Uploaded to VFC Website
~ October 2012 ~

This Document has been provided to you courtesy of Veterans-For-Change!

Feel free to pass to any veteran who might be able to use this information!

For thousands more files like this and hundreds of links to useful information, and hundreds of "Frequently Asked Questions, please go to:

Veterans-For-Change

Veterans-For-Change is a 501(c)(3) Non-Profit Corporation
Tax ID #27-3820181

If Veteran's don't help Veteran's, who will?

We appreciate all donations to continue to provide information and services to Veterans and their families.

https://www.paypal.com/cgi-bin/webscr?cmd=_s-xclick&hosted_button_id=WGT2M5UTB9A78

Note: VFC is not liable for source information in this document, it is merely provided as a courtesy to our members.

Item ID Number	01483
Author	
Corporate Author	
Report/Article Title	Typescript: Statement of Dr. Philippe Shubik, Senior Research Fellow, Green College, Oxford University
Journal/Book Title	
Year	0000
Month/Day	
Color	☐
Number of Images	19
Description Notes	

Statement of

Dr. Philippe Shubik
Senior Research Fellow
Green College
Oxford University

Ecclesiastes 3:22

> Wherefore I perceive that there is nothing better, than that a man should rejoice in how own works: for that is his portion: for who shall bring him to see what shall be after him?

Ecclesiastes 2:1

> Then I looked on all the works that my hands had wrought, and on the labour that I had laboured to do: and, behold, all was vanity and vexation of the spirit, and there was no profit under the sun.

Ecclesiastes 8:1

> Who is as the wise man? and who knoweth the interpretation of a thing? a man's wisdom maketh his face to shine, and the boldness of his face shall be changed.

The historical background of a role for chemical carcinogenesis in toxicology

The knowledge that chemical compounds or mixtures of them might cause cancer originates from clinical studies of occupationally exposed groups. The classic instance quoted frequently in textbooks concerns the discovery that chimney sweeps in England in the 18th century developed cancer of the scrotum from prolonged exposure to soot begun in early youth.

This observation by the English surgeon of note, Percival Pott, stimulated many experimental studies at the end of the 19th century and the beginning of the 20th. Various research workers tried to reproduce this disease in laboratory animals by painting solutions of soot and the related coal tar on different laboratory animals. They were uniformly unsuccessful until two Japanese research workers, Yamagiwa and Itchikawa persisted in their studies and continued to paint coal tar on the skin of the rabbit ear for many months.

These workers were not only persistent but were fortunate to have chosen the right tissue in the right animal. The factors involved in the success of this study have influenced the design and interpretation of many of the routine studies undertaken since that time. It is realized that it is often difficult to obtain a positive finding even with a chemical known to cause cancer in man. The dose, the route of application and the species used as well as the length of the experiment are crucial factors in obtaining a valid result.

During the period between the discovery of the cancer causing effects of coal tar and 1946 the subject of chemical carcinogenesis was largely confined to two major areas of investigation.

Firstly instances of occupational or so-called iatrogenic (drug or treatment) induced cancers were investigated both in human populations and the laboratory. Thus the causation of human bladder cancer in the aniline dye industry was finally elucidated when it was found initially that the chemical 20napthylamine caused the same type of cancer to occur in the dog; this time the positive finding took up to 7 years of administration of very large doses of the chemical to achieve. This finding determined the future course of much of the testing; the species, the time of the experiment as well as the very high dose required added other factors to be taken into account in determining the validity of studies.

In the instance of the coal tar observations it was found that a single compound polycylic hydrocarbon, called benzo(a) pyrene seemed to be the principle component responsible to the cancer producing effect. (Subsequent

studies have shown that it is probably that this is only one of several similar compounds with this property; these many years later this area still requires more work). It became apparent that this compound usually abgreviated to B(a)P was ubiquitous in the human environment. It occurs as the result of combustion of organic matter and is found in small quantities in polluted atmospheres, cigarette tobacco tars, charcoal broiled meats, etc. The significance of these lower levels in the causation of human cancer is anyone's guess.

In fact these so-called lower levels are, in the instance of the charcoaled meats in the range of several parts per million; with newer analytical methods this would be considered to be a high level. Common sense contemplation tells us that atmospheric pollution as seen in modern urban environments is not a major factor in the current epidemic of lung cancer; cigarettes are unequivocally a (if not THE) major factor; yet there is usually more available B(a)P in the polluted atmospheres.

