PEST CONTROL:
An Assessment of
Present and Alternative
Technologies

VOLUME I

# Contemporary Pest Control Practices and Prospects:

## THE REPORT OF THE EXECUTIVE COMMITTEE

Study on Problems of Pest Control
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# Health Hazards of Chemical Pesticides*

## Introduction

Monitoring Human Exposure to Pesticides The U.S. production of pesticides of all kinds is more than 1 billion pounds per year, with synthetic organic compounds making up more than 90 percent of the total. This includes some 900 different chemicals, about 100 of which are produced in quantities of more than a million pounds per year.†,‡ U.S. pesticide production is roughly half of the worldwide total. Inorganic and natural organic pesticides were used even in the last century. However, the large-scale use of synthetic organic pesticides is a relatively recent development, starting in the 1940s with the commercial production of the insecticide DDT and the herbicide 2,4-D.

Because pesticides must be released into the environment in order to perform their function, it is inevitable that some portion, however small, of these chemicals will reach the general population via the diet and other routes (National Pesticide Monitoring Program 1974). The FDA conducts a program for the analysis of "market basket" samples taken from various parts of the United States in order to monitor amounts of pesticides in the diet. Analyses have been reported for 22 different pesticide chemicals in market basket samples collected during the period FY 1965-1970 (Table 1). The results indicate that the average young adult American male, whose diet the market basket is intended to simulate, consumed about 40 mg of these residues per year, averaged over the 6 years studied. More than half of the total amount consisted of chlorinated hydrocarbon insecticides.

Although the principal route of exposure of the general population to most pesticides appears to be through the diet, some additional exposure results from pesticides in the air. The EPA conducted an air-monitoring program during 1970-1972 and is considering a proposal to resume pesticide monitoring of air on a continuing basis (Stanley et al. 1971).

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*Members of the Consultative Panel on Health Hazards of Chemical Pesticides are listed at the beginning of this volume. This section constitutes the Report of the Panel.

†See Chapter 4, "The Production of Materials for Pest Control," Estimated U.S Pesticide Production Volume, 1971.

‡A summary of properties of selected pesticides is presented in Appendix A to this volume.

TABLE 1 Pesticide Chemicals in Food[a]

| Compound | Daily Intake (mg) FY 1965 | FY 1966 | FY 1967 | FY 1968 | FY 1969 | FY 1970 | 6-year Average |
|---|---|---|---|---|---|---|---|
| *Organochlorine insecticides* | | | | | | | |
| DDT | 0.031 | 0.041 | 0.026 | 0.019 | 0.016 | 0.015 | 0.025 |
| DDE | 0.018 | 0.028 | 0.017 | 0.015 | 0.011 | 0.010 | 0.017 |
| TDE | 0.013 | 0.018 | 0.013 | 0.011 | 0.005 | 0.004 | 0.011 |
| SUBTOTAL | 0.062 | 0.087 | 0.056 | 0.045 | 0.032 | 0.029 | 0.053 |
| Dieldrin | 0.005 | 0.007 | 0.004 | 0.004 | 0.005 | 0.005 | 0.005 |
| Lindane | 0.004 | 0.004 | 0.005 | 0.003 | 0.001 | 0.001 | 0.003 |
| Heptachlor epoxide | 0.002 | 0.003 | 0.001 | 0.002 | 0.002 | 0.001 | 0.002 |
| BHC | 0.002 | 0.004 | 0.002 | 0.003 | 0.001 | 0.001 | 0.002 |
| Aldrin | 0.001 | 0.002 | 0.001 | T | T | T | 0.001 |
| Dicofol (kelthane) | 0.003 | 0.002 | 0.012 | 0.010 | 0.007 | 0.004 | 0.006 |
| Endrin | T | T | T | 0.001 | T | T | 0.000 |
| Methoxychlor | - | T | 0.001 | 0.001 | T | 0.001 | 0.001 |
| Heptachlor | T | - | T | T | T | T | T |
| Toxaphene | - | 0.002 | - | 0.002 | 0.004 | 0.001 | 0.002 |
| Perthane | T | 0.001 | - | 0.001 | 0.004 | - | 0.001 |
| Endosulfan | - | T | T | T | 0.001 | 0.001 | 0.000 |
| *Organophosphate insecticides* | | | | | | | |
| Malathion | - | 0.009 | 0.010 | 0.003 | 0.012 | 0.013 | 0.008 |
| Diazinon | - | 0.001 | T | T | T | 0.001 | 0.000 |
| Parathion | - | T | 0.001 | T | T | T | 0.000 |
| Ethion | - | T | 0.002 | 0.001 | 0.003 | 0.004 | 0.002 |

TABLE 1 (continued)

| Compound | Daily Intake (mg) FY 1965 | FY 1966 | FY 1967 | FY 1968 | FY 1969 | FY 1970 | 6-year Average |
|---|---|---|---|---|---|---|---|
| *Carbamate insecticide* | | | | | | | |
| Carbaryl | 0.15 | 0.026 | 0.007 | - | 0.003 | - | 0.031 |
| *Herbicide* | | | | | | | |
| 2,4-D | 0.005 | 0.002 | 0.001 | 0.001 | T | T | 0.002 |
| *Fungicide* | | | | | | | |
| PCP | T | 0.006 | 0.001 | 0.001 | 0.002 | - | 0.002 |

[a]Values are determined from analyses of foods prepared from "market basket" samples collected in five major U.S. cities and designed to simulate the diet of a 16-19-year-old male. T (trace) indicates an amount less than 0.001 mg. From Duggan, R. E., and P. E. Corneliussen (1972) Pestic. Monit. J. 5:331-341.

