah Oil

Q. With due respect to Professor Harrington I dont think he quite

no different. The problem that bothers me about this and this is why I sometimes wonder whose got their figures right, if the only tumours we seem to be picking up are the relatively rare ones how much are we losing in the general lish-lash of lung cancer and stomach cancer or what-have-you, because the rare ones are the ones that are going to be most noticable, they are the ones that Creesh and Johnsons of this world discover. But I would accept that for some of those, and I think mesothelioma probably exemplifies it, there is virtually no serious contender other than asbestos.

Dr. F.J.C. Roe

Ethylene oxide has recently been found to increase the risk of mesothelioma in rats. This points to a danger. We should not assume that all mesotheliomas are due to exposure to asbestos.

J M Harrington:

Yes, I think if you look at some of the earlier studies which were done saying that mesothelioma is assocaited with asbestos exposure that the range of percentage of people who had mesathelioma and were supposed to have asbestos exposure ranged from something like 50 to 95% and this seems to depend on the zeal with which the investigators inquired about asbestos and when you think about it we all are exposed in some form or another, it may not be occupational but there has been exposure there and then there the danger is as Dr. Roe says to go overboard and say that is the only cause, there isnt anything else.

Dr. Munn, Monsanto

Q. In relation to the point that Dr. Roe made about mesothelioma being caused experimentally by substances other than asbestos I wonder if he could perhaps say a little about the experimental technique that was used. Asbestos causes pleural mesothelioma as a result of inhalation. We all know that there are experimental techniques involving

implantation of other materials into the plural cavity which result in mesothelioma from other materials but this is not a common procedure in workmen, is he referring to the experimental induction of mesalthelioma as a result of inhalation of the new material by the animals?

Dr. F.J.C. Roe

I share Alex Munn's reservations about the interpretation of experiments in which mesothelioma is induced by the direct introduction of materials into the pleural cavity. Such experiments are uninterpretable in terms of humans exposed by the inhalation route. In the case of the rats exposed to ethylene oxide, exposure was by inhalation.

Chairman. You will remember of course Dr. Munn that the villages in Turkey that have, 50% of whom die of mesalthelioma, without any exposure to asbestos, I think the blocks there are called zeolite, which is perhaps similar physical structure but is a different material. Dr. Goulding to you want to say something? No.

R Hurd/

H.G. Parkes, British Rubber Manufacturers' Association

Q. Something he just happened to mention attracted my attention and thought he might be able to solve a mystery for me. He referred to an I.L.O. Report of 1921 Bladder carcinogens and it just happens that I have had occasion myself during the past ten days or so to re-read that extremely interesting and comprehensive Report in detail and he mentioned that

chiefly in that Report as being the principle carcinogens responsible for the bladder cancer experience but reading and re-reading, as indeed I did that Report, I was unable to discover how it was that the authors of that Report came to that particular conclusion because the Report in fact deals with a very wide range of aromatic amins and it doesn't seem to show why those two are specially selected. Can he tell us why?

R Murray:

A I wish I could. I think it was just probably the hunch of Carotzi. Carotzi was a great man because he had worked in the Clinic Adela Voro in Milan from early 1900's and in fact he was the first secretary of the Permanent Commission of International Association on Occupational Health and he was the first head of the I.L.O.'s Industrial Hygeine Division so he came to the I.L.O. in 1919 with a great deal of background of knowledge, I don't think anyone before that time had ever incriminated those substances specifically but I believe that it was probably Carotzi's hunch as a result of his observations rather than anything which he had heard from anybody else. But its fascinating that as early as that the substances responsible for the condition had been recognised.

Dr. J.R. Glover, Burmah Oil

Q. Could not a possible answer to that be (I can't give you names and dates) but it had been described in the Analyne Dye Industry hadn't it

and if Carotzi was working there he would know that they were the basic dyes and so the hunch might just have been going back to the basic aromatic amines because bladder cancer had been described in the Analyne Dye Industry in the 1880's I think. I think he was probably working backwards to the basic materials.