Other cancer causing chemicals identified in the smoke of the cigarette seem to be more likely candidates. Indeed there are a large range of potent animal carcinogens present in cigarette smoke including representatives of several different chemical classes and radio-active particles. Thus in the instance of the best established human carcinogen affecting the general population the research worker is faced with a mass of information and has not yet been able to sort out the mechanism or precise factor(s) concerned. In this instance it is, of course, possible to control the disease by stopping smoking of cigarettes; it is not, however, possible to introduce a "safe" cigarette with any degree of confidence.

Other practical aspects of research into the other causes of cancer involved the demonstration that certain medical procedures such as the use of certain diagnostic procedures such as the use of a radioactive material, Thorotrast, used for outlining parts of the body to be x-rayed caused local cancers; naturally occurring hormones were found to be able to cause certain kinds of cancer in animals and this correlated well with observations in the human.

In the late 1920's a major event to have a considerable effect on this era was the discovery that a food additive known as "butter yellow" (chemically p-dimethylaminoazobenzene [dab]) could give rise to liver cancers when fed to rats. This finding was particularly influential in the development in the 1940's of routine testing of food additives for possible cancer producing effects in animals. Butter Yellow (dab) was no longer permitted for use even though there was no evidence that it had had any effect on the cancer incidence in man.

In the instance of a deliberately added food additive no one wishes to know whether or not it was a human carcinogen; it was felt more prudent to assume that it might be potentially hazardous and to get rid of it. Since the use of this compound was not particularly important economically this posed none of the problems encountered later. Indeed this same dye was used to colour chemical smoke for military purposes and it was said by the late Dr. W.C. Hueper of the U.S. National Cancer Institute on several occasions but without published figures that no occupational hazard had been observed from massive exposure to this compound in the U.S. arsenal. Even if this were the case few would have advocated reintroducing this compound in the U.S. arsenal. Even if this were the case few would have advocated reintroducing this compound in the food supply.

A second key incident was the testing of a proposed pesticide then called 2-acetylaminofluorene in rats for a two year period by a series of research workers in the U.S. Department of Agriculture's research facility. This compound proved to be a new kind of cancer producing agent giving rise to many cancers in many different organ sites. As time has gone on this chemical has proved to be an invaluable tool for the research worker.

However the impact of this study was to result in the beginning of long term routine testing of food additives and pesticides notably in the U.S. regulatory agencies. This leads us into the next era starting in the 1940's and I will deal with this later.

The second major approach taken to research into chemical compounds causing cancer subsequent to the discovery of the effects of coal tar components was a major effort to try and understand how these compounds worked. Needless to say this effort continues and above all things it must be borne in mind when considering the practical aspects of cancer control that we still do not understand and the mechanisms of action of a single causal factor of cancer and do not understand the nature of cancer. Theories abound and some are based on enough facts to be useful guidelines for preventive measures.

Studies into this field between 1920 and the end of the 2nd World War took three distinct approaches; first a series of compounds closely related to those first discovered (B[a]P, or dab) were synthesized by able chemists and tested in animals usually by painting them on the skin or injecting them subcutaneously in the first case or feeding them in the second instances. It was hoped that a clear cut relationship between chemical structure and biological activity would be established and that, from this, a mechanism of action would be obvious. This logical idea was doomed to failure. For these two decades it was firmly believed that only a very few types of chemical structure had the capability of giving rise to cancer and the older cancer research workers were quite

unprepared for the great onslaught when many new types of compound were demonstrated to have somewhat similar activity.

The second approach was to study the metabolism or these established cancer producing agents in animal systems. The studies revealed that some compounds seemed to have to be changed into other forms before they became active; this type of study which is painstaking and long term still continues and a large body of knowledge has been accumulated which has both practical implications to control and can be counted upon to play a major role in the eventual understanding of mechanisms.

The third approach was the investigation of biological and pathological factors affecting the process of cancer induction. For example one scientists, Deelman, in the 1920's found that he could greatly augment the effects of skin application of coal tar by incising the skin simultaneously. The healing would appeared to enhance the cancer producing effects. This and a variety of other studies resulted in the demonstration that at least for cancer induction in the skin it seemed likely that a multiphased process was involved. This has led to many studies on so-called "Initiation" and "Promotion."

Other factors were found to inhibit the action of these compounds and studies led to the discovery of many of the modern chemotherapeutic drugs now in use. Much of this work was stimulated by the discovery that mustard gas (also known to be able to induce cancer) could inhibit cancer induction.