Analyses for pesticides in streams and surface waters are conducted by the U.S. Geological Survey and the EPA. The EPA is embarking upon a program to analyze drinking water for pesticides and other chemicals, as is required under the Safe Drinking Water Act (P.L. 93-523). Tap water is monitored to the extent that it is employed in the preparation and cooking of foods for FDA market basket samples.

Another possible route of exposure is adsorption through the skin of pesticides that may be present in soaps and various cosmetic preparations, and in clothing. Also, a definite although not well known degree of exposure of the general population must result from direct contact with insecticides at the site of their use.

The levels of several chlorinated hydrocarbon insecticides in human adipose tissue are monitored by the EPA. Adipose tissue is a principal repository in the body for pesticides that are insoluble in water, soluble in fat, and resistant to metabolic degradation, as are certain of the organochlorine insecticides. Results from the first 5 years of the program, FY 1970-FY 1974, show an average total of about 11 parts per million (ppm) in body fat for the pesticides studied, corresponding to approximately one-tenth of a gram for an average adult (Tables 2 and 3). Considerable variation is observed among individuals, and values tend to be somewhat higher in southern states.

The relationship between the total quantity of a pesticide used and the amount that reaches the human diet depends on several factors, including the pattern of use, environmental mobility, water and lipid solubility, and chemical and metabolic stability. The propensity of a pesticide to reach the diet is relatively great for stable, water-insoluble, lipid-soluble compounds, such as some of the chlorinated insecticides, including DDT and dieldrin. For these compounds, under conditions of rather steady and prolonged application, a few hundredths of a gram enter the U.S. diet for each pound used.

Pesticide Regulations and Public Health Because of the exposure of the general public to pesticide residues and the risk of higher exposures to formulators, applicators, farm workers, and other special groups, intensive efforts are being made by government, industry, and other organizations to test the toxicity of current and proposed pesticides in an attempt to avoid chemicals or practices harmful to human health.

Under the Federal Environmental Pesticide Control Act of 1972 (FEPCA), the registration of a pesticide may be

TABLE 2 Chlorinated Hydrocarbon Pesticides in Human Adipose Tissue, U.S., FY 1970[a]

| Pesticide | Concentration in Lipid (ppm) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Lim. of Detect-ability | Percent Pos. | Range | | Arith-metic Mean | Geo-metric Mean | Median |
| | | | Maximum | Minimum | | | |
| Total DDT equivalent[b] | 0.02 | 99.93 | 270.05 | 0.00 | 11.65 | 7.87 | 8.10 |
| Alpha-HCH[c] | 0.01 | 2.05 | 0.14 | 0.00 | 0.01 | 0.02 | 0.00 |
| Beta-HCH | 0.02 | 99.15 | 26.93 | 0.00 | 0.60 | 0.37 | 0.34 |
| Gamma-HCH (Lindane) | 0.01 | 1.77 | 0.18 | 0.00 | 0.01 | 0.02 | 0.00 |
| Delta-HCH | 0.01 | 0.07 | 1.11 | 0.00 | 0.01 | 0.02 | 0.00 |
| Dieldrin | 0.01 | 96.46 | 15.20 | 0.00 | 0.27 | 0.18 | 0.18 |
| Heptachlor epoxide | 0.01 | 94.76 | 10.62 | 0.00 | 0.17 | 0.09 | 0.08 |

[a]Values are determined from 1,412 autopsy and surgical samples systematically collected in 31 U.S. cities. The monitoring program is gradually being expanded to include additional pesticide residues. From Kutz, F. W., A. R. Yobs, W. G. Johnson, and G. B. Wiersma (1974), U.S. Environmental Protection Agency.
[b]77.15 percent of total DDT equivalent was found to be DDE.
[c]HCH = hexachlorocyclohexane (= BHC).

TABLE 3 Chlorinated Hydrocarbon Pesticides in Human Adipose Tissue, U.S., FY 1970-1974[a]

| Pesticide | Concentration in Lipid (Arithmetic Mean) (ppm) | | | | |
|---|---|---|---|---|---|
| | FY 1970 | FY 1971 | FY 1972 | FY 1973 | FY 1974 |
| Total DDT equivalent | 11.65 | 11.55 | 9.91 | 8.91 | 7.83 |
| Beta-HCH | 0.60 | 0.48 | 0.40 | 0.37 | 0.32 |
| Dieldrin | 0.27 | 0.29 | 0.24 | 0.24 | 0.20 |
| Heptachlor epoxide | 0.17 | 0.12 | 0.12 | 0.12 | 0.10 |
| Oxychlordane[b] | -- | -- | 0.15 | 0.15 | 0.15 |
| Sample size | 1412 | 1612 | 1916 | 1092 | 898 |

[a]From U.S. Environmental Protection Agency (1974).
[b]First full year in which oxychlordane was analyzed was FY 1972.

denied, canceled, or modified by the Administrator of the EPA on the basis of evidence for ". . . any unreasonable risk to man or the environment, taking into account the economical, social, and environmental costs and benefits of the use of any pesticide." Although specific guidelines are still being designed by the EPA, a presumption of risk to human health may be based on evidence of acute, subacute or chronic toxicity, including tests on laboratory animals showing carcinogenicity, teratogenicity, or mutagenicity.

The "Report of the Secretary's Commission on Pesticides and Their Relationship to Environmental Health," issued by the Department of Health, Education, and Welfare (USDHEW) in December 1969, provides a broad overall perspective as well as much information on individual pesticides (USDHEW 1969). The Commission recommended that all uses of DDT be terminated within 2 years except for specific, individual cases unanimously judged essential to the public health or welfare by the Secretaries of the USDHEW, USDA, and USDI (U.S. Department of the Interior). In a separate recommendation, the Commission called for similar restrictions on the use of other pesticides with highly persistent residues, including aldrin, dieldrin, endrin, heptachlor, chlordane, benzene hexachloride, lindane, and compounds containing arsenic, lead, or mercury. The Commission further recommended minimizing human exposure, pending additional studies, to several pesticides for which there existed indications of carcinogenic or teratogenic activity in test animals (see Appendix A).