R Murray:

Dr One of the interesting things about this is that the first description although it may have been recognised, the first description was in 1895, and at that time Rehn thought it was due to analyne and this error still appears in the literature. People still talk about analyne cancer and analyne is not a carcinogen and the reason for this was revealed by my late colleague Michael Williams and his colleague Walpole, who were able to demonstrate that the analyne as manufactured at the time of Rehn's discovery contained as an impurity foraminodyphenile so it was probable that it was the foraminodyphenile which Carotzi did not recognise which was responsible for the so-called analyne cancer.

Dr. A. Munn, Monsanto Europe S.A.

Q. In relation to Dr. Glover's comments I really must point out that neither
they are as carcinogens and however many tragic cases of occupational bladder cancer they may have caused, they were not really major raw materials in the dye stuffs industry, they were relatively minor. The major raw material was in fact analyne, as has been suggested by Dr. Murray, it was not in fact until the publication of the work which Case carried out sponsored by the Dye Stuffs Manufacturing Industry it was possible to exonerate analyne from responsibility in the bladder cancer associated with dye stuffs manufacture. I wonder if I might take Dr. Murray up on a relatively minor point which, its a minor technical point but one which I think has or could have fairly profound commercial repercussions. It was his reference to aromatic amines being responsible for bladder cancer in the rubber industry in the past. It was not an aromatic amine that was responsible it was a product called Nonex S. It was not an aromatic amine

which was a condensation product of betanaphthalamine itself an aromatic amine with Paralderhide and the reason why I say its commercially important that this should be clearly understood and recorded is that many aromatic amines are currently in use in the rubber industry many of them have been extensively tested, animal studies for carcinogenicity and have been cleared, and there is one country in Europe Italy, which introduced regulations about aromatic amines two or three years ago singularly stringent regulations which will be very relevant in respect of betanaphthalamine or benzadine or non excess for that matter but which are totally irrelevant to the very important anti-oxidents which are currently in use today and which are complex aromatic amines, so I am anxious that this myth of aromatic amines having caused bladder cancer in rubber workers should be dismissed and that it should be so recorded in the proceedings at least of this meeting.

R Murray

Dr I bow to Dr. Munn's knowledge of this subject. I had always believed that the bladder cancers in the rubber workers were due to the betanaphthalamine impurity in nonoxes, I accept his point that there are many aromatic amines which are not carcinogens. They tend to come under suspicion and the most recent one is menthalinebisoxychloranaline and I am not sure about the carcinogenicity of mocca but I take his point that you cannot make regulations about aromatic amines in general as though they were all carcinogens. I think that this point ought to be stressed.

Dr. F.J.C. Roe, Consultant

Q. Would Dr. Murray tell us, please, the present position in the jute industry, I imagine it is/now more or less a dead industry, but during the 1960's my colleagues and I looked at an oil that was/than currently being used for jute-batching in Dundee and we found it to be highly carcinogenic in our mouse skin studies - indeed it was one of the most carcinogenic oils I had ever seen. There was evidence in the literature that keratoses and skin cancers had been

occurring in the women doing this work during the 1950's and early 60's. I wonder what the present position is. As far as we know we launched our paper and nothing ever happened. Did anything happen? Is there still a problem, or is the jute industry dead, or has it gone back to Pakistan?

R. Murray

I remember when this problem was first raised and my colleague Rogers, a dermatologist in Dundee, described cases not only of skin cancer but of keratosis in jute-batchers. There was a suggestion at the time that the batching oil should be replaced by technical white oil or solvent refined oil. I think this was probably only one of the wider reasons why the jute industry disappeared from Dundee. It was a crazy industry to have in Dundee anyway because you can't possibly grow jute any where else than in East Pakistan and I think the jute work is all done there and far as I know there are no longer any jute factories operating in Dundee. I don't know what the situation in Pakistan is.