Many efforts were made to study the effects of different routes of administration of chemicals and it was found that this was of great significance; certain compounds active on the skin had no apparent effect when administered by mouth and visa versa. It was observed that many experimental rodents developed tumours in the untreated state and that chemicals could be seen sometimes to have a dual effect - both inducing local cancers at the site of administration and "augmenting" the incidence of some of these "spontaneous" cancers.

The distinction between these two effects still puzzles the research workers and poses a major problem in the assessment of modern cancer bioassays in practical terms.

This early era involved the discovery that changes - perhaps equatable with cancer - could be produced in tissue cultures.

The knowledge that many species differences existed was noted with interest and formed the basis for interesting discoveries into mechanisms of action later on. A discovery made accidentally by Oppenheimer at the end of this first era, that inert plastics implanted under the skin of rodents

caused cancer, gave rise to great confusion which, in truth, has never been dissipated.

All the theories of chemical interactions being essential for the production of cancer seemed to require revision. At the same time it became apparent that certain results attributed to specific chemicals might, in fact, be quite non-specific and only a result of the physical nature of the material.

SUMMARY

The first era of the scientific study of chemical carcinogens spanning the period from 1918 to the end of the Second World War established a large base of knowledge that several groups of chemicals could be shown to be responsible for cancer in man and that these cancers could in most instances be reproduced in animal models. The first inroads into understanding of mechanisms of action were made. At the same time a series of other chemicals were found to be capable of inducing different kinds of cancers in animal systems. It started to be apparent that this characteristic of chemicals was not as limited to a few types of chemical structure as originally appeared.

The different end points possible in bioassays introduced complexity that had not originally been anticipated.

THE PRESENT ERA

For the purposes of this discussion the present era will date from the end of the Second World War, although in truth major changes started taking place about 10 years later.

The first area of concern about the effect of chemicals, and particularly new chemicals as potential causes of cancer centered around the food additive and pesticide problem. More food additives and more widespread use of pesticides that resulted in residues in food appeared during this era than perhaps altogether before that time.

Initially these chemicals were tested in a bioassay that was designated as a 2 year chronic toxicity test. This test was undertaken using the rat as the principal species although some tests were done in mice. It was presupposed that this test would uncover a variety of possible chronic effects and there was no special emphasis placed on this test as one for carcinogenesis.

The well known toxicologists, Barnes and Denz from the U.K. believed such tests to be of little value and felt that a subacute test of three months, if conducted properly, would reveal the majority of toxic effects. Indeed their views eloquently expressed in a review article in 1953 in advance echoed some of our more modern attitudes.

In the course of some of the earlier chronic toxicity tests undertaken by the U.S. Food and Drug Administration many subsequent findings were predicted. D.D.T., for example, was found to be productive of liver tumours in mice; this was not considered to be of practical importance at that time since the tumors were all benign and only malignancies were thought to be of relevance.

A variety of other food additives were found to augment or induce various tumors in rodents and some were banned as a result.

By the 1960's it had become apparent that the primary use of the chronic toxicity test was as a test for carcinogenesis and a survey of the literature reveals that little else was detected in such studies.

In revising the Food Additives regulations in the 1960's the U.S. Congress took the far reaching and unusual step of singling out carcinogenesis as a special form of toxicity that required the regulatory agency to ban a compound. The freedom of the regulator to make a value judgement was removed. The regulation known as the Delaney amendment says, in effect, that any food additive found to give rise to cancer in man or in animal tests using an appropriate route of administration shall not be used. This drastic regulation was enacted after a considerable debate; a major factor in its adoption was research undertaken in Germany by Druckrey and his co-workers that had concluded that chemicals causing cancer acted by a mechanism that was different from other chemicals.

Whereas the cumulative effects of the majority of chronic toxic effects were a result of an accumulation of the chemical in question the effects of cancer causing chemicals were visualized as an accumulation of irreversible changes in the cells. There were several reasons for believing this to be the case. The practical result of such a view of mechanisms was that no tolerance level for such chemicals could be determined; any dose whatsoever could be visualized as one that produced an irreversible cellular change that potentially could lead to cancer.

Although there is much validity in some of the deductions drawn from some of these experiments it is also apparent that tolerance levels for carcinogens are likely to exist.

Additionally the requirements of the Delaney amendment assume tests for carcinogenesis to be much more easily interpretable than is in fact the case. Since 1957 numerous bioassays of chemicals for cancer induction have been made and it is now quite apparent that many of these results are extremely difficult to assess.