In 1972 the EPA prohibited nearly all uses of DDT in the United States. The 1974 U.S. production of DDT was largely for export for malaria control and other uses. It was slightly under half of the 1950-1970 average production of 130 million pounds per year. Recently, the EPA suspended registrations for nearly all uses of aldrin and dieldrin (Federal Register 1974). In this case, as well as in that of DDT, the regulatory decision cited human exposure levels and the results of animal studies suggesting adverse health effects to man.

Scope of the Health Hazards Discussion It was not the assignment of the Health Hazards Panel to conduct an overall and detailed review of the toxic hazards of pesticides, as did the Secretary's Commission. Instead, our charge was to summarize the current state of epidemiological and laboratory approaches to detecting and averting major environmental health hazards from pesticides, particularly regarding carcinogenesis.

As its first area of inquiry the Panel reviewed national mortality statistics (see pp. 61-65) for the leading causes of death, including cancer, for any recent indication of adverse effects that might be attributed to environmental factors, including the use of pesticides.

The recommendation of the Secretary's Commission that human exposure to certain pesticides be reduced rested in part on tests in which animals receiving relatively high doses of these chemicals developed significantly more tumors than did the controls. Concern regarding possible carcinogenic hazard played a major role in the EPA decisions to withdraw registrations of DDT and aldrin/dieldrin and appears likely to be given prominence in future regulatory actions.

Cancer is a major human illness that is strongly correlated with environmental factors. This is shown by the fact that the incidence of many types of cancer among immigrant groups differs from that found in the country of origin and approaches the incidence prevailing in the adopted country (Haenszel 1961, Kmet 1970, Lilienfeld et al. 1972). From occupational and therapeutic exposures to certain chemicals, it is well known that man is subject to chemical carcinogenesis (IARC 1974). In these cases there is generally a delay of years, or even decades, between the time of first exposure and the occurrence of the disease. Hence, it is possible that major effects resulting from an environmental carcinogen would begin to show up in mortality statistics only many years after its introduction into widespread use. As its second area of inquiry, the Panel therefore considered the present basis of risk estimation from carcinogenicity tests on laboratory animals (see pp. 64-68).

## Mortality Statistics

Death rates in the United States at all ages and especially for infants declined rather steadily during the twentieth century until the middle 1950s, when mortality leveled off and then, in the 1960s, showed indications of rising. Although the epidemic of lung cancer in men accounted for some of the change, other causes of death participated as well, including circulatory disease, emphysema, and cirrhosis of the liver. Similar trends were evident in Europe and Japan. This caused some apprehension that changing environmental factors might be adversely affecting man's health on a global scale (USDHEW 1971, 1973, 1974; U.S. Public Health Service 1964).

Statistics for the last few years, however, show that a general upswing of death rates has not materialized (National Center for Health Statistics 1952-1972). In 1970 and 1971 most age groups experienced the lowest death rates on record. Considering the major causes of death, data for the period 1968-1973 show that on an age-adjusted basis there have been small decreases in heart and vascular disease, stroke, diabetes, and in the category recorded as bronchitis, emphysema, and asthma. There has been a continued rise in mortality due to cirrhosis of the liver. The age-adjusted mortality rate for all types of cancer combined has been essentially constant, although there have been definite increases for some types of cancer and decreases for others.

The Panel examined age-adjusted mortality data for the period 1950-1967 for the 10 leading primary sites of cancer (lung, large intestine, breast, lymphoma, prostate, pancreas, leukemia, stomach, bladder, uterus plus cervix), which account for more than two-thirds of the total mortality due to the disease in the United States (Burbank 1971). For cancers for which recorded mortality is clearly increasing, such as lung, pancreas, and leukemia, the upward trends appear to have become established before the widespread introduction of modern pesticides beginning shortly after World War II. No clear trend associated with the rising use of pesticides is apparent for any type of cancer examined in age-adjusted data for the general population.

This of course does not exclude the possibility of less drastic, but still important, trends in mortality statistics. In this regard it would be important to conduct a more detailed epidemiological study than the Panel has carried out, extending the period of observation more nearly up to the present time. Mortality rates among different age groups should be examined for each separately recorded type of cancer. Particularly, a comparison should be made of geographical and other subpopulations for which pesticide exposure may vary. For example, the recent National Cancer Institute compilation of data on cancer mortality by county in the United States should be examined for possible "hot spots," especially among young adults, that might yield clues to important geographically varying carcinogenic factors (Mason and McKay 1974). Finally, studies on occupationally exposed populations would be useful, particularly where large numbers of persons are exposed for long periods of time.

Unfortunately, among other problems with the epidemiological approach, mortality statistics are likely to be

very slow to reflect the effects of newly introduced environmental carcinogens. There will generally be a build-up period of several years from the introduction of a new product to the attainment of near-steady levels of production and human exposure. Also, a delay exists between the first diagnosis of a fatal tumor and its contribution to published mortality statistics. Currently this amounts to roughly 6 years (USDHEW 1972, U.S. Public Health Service 1975).* For a few types of cancer, improvements in therapy may obscure important trends in incidence as opposed to mortality. Few states regularly report cancer incidence. The Third National Cancer Survey gives cancer incidence rates for the period 1969-1971 for two states and seven metropolitan areas (Cutler et al. 1974). Although the sample is limited, the results deserve detailed study for trends that may not be apparent in mortality statistics.