J.M. Gilks, Shell International:

Q. If I may just ask a question. My understanding is that the traditional or the well recognised aromatic amine carcinogens are in fact double ring compounds. There are some, and I am not aware of anyone that is truly recognised as a single ring compound, but there are indeed now some toxicological reports in animals, mice and one or two rats I think, that single ring compounds have also been reported to cause bladder cancer. I would be interested to get the opinion if I may of the Chair and your self, what view they would take of these reports that some of the single ring compounds in animals are carcinogenic when so far as I am aware its generally been accepted that the human carcinogens are all double ring compounds.

R Murray:

A I think this is one of the things I am hoping to learn myself over the next couple of days.

Dr. Munn: The major aromatic amines which has been found to be

carcinogenic in the mouse I think, I am not certain about the rat, is arthatalodine. I say major in terms of volume of production and use and its general industrial and technological importance. There has never been any study, so far as I am aware, any good epidemiological study of workers exposed to arthatalodine. What I am very clear about however is that in the case study, the study by Bob Case of the British Dye Stuffs Industry, the Report of which was published in 1953, and in which analyne was exonerated, all of the arthatalodine being manufactured in Britain at that time was being made in analyne plants. The process was very similar analyne is manufactured by the reduction of microbenzine the nitro-group and nitrobenzine to analyne, arthatalodine is made by the reduction of the nitro-group in arthonitrotauluine to arthatalodine so that the tauluidine workers where included in that study. Those engaged in the manufactur of the tauluidine. I was familiar with working conditiond in the plants of these, it was quite soon after I joined the industry and working conditions really were pretty appalling. I Know that Dr. Murray was familiar with them as well. I find it difficult to believe that if, in fact arthatalodine had been causing bladder cancer in workers it would not have been revealed in that population studied by Professor Case. The analyne studied by Professor Case. Of course there was the lotion and one cannot be certain. There is no absolute certainty that arthatalodine has not caused cancer in man.

Dr. R. Goulding, Ministry of Agriculture

Q. Can I depart Mr. Chairman with your permission, with this preoccupation of aromatic amines and go to a rather more general if philosophical view, Dr. Murray quoted from the classics, there is another Shakespearean character who talked of books in the running, brookes sermons in stones, good in everything, I think its common parlance nowadays perhaps more from the other side of the Atlantic than here that there are carcinogens everywhere. I have been partaking a very sceptical view of this and wanted some pretty convincing proof, I think what Dr. Murray has done for me this morning has thrown away some of that sceptism because throughout his account he has given us incidences of

slight suspicions, rejected, not seriously considered, and only after a passage of many years has convincing evidence been substantiated and I am wondering Sir, and I am really looking to you as an epidemiologist should we not take all these alarms we have presented to us now, a lot more seriously and follow them up a lot more energetically so that we may or may not recapitulate this story that Dr, Murray has shown us over the last 100 years.

R Murray: I agree very much with what Dr. Goulding says. I think we must listen to the alarms but without getting alarmed. I think the most important thing is that knowledge drives out fear. If you look at the epidemiology of exposures as I know is being done at the present time by our Chairman and by Donald Aitchison in respect of styrene and falmaldihide. The evidence ought to be there and we ought to listen very seriously and do such human epidemiology as is possible. How much we can do as a result of experimental animals or of bacterial or other tests how much we, reliance we ought to place on those, is something which I am hoping we will be hearing more about in the next couple of days.

Chairman. My answer is almost identical with Dr. Murray's. The only thing I would add to it is that to re-emphasise what I said at the beginning that we are not in the midst of a developing cancer epidemic which is what is so widely believed and I would therefore back up very strongly his a statement about not being alarmed, but at the same time taking seriously in an objective scientific spirit the hints that materials may be carcinogenic to see when we do have human exposure whether there is in fact any evidence of this and I would like to add that as far as this country is concerned the evidence is that with the exception of one or two tumours, particularly melanoma, that the incidence of cancer at any specific age and particularly in the young age groups where you are likely to see the first effects of new materials, the incidence of cancer is if anything going down. This is of course dramatically true in the case of lung cancer for obvious reasons but is true over a wide range of cancers which cannot easily be attributed to artefact as a result

of improved treatment reducing mortality but is probably reflecting actually reducing incidence rates.