In summary the Delaney amendment represents a gross over-simplification; any detailed re-examination of this legislation now would require a much more explicit statement on the details of the animal studies.

The testing of food additives is emphasized since it preceded the other uses of such tests and set the stage for the use of these bioassays for chemicals of general environmental interest, as well as extending the procedures used for evaluating the potential toxicity of drugs.

A comparison of the problems associated with the toxicity of drugs and of environmental contaminants illustrate almost opposite ends of the spectrum in several regards. The drugs are almost invariably administered in relatively high biologically active doses whereas the environmental contaminants are usually present at very low levels - often at levels that have only recently become detectable because of the numerous advances in analytical chemistry that have taken place. There is often little or no knowledge of the effects of these very low doses; they can only be inferred by theoretical extrapolation from studies undertaken at much higher doses.

On the other hand the effects of the drugs are often found at levels quite comparable with those used under therapeutic conditions. Drugs, however, are usually visualized as useful, sometimes life saving, agents; environmental contaminant chemicals, on the other hand are only seen as undesirable.

It is, therefore, the case that many drugs that are clearly potential cancer producing chemicals (some even with evidence obtained from human studies) are permitted for use whereas some other chemicals, often pesticides, resulting in contamination of the environment as parts per billion levels only have been banned.

One of the clearest examples of this perhaps anomalous situation is the instance of the oral contraceptives where initial findings that liver tumors were induced on enhanced in experimental rodents was considered irrelevant to human health on the basis that the endocrine physiology of the rodents was not similar to the human. Subsequent epidemiological studies revealed that these liver tumors did, in fact, occur in women taking these drugs, albeit at very low incidence. This finding has been ignored by regulators on the basis that the benefit of the oral contraceptives outweighs this level of risk. It may well be that this is an appropriate decision to have made for society and unfortunate that such leeway is not available in other instances.

The bioassay of chemicals for possible carcinogenic activity has proceeded particularly in the U.S. both in the regulatory areas where food additives, pesticides and drugs have largely been tested by manufacturers in order to obtain the necessary rights to market these products. These requirements are commonly applied in a similar manner on a world wide basis and many of these studies are carefully reviewed by committees of the WHO and FAO such as the Joint Expert Committee on Food Additives (JECFA) and the corresponding committee on pesticide residues (JMPR). Both these committees review procedures regularly and set approved levels for use of these chemicals.

Although not bound in any way by such rigid and codified procedures as those in inherent in the U.S. food laws the philosophy inherent in the "Delaney amendment" has considerable influence on the decision making of these international bodies. More recently there has been a tendency to review this attitude and there is now a clear desire to try and introduce a more scientific and flexible judgement into these approaches.

The National Toxicology Program (N.T.P.) of the U.S. has introduced another dimension into this problem. In this program selected chemicals are, in essence, "screened" for cancer induction in set tests in mice and rats; no account is taken of use conditions in many of the tests performed so far; thus the route of administration is not necessarily determined by use conditions and dosage rarely takes use conditions into account.

This approach has resulted in the accumulation of much data showing some effect or another on tumor incidence in rodents and the practical significance of this data has been hotly debated. The assessment of such tests will be discussed at greater length in the next section.

It is said that the protocols for these N.T.P. tests are to be modified and to be made more relevant to use conditions in the future.

SUMMARY

Certain specific product categories are now routinely tested for carcinogenicity according to planned protocols. Other more generalized long term animal tests are carried out notably in the U.S. in large scale "screening" programs. Many of the results obtained have been exceptionally difficult to interpret in practical terms.

Research patterns in chemical carcinogenesis: 1945-date

The first part of this era was concerned with following up leads obtained in the three preceeding decades. Many new classes of chemical carcinogen were discovered. Some of these were more readily amenable to biochemical and molecular biological study and thus more in-depth investigation of the interaction of these compounds with cellular components has become possible.

Also newer techniques of cell biologists involving the use of tissue cultures and of bacterial systems have played an increasingly important role in such studies.

So far many of these interesting studies have not played a major role in understanding the meaning of the practical bioassays but it is not difficult to visualize a situation in which much of this research may well play a role in elucidating practical problems in the near future.

Since the early part of this century Bovari's theory that cancer may be the result of a somatic mutation has been considered possible. In the past decade a series of techniques have been introduced for detecting mutations in various bacterial and other systems. There have been those who have wished to correlate this effect with chemical carcinogenesis; more recently of such correlations have been shown to be less and less predictive.