An even more serious limitation to the utility of mortality and morbidity statistics for the detection of environmental carcinogens arises from the long delay that can occur between the first exposure and the appearance of tumors. Evidence from animal experiments and from the age distribution of cancer in man suggests that the incidence of cancer induced by continuous exposure to a carcinogen depends very strongly on the duration of exposure.†

*This estimate is the sum of the 2-year average survival time following the first diagnosis of a fatal cancer plus the current 4-year lag in publication of mortality statistics.

†Druckrey, H. (1967) Potential Carcinogenic Hazards From Drugs, UICC Monograph Series 7, R. Truhaut, ed., pp. 60-78. New York: Springer-Verlag; Cook, P. J., R. Doll, and S. A. Fellingham (1969) Int. J. Cancer, 4:93-112. The mathematical relationship discussed by the latter authors giving the incidence $I$ of numerous types of cancer in a population continuously exposed to a carcinogen is $I = f(d)(t-k)^n$, where $f(d)$ is a function of the dose rate $d$ alone and $t$ is the exposure time. The quantities $k$ and $n$ are constants characteristic of the carcinogen and $k$ is the minumum delay between first exposure and the expression of cancer. The relation deduced by Druckrey relating time and dose rate at 50-percent accumulated induced incidence is $dt^n$ = constant. This is a special case of the former equation with $k \ll t$ and $f(d)$ equal to $d$ itself. *See also* Peto, R., P. N. Lee, and W. S. Paige (1972) Brit. J. Cancer, 26:258-261.

Indeed, it would appear that, after a delay, the induced incidence of most types of human cancer rises as the fourth power of the time.* Hence, the incidence even as long as approximately 20 years after the introduction into use of a chemical carcinogen may be only a very small fraction of the eventual incidence it induces. Such a time dependence can give the impression of a "latent period" of many years or even several decades before cases begin to appear with noticeable frequency. Thus it is possible that a serious environmental hazard could go undetected in mortality statistics for many years and then appear with seemingly explosive force.

## Laboratory Studies on Animals

Because epidemiological surveillance for trends linking pesticides or other environmental factors to major illness in the population might indicate hazard only after serious damage has already occurred, other information must be used to establish standards for the protection of public health. Where widespread damage to health may be long delayed after the introduction into use of a chemical, as with agents that may induce cancer or cause heritable mutations, the establishment of safety standards is particularly dependent upon tests on animals or other laboratory systems.

For carcinogenesis, the principal test systems in current use are laboratory mice and rats. A large proportion of such testing is done or overseen by the National Cancer Institute (NCI) of the U.S. Public Health Service (USPHS), using standard protocols for administration, diagnosis, and evaluation. Approximately 200 compounds are currently under test by the NCI and its contractors, at a cost of approximately $100,000 per test. The testing and evaluation of a compound for carcinogenicity requires approximately 3 years. For pesticides, the compound is administered in the daily diet. In order to simulate the usual conditions of human exposure, the most realistic

*It may also be noted that this relation predicts that the age distribution of induced cancer will be independent of dose unless the induced incidence is so great as to deplete the older age ranks. For the present age distribution of the U.S. population and in the case with $n = 4$ and $k = 2$ years, about one-quarter of the incidence would occur before age 55 and about half by the age of 68.

administration of a compound would begin with the mothers of the test animals before conception and continue throughout life. For convenience, however, the current NCI protocol specifies that administration begin at the time of weaning and terminate in late middle age. The animals are divided into several groups, each receiving a different concentration of the compound in the diet. An undosed group of animals serves as a control. There are usually 30-100 animals in each dosage group. Animals are allowed to die spontaneously or are sacrificed shortly after dosing is terminated or earlier if tumors are evident. Postmortem examinations are performed to determine the type and number of cancers. A compound is considered carcinogenic to the test animals if the treated groups show a statistically significant increase in the age-specific frequency of one or more specific types of cancer, as compared to the control group. As a check on the reliability of the experiment and for the quantification of carcinogenicity, a positive test is generally not considered adequate unless the frequency of cancers is found to be dose dependent.

The sensitivity of such tests is inherently limited by the number of animals employed. For example, even if no cancers are found in a group of, say, 100 animals, one can conclude with 95-percent confidence only that the true frequency of cancer induction at the given dose is less than 3 percent. Clearly, in extrapolation to man, a likelihood of inducing cancer in no more than 3 out of 100 individuals would hardly be reassuring. In practice, animal tests may be even less sensitive than the foregoing example suggests. This is because the control animals themselves may develop a substantial frequency of various kinds of cancer, making the problem one of detecting a significant increase above an already appreciable background. In order to increase the sensitivity of animal tests, administered doses are chosen to be considerably higher than the level to which humans usually are exposed. This procedure may fail if the test compound greatly shortens the life span of the animals as a result of toxic effects other than cancer. In that case, the older ages at which carcinogenesis is likely to be most manifest cannot be studied.

Attempts to utilize data from animal experiments in order to quantify carcinogenic risks to man must be based on assumptions for which available evidence is suggestive but far from complete. Two basic kinds of assumptions are generally involved. One concerns the relative susceptibility of man and the test animal to the chemical in

question. The other concerns the relationship between the dose and the response. The following is a simplified description of the current basis for estimation of carcinogenic risk for environmental agents such as pesticides.