A great deal of experimental work has been undertaken to expand the concepts of "initiation" and "promotion" but so far few basic mechanisms have been elucidated.

CURRENT VIEWS ON CRITERIA FOR EVIDENCE OF CARCINOGENICITY OF CHEMICALS

Criteria for assessing evidence for the carcinogenicity of chemicals were reviewed by a panel of the National Cancer Advisory Board of the U.S. in 1977. In its introductory statement this group stated that "The criteria that are described are guidelines and not rigid, universal criteria. The complexity of the problem dictates that the evaluation of potential human hazards of a given agent must be individualized in terms of the chemical and metabolic aspects of that agent, its intended use(s), the data available at the time the decision must be made, and other factors pertinent to the case under consideration. Each case must considered on its own and the criteria appropriate for one agent may not necessarily apply to another."

This general statement of philopophy was accepted as still valid by a more recent committee which has addressed the same problems in an effort to update the situation. The report of this committee that I had the privilege of chairing will be published in the journal Science within the next few weeks and a preprint of the article has been made available to the Royal Commission.

This article deals with problems in assessing evidence derived from (1) Human studies, (2) Long term bioassays in animals, (3) Short-term tests, (4) Mechanisms of carcinogenesis, (5) Problems in extrapolation of experimental data, (6) the overall assessment process.

The last section of this report is felt to be particularly pertinent to present discussions and is recorded below:

The Overall Assessment Process

Chemical carcinogenesis is a rapidly moving field, and great quantities of data have been accumulated during the past decade. Even though an individual experiment may yield only suggestive information, this information may be of considerable importance when considered together with other data.

Clearly, when the primary source of data comes from epidemiological studies in man, it may be possible to evaluate a chemical and institute scientifically-based preventive measures. However, even in the instances where data are available from humans, the data must be supplemented with information from other sources before a conclusion can be reached.

For example, toxicological evaluation of carcinogenicity has classically relied upon long term in vivo studies as the primary source of data. Such studies have been performed in a routine manner, and evaluations have followed predetermined formulas. This rote method is rapidly giving way to evaluations that take into account findings from vitro tests, metabolism studies, and biometric analyses as well as any other available information. One of these methods alone cannot produce a reliable estimate of a chemical's risk to man, but taken together they provide an estimate with a high level of confidence.

Carcinogens act via different mechanisms, which results in their having different magnitudes of risk to man. Even though there is no basis for the exact extrapolation of risk from experimental animal to man, current advances, if exploited to the fullest, can provide a basis for distinguishing the degrees of risk from different carcinogens. The scientific criteria should be reviewed often, and scientific advances should be fully adopted.

The scientific criteria should be reviewed often, and scientific advances should be fully adopted.

The scientific characterization of human risks from carcinogens involves the evaluation and integration of data from nany disciplines. It requires scientific impartiality to review all appropriate data, both negative and positive, including statistical estimations of low-dose response. Quantitative characterization of human risk requires scientific experience and judgement. Because of the strengths and

weaknesses of the data to be evaluated in the assessment of human risk and the complexity of the problem, case-by-case analysis is most appropriate.

Although it would perhaps be most reliable to quote extensively from this report in other areas certain specific matters can be dealt with in summary. Thus the report concurs with the findings of a recent IARC worker who concluded that although the distinction between carcinogens found to be mutagenic in short term tests and those that are not in most interesting it does not yet serve a purpose to divided carcinogens into genotoxic and non-genotoxic types. This does not preclude the use of knowledge of mechanisms in the evaluation of specific carcinogens.

In certain situations, the particular mechanisms of action of some carcinogens provide guidelines for preventive measures. These situations include carcinogenic effects directly related to the hormonal changes caused by certain compounds and carcinogenic effects in the bladder caused by compounds that induce bladder calculi. These carcinogenic effects can be dealt with differently from those of compounds that induce cancer without the apparent intervention of other physiological or pathological factors.

In spite of the inability to derive a generic classification of carcinogens, chemical carcinogens can, in principle, be divided into two types. One type gives non-threshold dose responses, is stochastic in mechanism, and has some probability of producing carcinogenic effects at any dose. The second type gives threshold dose responses and, theoretically, has a no-effect level. A few chemicals can be placed, provisionally, in one category or the other; but for the bulk of chemical carcinogens, we are currently unable to discern in which compartment they fall. By dealing with chemicals case-by-case and by studying mechanism, we can look forward to doing better than this.

Individual Compounds

2, 4 dichlorophenoxyacetic acid (2,4-D)

2,4-D was reviewed by the IARC in 1977 (1) and again in 1982 (2). It is reported that there were studies in mice employing a combination of gavage and dietary administration. (3) The butyl, isopropyl and isoctyl esters were also studies. These 1969 studies used high doses and lasted 78 weeks. These studies were deemed to be inadequate as result primarily of the small numbers of animals used.

It should be noted, however, that this was part of a large study of many pesticides; one group in this study recorded positive findings with DDT and this was considered to be an adequate demonstration of carcinogenicity.

Osborne-Mendel rats were fed for two years with diets containing 4,25,125,625 or 1250 mg/kg 2,4-D (4). This study has been variously reported. The original authors must be awarded a prize for recording one of the most confused and contradictory conclusions in the literature, namely "When tumor incidence was analysed statistically a higher incidence of tumors occurred in male rats fed 2,4-D at 1250 ppm, and a trend toward increased tumor formation with log dose in the female rats was noted. The raw data, however, support the pathological interpretation that a carcinogenic effect of 2,4-D has not been shown." I would concur with this second sentence rather than the IARC view that carcinogenicity "could not be evaluated."

It should be noted that this study by Hansen et al has been re-recorded in a most unusual and unorthodox manner by Reuber (5). This paper is presented as if it were original data; it is, however, merely a re-evaluation of the previous study that concludes that carcinogenic effects were, indeed, seen in several different organ sites. These conclusions are not supported in any way by the data.

In one other study random bred rats are recorded as having been fed one dose level; no increased tumor incidence is recorded but this study cannot be interpreted on the basis of recorded information. (4)

In the 1969 (3) study mice were tested subcutaneous injection using doses of 215 mgm/kg/body weight in dimethyl sulphoxide and observed for 78 weeks. This study was negative. I believe that this negative finding must be viewed with interest in the context of the controversial reports of sarcoma occurrence in man. It cannot be denied that additional animal data using contemporary standards might be useful in the instance of this compound. Apparently such data will be forthcoming. As matters stand it would be my conclusion that 2,4-D should be classified as non-carcinogenic in animal systems, and therefore unlikely to be in humans.

2,4,5-trichlorophenoxyacetic acid

2,4,5-T was reviewed by the IARC in 1977(1) and 1982(2). It was tested in a 1969 mouse study by a combination of gavage and dietary administration (3) and was not found to be carcinogenic. Identical comments made above for 2,4-D apply to the evaluation of this study.

A further mouse study (6) is made difficult to critique because of inadequate reporting by the authors and the use of less commonly used strains of mice. The authors report that 2,4,5-T was found to be non-carcinogenic when administered orally to mice of the XVII/G strain at levels of 80 ppm in the diet. The 2,4,5-T was said to contain 0.05 ppm of several dioxins that are listed.

On the other hand it is reported that there was a significant increase in tumor incidence in C3HF mice in this same study. This contention is virtually impossible to check since the tumors are classified into incidental tumors and non-incidental tumors for purposes of evaluation. It is then concluded that the incidence for non-incidental tumors is significantly increased whereas the incidence of incidental tumors is not. There is no precise listing in this paper of which tumors were placed in which category and this statistical manipulation of the data cannot be checked. My personal conclusion from reviewing the data is that this was an entirely negative study. In this instance, perhaps, it is safest to conclude that this study does not add anything of consequence one way or the other.

A parallel subcutaneous injection study in mice to that recorded for 2,4-D was undertaken. The 2,4,5-T was also administered as a single dose of 215 mg/kg body weight in dimethyl sulphoxide and the mice observed for 78 weeks. This study was again negative.

It is repeated continuously in IARC and other reports that the evidence from studies with 2,4,5-T is inadequate and does not permit a negative conclusion on carcinogenicity.

Whilst it is undoubtedly true that additional data might permit a more definitive conclusion to be drawn the available data certainly cannot just be dismissed.

In my view it indicates that it is most unlikely that any further studies would find 2,4,5-T to be carcinogenic. Having regard to the limited resources for testing for carcinogenesis by long term animal investigations, I do not think this compound should be accorded research priority over the many others requiring much more urgent evaluation for public health purposes.