Carcinogenesis in Man and Laboratory Animals Notwithstanding the difficulty of identifying specific carcinogens affecting man, about a dozen agents are now recognized as human carcinogens. All of these but one are definitely carcinogenic in tests on laboratory animals, as indicated in Table 4. The only exception is arsenic, which is still under test on animals. It may be noted that the organs affected in man are not always the same as those that are found to develop tumors in laboratory animals, nor is the organ specificity the same in different species of rodents. Nevertheless, the evidence, based on a limited number of carcinogens, suggests that most agents that pose a carcinogenic threat to man will be carcinogenic in laboratory tests on animals. However, this leaves open the possibility that such tests may also identify chemicals carcinogenic to rodents that do not pose such a threat to man.

It would be desirable to have some idea of the proportion of useful chemicals that are carcinogenic in standard animal tests. In this regard, it is of interest that only a minority of pesticides that have been subjected to standard rodent tests have been found positive. In a test of 120 different pesticides and industrial chemicals conducted under contract with the NCI, 11 were judged positive, 89 gave no significant indication of carcinogenicity, and 20 were designated for further evaluation (Innes et al. 1969). It should be noted that one of the criteria used in selecting the 120 pesticides to be tested was structural or other prior indication of possible carcinogenicity. This suggests an upper limit of about 25 percent on the proportion of currently used pesticides that might be suspected of human carcinogenicity on the basis of such tests.

Research on molecular mechanisms in carcinogenesis has provided evidence that the actual carcinogen is often not the compound administered but instead is a metabolite of that compound (Miller and Miller 1971). Active carcinogens tend to possess particular features of chemical structure by which they may be recognized. Although apparent exceptions are known, similarities in the metabolic fate of a compound in different species may imply similar carcinogenic properties. Hence, metabolic studies using human and animal tissues can support the case that

TABLE 4 Results of Rodent Tests on Substances Known to be Carcinogenic to Man

| Compound | | Site | References |
|---|---|---|---|
| Aflatoxin | Mouse | Lung | Wieder et al. *J. Nat. Cancer Inst. 40*, 1195 (1968) |
| | | Liver | Vesselinovitch et al. *Cancer Res. 32*, 2289 (1972) |
| | Rat | Liver | Newberne and Wogan *Cancer Res. 28*, 770 (1968) |
| | | Stomach | Butler and Barnes *Nature 209*, 90 (1966) |
| | | Kidney | Lee et al. *J. Nat. Cancer Inst. 43*, 1037 (1969) |
| | Man | Liver | IARC 1, 145 (1972)[a] |
| 4-Aminobiphenyl | Mouse | Liver | Clayson, Lawson, and Pringle *Brit. J. Cancer 21*, 755 (1967) |
| | | Liver, bladder | Clayson et al. *Brit. J. Cancer 19*, 297 (1965) |
| | Rat | Intestine, injection site | Walpole, Williams, and Roberts *Brit. J. Industr. Med. 9*, 255 (1952) |
| | | Intestine, injection site | Hendry et al. *Nature 175*, 1131 (1955) |

TABLE 4 (continued)

| Compound | | Site | References |
|---|---|---|---|
| | Rabbit | Bladder | Wood *Industr. Med. 39*, 55 (1970) |
| | Man | Bladder | IARC 1, 74 (1972) |
| Arsenic | Mouse | Negative in several tests. Recent reports of skin, lung and other tumors await confirmation | IARC 2, 48 (1973) |
| | Rat | Negative in several tests | IARC 2, 48 (1973) |
| | Man | Lung, skin | IARC 2, 48 (1973) |
| Asbestos (Crocidolite) | Mouse | Lung, injection site | Roe et al. *Food Cosmet. Toxicol. 6*, 566 (1968) Wagner et al. *Brit. J. Cancer 29*, 252 (1974) |
| | Man | Lung | IARC 2, 17 (1973) |
| Auramine | Mouse | Liver, kidney, intestine | Bonser, Clayson, and Jull *Brit. J. Cancer 10*, 653 (1956) |
| | | Liver, kidney, intestine | Williams and Bonser *Brit. J. Cancer 16*, 87 (1962) |
| | | Liver | Green *Brit. Emp. Cancer Campaign Rept. 34*, pt. 2, 434 (1961) |
| | | Liver | Walpole *Acta Un. Int. Cancer 19*, 483 (1963) |
| | Rat | Liver, injection site | Bonser, Clayson, and Jull *Brit. J. Cancer 10*, 653 (1956) |
| | | Liver, injection site | Williams and Bonser *Brit. J. Cancer 16*, 87 (1962) |
| | Man | Bladder | IARC 1, 69 (1972) |
| Benzidine | Mouse | Liver | Bonser *Brit. J. Cancer 10*, 653 (1956) |
| | | Liver | Profofjeva *Vop. Onkol. 17*, 61 (1971) |
| | Rat | Liver, ear duct, colon, injection site | Spitz et al. *Cancer 3*, 789 (1950) |
| | | Liver, ear duct, cholangioma | Boyland et al. *Brit. J. Cancer 8*, 647 (1954) |
| | | Liver, ear duct, injection site | Pliss *Vop. Onkol, 10*, 50 (1964) |
| | | Mammary carcinomas | Griswold et al. *Cancer Res. 28*, 924 (1968) |
| | Hamster | Liver, cholangiomas | Saffiotti et al. In *Bladder Cancer, A Symp.* p. 129 (1967) |

TABLE 4 (continued)

| Compound | | Site | References |
|---|---|---|---|
| | Man | Bladder | Zavon, Hoegg and Bingham *Arch. Environ. Health 27*, 1 (1973)<br>IARC 1, 80 (1972) |
| Bis-(chloromethyl)ether | Mouse | Lung | Leong et al. *Arch. Environ. Health 22*, 663 (1971) |
| | | Skin | Van Duuren et al. *Arch. Environ. Health 16*, 472 (1968) |
| | | Skin | Van Duuren et al. *J. Nat. Cancer Inst. 43*, 481 (1969) |
| | Rat | Injection site | Van Duuren et al. *Arch. Environ. Health 16*, 472 (1968) |
| | | Injection site | Van Duuren et al. *J. Nat. Cancer Inst. 43*, 481 (1969) |
| | | Lung, nasal sinuses | Laskin et al. *Arch. Environ. Health 23*, 135 (1971) |
| | Man | Lung | IARC 4, 231 (1974) |
| Chlornaphazine N,N-bis(2-chloroethyl)-2-naphthylamine | Mouse | Vagina and cervix | Boyland et al. *Brit. J. Cancer 15*, 252 (1961) |
| | | Lung | Shimkin et al. *J. Nat. Cancer Inst. 36*, 915 (1966) |
| | Rat | Injection site | Koller *Heredity 6*, 181 (1953) |
| | Man | Bladder | Thiede and Christensen *Acta Med. Scand. 185*, 133 (1969)<br>IARC 4, 119 (1974) |
| Cigarette smoking | Mouse | Lung | Harris et al. *Intern. Journal of Cancer 14*, 130-6 (1974) |
| | Hamster | Larynx | Dontenwill et al. *J. Nat. Cancer Inst. 51*, 1781 (1973) |
| | Man | Lung | Doll and Hill *Brit. Med. J. 1(5396)*, 1460 (1964) |
| | | Lung | Haenszel, Ed. *National Cancer Inst. Monograph No. 19*, 127 (1966) |
| Diethylstilbestrol (DES) | Mouse | Mammary | Gass et al. *J. Nat. Cancer Inst. 33*, 971 (1964) |

TABLE 4 (continued)

| Compound | | Site | References |
|---|---|---|---|
| | | Vagina, cervix and other tumors | Dunn and Green *J. Nat. Cancer Inst. 31*, 425 (1963) |
| | Rat | Pituitary | Waelbroeck et al. *Compt. Rend. Aca. Sci. (Paris) 262*, 1646 (1966) |
| | | Mammary | Gibson et al. *Toxicol. Appl. Pharmac. 11*, 489 (1967) |
| | Hamster | Kidney | Polkina *Prob. Oncol. 7(7)*, 969 (1961) |
| | | Kidney | Ward et al. *Cancer Research 24*, 319 (1964) |
| | | Kidney | Horning *Brit. J. Cancer 10*, 678 (1956) |
| | Man | Vagina and cervix | IARC 6, 55 (1974) |
| 2-Naphthylamine | Mouse | Liver, injection site | Bonser et al. *Brit. J. Cancer 6*, 412 (1952) |
| | | Liver, injection site | Bonser et al. *Brit. J. Cancer 10*, 533 (1956) |
| | Hamster | Liver, bladder | Saffiotti et al. In *Bladder Cancer*, p. 129 |
| | Man | Bladder | IARC 4, 97 (1974) |
| Bis (2-chloroethyl) sulfide (Mustard gas) | Mouse | Lung | Heston *J. Nat. Cancer Inst. 11*, 415 (1950) |
| | | Lung, liver | Heston *J. Nat. Cancer Inst. 14*, 131 (1953) |
| | Rat | Injection site | Haddow In *Physiopathology of Cancer*, p. 606 (1959) F. Homburger, ed. |
| | Man | Lung | Wada et al. *Lancet*, 1161 (1968) |
| Vinyl chloride | Mouse | Lung, mammary, liver | Maltoni and Lefemine *Accad. Nazional dei Lincei Rend Cl Sci. Fis 66*, 1 (1974) |
| | Rat | Liver, zymbal gland, kidney | Maltoni and Lefemine *Accad. Nazional dei Lincei Rend Cl Sci. Fis 66*, 1 (1974) |
| | | Lung, skin, bones | Viola et al. *Cancer Res. 31*, 516 (1971) |
| | Man | Liver | *Report of a Working Group on Vinyl chloride, IARC Internat. Tech. Report, No. 74/005 Lyon* (1974) |

[a](IARC) references refer to monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, vols. 1-6, International Agency for Research on Cancer, Lyon, France.

a given compound that is carcinogenic in animals may or may not be carcinogenic in man. At present, however, such information is available only for very few compounds.

Recent evidence suggests that within several broad chemical classes, compounds that are carcinogenic in standard rodent tests are also mutagenic to bacteria in the presence of mammalian activating enzymes and vice versa (Ames et al. 1973, McCann et al. 1975). The test is sensitive, rapid, and inexpensive, and offers high promise as a preliminary screen for the many chemicals in man's environment that have not been evaluated for carcinogenicity. A further important implication of the finding that many carcinogens are also mutagens is that measures taken to protect a population against chemical carcinogenesis may also offer a significant measure of protection against chemical mutagenesis.

The finding that most compounds known to cause human cancer are demonstrably carcinogenic to laboratory animals is a qualitative one. For risk estimation it is necessary to have some quantitative estimate regarding the sensitivity of man relative to that of laboratory animals. In order to simulate conditions of long-term human exposure to environmental carcinogens, it would be of interest to compare the induced cancer incidence as a function of age for man and for laboratory animals exposed to the same carcinogen via comparable routes of administration throughout life. However, reliable data for such comparisons do not exist. For the few carcinogens for which comparisons may be undertaken, the total induced incidence in man and the intensity of exposure are usually very poorly known, and the duration and conditions of exposure are often not comparable in the available studies on animals. Nevertheless, in order to bring together some of the data and to encourage more adequate comparative studies, the Panel reviewed the available data for the small number of carcinogens for which human exposure and induced incidence may be at least roughly estimated. These carcinogens are benzidine, chlornaphazine, DES, aflatoxin $B_1$, vinyl chloride, and cigarette smoke. The results are outlined in Table 5. Dose is expressed as the total amount of carcinogen ingested, injected, or inhaled per kilogram of body weight. Where several animal tests involving prolonged exposure are published, the ones indicating the highest sensitivity for each species have been chosen. In the case of DES, a single dose experiment on newborn female mice is also included since it more closely simulates the conditions under which prenatal exposure is known to cause cancer in women.