2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)

There are three recorded studies claiming to demonstrate some degree of carcinogenicity in TCDD. In the first of these studies Kociba et al (7) reported that Sprague Dawley rats were fed on diets providing 0.1.0.01 or 0.001 micrograms/kg/day for two years. At the highest level of feeding they report an increased incidence of hepatocellular carcinomas, and squamous cell carcinomas of the lung, nasal turbinates, hard palate and tongue. At the median level of 0.01 only lesions described as hepatocellular nodules were observed. At the lowest level no toxicity or neoplasms were reported. The authors of this paper draw attention to the toxicity observed at the highest level and suggest that this may have had an effect on the carcinogenic effects observed.

In a bioassay reported from the U.S. National Toxicology Program (N.T.P.)(8) Osborne Mendel and B6C3F1 mice were given TCDD by gavage for 104 weeks. The compound was administered in a corn oil-acetone vehicle at doses of 0.01, 0.05 and 0.5 micrograms/kg/week to rats and male mice and 0.04, 0.2 and 2.0 micrograms/kg/we to female mice. It is reported that male rats developed a significantly increased incidence of follicular cell adenomas of the thyroid in the high dose group only and that female rats developed an increased incidence of hepatocellular carcinomas was significantly increased at the two highest dose levels.

The peer-review panel of the NTP was most critical of the interpretation of this study and concluded that the liver and thyroid tumors could well be attributed to the hepatoxicity induced. It was also pointed out that the analysis of the significance of the mouse liver tumors had not taken into account the high levels of similar tumors reported in historical controls of this strain of mice.

It is my view that an objective analysis of the NTP study must dismiss it as flawed in design and interpretation. It is surprising to note that the peer review group haveing been scathing in their criticism finally agrees with the view that this study has demonstrated the compound to be carcinogenic. I would be unable to draw a similar conclusion.

The comparison of the NTP test and the Kociba et al study is made difficult by the different modes of administration, different strains of rat etc. It is difficult to dismiss the findings of the Kociba study but one is puzzled by occurrence of the tumors in the respiratory epithelium (lungs, nasal sinuses, tongue) and their total absence in the NTP study. It might be that there is a greater local exposure in the diet study and it would be interesting to know this. The discrepancy between these two studies demands added investigation.

The third study is an NTP study (8) in mice in which TCDD was applied repeatedly to the skin of mice alone or following a single initiating dose of the carcinogen 7,12-dimethylbenz(a)anthracene. The doses used were 0.005 micrograms per application in the females and 0.001 micrograms per application in the males; acetone was the vehicle. The higher doses female mice are said to have developed a significant number of fibrosarcomas.

Once again, as in the previous study, the NTP group was exceptionally critical of this study. The portion of the study in which DMBA was administered first is disregarded since no DMBA control alone was used. There was a dispute amongst the reviewers as to the validity of the contention that a significant number of fibrosarcomas had in fact been induced. One reviewer felt that this finding should be

"interpreted with caution" and that "an assessment of human risk cannot be made." I would concur completely with this review and do not believe that the data in this study provides an adequate foundation for concluding that TCDD is a carcinogen in this model system.

TCDD has been tested in a variety of so-called two stage studies as both an "initiator" or as a "promotor." I do not believe that these studies have provided any information of practical significance to the assessment of TCDD as a potential carcinogen.

Conclusion

In spite of considerable effort long term experimental results obtained with TCDD present a confused picture. Only one study has provided positive results that appear to be incontravertible (7) but in view of the lack of confirmation of this finding additional studies are required using the same conditions as those employed in this study. The Dow study even though not confirmed by NTP (perhaps as anxious to confirm it as Dow was unhappy to conclude as it did) must until explained leave TCDD in the very suspect compartment.

Picloram (4-amino-3,5,6-trichloropicolinic acid)

This compound was assayed in a standard U.S. National Cancer Institute bioassay using Osborne Mendel rats and B6C3F1 mice. The rats were given 744 or 372 mgm/kg/day and the mice fed either 640 or 320 mg/kg/day. Only the female rats were reported to have had an increased incidence of benign liver tumors. M. Reuber has reported that on re-reviewing this study that there was an increased incidence of various malignant tumors. The recent review of this literature by Clements Associates, Inc., takes issue with the techniques used by Reuber in selecting his material. It is not possible for me to take a stand in this instance without additional information.

In view of the other characteristics of picloram - namely that it appears not to be metabolized it seems unlikely that it will prove to be carcinogenic in the study that is now apparently underway. Judgement of the potential hazard from this compound should await the completion of the new study.

Cacodylic acid - Dimethylarsinic acid

Althouth the only term study on this compound was undertaken in 1969 by Innes et al (3) and has been deemed inadequate, the compound was reported as negative. The particular study must be viewed in the context of this overall study in which several other compounds which including DDT were reported to have been carcinogenic.

From a biochemical standpoint cacodylic acid seems most unlikely to be carcinogenic since it is a detoxification product. It would be quite inappropriate to equate the possible activity of this compound with the inorganic arsenicals said to be carcinogenic in man.

Malathion

This compound has been bioassayed in the U.S. by mouth in rats and mice and has been pronounced non-carcinogenic. The only suggestions to the contrary have not been based on any data.

It would seem most unlikely that this compound poses a potential carcinogenic hazard, and in my opinion its use as an insecticide will cause no cancers in veterans.

DDT

DDT induces liver tumors readily in mice and less so in rats and not at all in hamsters. There is a considerable amount of work on the metabolism of this compound encouraged by these interesting species differences.

There is a great deal of frustration present in many of the toxicologists that several decades after the introduction of this widely used, persistent and easily detectable compound, no one is prepared to say whether or not it has proved to be safe in man. My view is that if hazard were present there should have been some indication of it by now.

Efforts to mount studies in which levels of DDT in human fat are related to tumor incidences have foundered. One can do no more than have a common sense opinion in this instance; my personal view is that it is most unlikely that DDT is a human health hazard in any respect.

Dapsone-4,4'-sulphonylidianiline

Of all the compounds included in the list for discussion at the Royal Commission I would select Dapsone as the most likely compound to pose a potential carcinogenic hazard.

This compound is an aromatic amine which has been found to give rise to mesenchymal tumors of the spleen and thyroid tumors in rats.

The exposure levels are of a much higher order of magnitude from those encountered in dealing with herbicides or pesticides. I recommend an epidemiological study of those individuals exposed to this drug in Vietnam and a control from who went to Vietnam who received other therapy.

On present data I am unable to say whether dapsone is actually carcinogenic in humans.

I was unable to locate any pertinent data on the possible carcinogenicity or paludrine or primaquine and have no additional comments.

Chlordane

This is another representative of the group of compounds giving rise to hepatomas in mice; data in rats is inconclusive. No epidemiological evidence is available. This compound is in my view unlikely to be carcinogenic in humans.

Dieldrin

This chlorinated hydrocarbon, although more acutely toxic than DDT, presents similar problems from the standpoint of carcinogenesis. It enhances the incidence of hepatomas in mice but is apparently inactive in rats and hamsters.

Lindane

This chlorinated hydrocarbon again gives rise to hepatomas in mice; evidence in other species is said to be inconclusive. It is in my opinion unlikely to be carcinogenic in humans.

Diazinon

This compound has been tested in a U.S. National Cancer Institute bioassay and pronounced negative for carcinogenicity in rats and mice.

I have been asked to speculate on the matter of possible synergism between the various herbicides, pesticides, drugs and possible environmental factors on any potential cancer producing effects that may have occurred.

I can only respond that I have no knowledge of any studies that would suggest that any of the agents involved have ever been evaluated in any combinations to examine this possibility. Neither am I familiar with any studies that would suggest theoretically that such a possibility exists.

It should be remembered that the two unequivocally established carcinogens to which Vietnam veterans were exposed were cigarette smoking and sunshine. In addition it is my understanding that a certain number of soldiers were exposed to Hepatitis B virus which can certainly be considered to be at least a co-factor in the occurrence of hepatocellular carcinoma. The possible exposure of troops in Vietman to the naturally occurring carcinogen, Aflatoxin, a product of fungal contamination and prevalent in Southeast Asia should also be considered.

REFERENCES

1. IARC Monographs Vol 15. 1977

2. IARC Monographs Supplement 4.1982

3. Innes, J.R.M. et al Journal of the National Cancer Institute 42.1101-1114. 1696

4. Hansen W.H. et al Toxicology and Applied Pharmacology 20. 122-129. 1971

5. Reuber M.D. The Science of the Total Environment 31.203-218. 1983

6. Muranyi-Kovacs I, Rudali, G., and Imbert, I., Brit. J. Cancer 33.626-633. 1976

7. Kociba R.J. et al Toxicology and Applied Pharmacology 46.279-303. 1978

8. National Toxicology Program Technical Reports 209 and 201