TABLE 5 Degree of Exposure and Reported Cancer Frequencies for Agents Carcinogenic to Man and Laboratory Animals

| | Conditions of Exposure | Accumulated Dose (mg/kg) | Cancer Induction | Reference |
|---|---|---|---|---|
| *Benzidine* | | | | |
| Man | 13.6 yr avg occupational | 200 avg | 50% bladder 13/25 | Zavon, Hoegg, and Bingham *Arch. Environ. Health 27*, 1 (1973) |
| | >1 yr occupational | 50 avg | 22% bladder 47/210 | Vigliani and Barsotti *Med. Lavoro 52*, 241 (1961) |
| Mouse | 1/wk for 8-13 mo subcutaneous | about 10,000 | 67% liver 31/46 | Prokofjeva *Vop. Onkol. 17*, 61 (1971) |
| Rat (female) | 1/3 da for 1 mo gastric intubation | 100<br>50<br>control | 80% mammary 7/9<br>50% mammary 5/10<br>2% mammary 3/132 | Griswold et al. *Cancer Res. 28*, 924 (1968) |
| *Chlornaphazine* | | | | |
| Man | 3 yr avg therapeutic | 60-6000<br>2000 avg | 16% bladder 10/61 | Thiede and Christensen *Acta Med. Scand. 185*, 133 (1969) |

TABLE 5 (continued)

| | Conditions of Exposure | Accumulated Dose (mg/kg) | Cancer Induction | Reference |
|---|---|---|---|---|
| Mouse | 3/wk for 1 mo intraperitoneal | 4800<br>1200<br>300<br>75<br>control | 100% lung 25/25<br>86% lung 25/29<br>62% lung 18/29<br>40% lung 12/30<br>38% lung 124/330 | Shimkin et al. *J. Nat. Cancer Inst. 36*, 915 (1966) |
| *DES* | | | | |
| Man (woman) | During pregnancy therapeutic, oral | 0.5-300<br><100 avg | 0.2% vaginal and cervical adenocarcinoma in daughters | Herbst et al. *New Eng. J. Med. 287*, 1259 (1972) |
| Mouse (male) | 20 mo in the diet | 13<br>3.5<br>2<br>control | 27% mammary 30/112<br>7% mammary 9/134<br>4% mammary 6/139<br>0/251 mammary | Gass et al. *J. Nat. Cancer Inst. 33*, 971 (1964) |
| Mouse (newborn female) | Single injection subcutaneous | about 400 | 33% cervix and vagina 9/27 | Dunn and Green *J. Nat. Canc. Inst. 31*, 425-438 (1963) |
| *Aflatoxin $B_1$* | | | | |
| Man | In the diet | 0.1 | 0.5% liver | Peers and Linsell *Brit. J. Cancer 27*, 473 (1973) |
| Mouse | 1/3 da, 1-5 times, intraperitoneal | 1.25-6.0<br>control | 23-100% liver<br>3% | Vesselinovitch et al. *Cancer Res. 32*, 2289 (1972) |
| Rat | About 25 mo in the diet | 1.5<br>0.9<br>0.3<br>control | 100% liver 28/28<br>80% liver 20/25<br>19% liver 4/21<br>0/18 | Wogan et al. *Fd. Cosmet. Toxicol. 12*, (in press) |
| *Vinyl chloride* | | | | |
| Man | 18 yr avg occupational | 70,000 (based on est. of 150 ppm avg in factory air) | 0.2% liver | *Report of a Working Group on Vinyl Chloride*, IARC Internal Tech. Report No. 74/005 Lyon, 1974 |
| Mouse | 250 ppm in air 4 h/da, 5 da/wk for 30 wk inhalation | 30,000<br>control | 25% lung 4/16<br>13% mammary 2/16<br>0/28 | Maltoni and Lefemine *Rend. Sci. Fis. Mat. Nat. (Lincei) 66*, 1 (1974), as quoted in above |
| Rat | 250 ppm in air 4h/da, 5 da/wk for 52 wk inhalation | 40,000<br>control | 9% kidney 6/67<br>6% liver 4/67<br>0/68 | Ibid. |

TABLE 5 (continued)

| | Conditions of Exposure | Accumulated Dose (mg/kg) | Cancer Induction | Reference |
|---|---|---|---|---|
| *Cigarette smoking* | | | | |
| Man | 40 yrs, est | Smoke from 1,000 cigarettes per kg | 2.5% | *Smoking and Health*, Report of the Advisory Group to the Surgeon General, 1964 |
| Mouse | 12 min/da 2 da/wk for life inhalation | Smoke from 400 cigarettes per kg | 4.9% lung 16/326 | Harris et al. *Int. J. Cancer* 14, 130 (1974) |
| | | control | 1.3% lung 4/319 | |
| Hamster | About 9-26 min/da 5 da/wk for life inhalation | Smoke from 6,000 cigarettes per kg control | 6% larynx 29/480 | Dontenwill et al. *J. Nat. Cancer Inst. 51*, 1781 (1973) |
| | | | 0% 0/160 | |

NOTES FOR TABLE 5

Benzidine

1. *Human dose.* Estimate 0.05 mg/day average in urine × 70 recovery factor × 250 working days/year × 11 years average employment ÷ 70 kg man = *ca* 150 mg/kg average total intake (Zavon, Hoegg and Bingham 1973).

   Estimate 0.02 mg/day average in urine × 70 recovery factor × 250 working days/year × 10 years assumed average employment ÷ 70 kg man = *ca* 50 mg/kg average total dose (Vigliani and Barsotti 1962).

2. Approximately 1/70 of benzidine ingested by Rhesus monkeys is excreted in the urine as benzidine and monoacetyl benzidine (Rhinde and Troll, *J. Nat. Cancer Inst.*, in press).

3. The estimated doses may be underestimates of the actual averages due to improvements in factory conditions before urine samples were collected.

4. In both the United States and the Italian studies, part of the study population was still at risk at the time of the reports.

5. The periods of observation from the start of exposure in the experiments on mice and rats were 27 months and 10 months, respectively.

Chlornaphazine

1. There were 24 surviving patients still at risk at the time of the 1969 report.

2. Nine of the patients with bladder carcinoma received $^{32}P$ and three received busulfane in addition to chlornaphazine.

3. Shimkin et al. continued observations on treated mice for 43 weeks after the start of exposure.

DES

1. *Human dose.* Range among mothers of cancer patients 0.03-18 g total. Average is less than 6 g ÷ 60 kg woman (Herbst et al. 1974).

2. *Human incidence.* The annual incidence has increased rather steadily up to 1972, the most recent year

reported. In that year, there were 21 cases with medical records of administration of DES or related drugs to the mother during pregnancy. Several additional cases occurred for which adequate medical records are not available. Assume that the annual rate will not continue to rise as the population at risk continues to age and that it represents a steady state, reflecting the average usage pattern of DES in the United States since the middle 1940s. Assume further the number of women treated with DES during pregnancy giving birth to daughters has been 13,000 per year, the average of the range estimated for the period 1960-1970. Then the incidence is 21/16,000 or 0.16 percent (Herbst et al. 1974; Heinonen 1973 *Cancer*, *31*, 573).

3. The apparent carcinogenic activity of DES in humans is higher than that estimated above in the special case of endometrial carcinoma after DES therapy for gonadal dysgenesis (Cutler et al. 1972 *New England J. Med.*, *287*, 628).

4. The observations of Gass et al. continued for about 20 months and those of Dunn and Green for up to 26 months.

Aflatoxin $B_1$

1. *Human dose.* Average dietary intake for three areas in Kenya is estimated as 7.7 nanograms/kg/day. Assume average exposure time is 40 yr. Then estimated total dose is *ca* 0.1 mg/kg (Peers and Linsell 1973).

2. *Human incidence.* Average incidence for above population is 7 per 100,000 adults per year. Assume an annual death rate of 1.5 percent. Then the total incidence is *ca* $5 \times 10^{-3}$ (Peers and Linsell 1973).

3. The observations of Vesselinovitch et al. continued for up to 82 weeks.

Vinyl chloride

1. *Human dose.* Estimate an average of 0.4 mg/liter (150 ppm) in factory air breathed by polymerization workers. Average employment of known cases is 18 yr. Assume 5 years average employment for the exposed population. Assume 40 h/wk, 50 wk/yr work schedule and 10 l/min breathing rate. Then average inspiration for 70 kg

man is *ca* 70,000 mg/kg (Baretta, Stewart and Mutchler 1969 *Amer. Industr. Hyg. Assn. J.*, *30*, 537; IARC 1974).

2. *Human incidence.* Liver angiocarcinoma cases among polymerization workers reported through June 1974:

| | | |
|---|---|---|
| U.S. | 13/20,000 | = 0.07% |
| F.R.G. | 3/3,600 | = 0.08%* |
| Sweden | 2/790 | = 0.25%† |
| U.K. | 1/1,366 | = 0.07% |
| Total | 19/25,756 | = 0.07% |

*One was not a polymerization worker.
†If 790 represents essentially all polymerization workers.

The first reported case occurred 13 years ago. More than half of all reported cases occurred in the past 4 yr. Assume that for the population currently at risk the annual incidence is at or near its peak and will soon decline, giving a total incidence, with complete reporting, about three times that reported thus far. This gives an estimate of *ca* 0.2 percent (IARC 1974).

3. Assume a breathing rate of 0.03 1/min for the mouse and 0.14 1/min for the rat.

Cigarette smoking

1. *Human incidence.* Men smoking approximately 10 cigarettes per day have an age standardized death rate from lung cancer of approximately 0.05 percent. Assume that the annual death rate from all causes among smokers is about 2 percent. Then the total incidence associated with smoking 10 cigarettes per day is about 2.5 percent (Doll 1967).

2. *Human dose.* Assume that the average duration of smoking is 40 yr and that half of the smoke is inhaled. Then ten cigarettes per day represents the smoke from $1/2 \times 10 \times 365 \times 40 \div 70 =$ *ca* 1,000 cigarettes/kg.

3. It is to be noted that questions have been raised as to whether the observed mouse lung tumors were actually caused by smoke and as to whether the nose breathing of mice results in filtering out carcinogens to which the human smokers' lungs are exposed (*Lancet*, 506, 1974).

4. The breathing rate of the hamster is taken as 0.08 1/min.

The carcinogens for which comparisons can be made are those already known to affect humans. In generalizing to other compounds, this selection may impose a bias, exaggerating the sensitivity of man relative to laboratory test systems. Other factors may introduce an opposite bias. For two carcinogens, vinyl chloride and DES, observations on man are for considerably less than a full lifetime so that the reported incidence may be a serious underestimate of the eventual total. Also, these two compounds and aflatoxin are known as human carcinogens because they are associated with types of cancer that are otherwise rare. If these carcinogens also induce more common types of cancer, even at much higher frequency, this could go undetected, again giving rise to an underestimate of their overall carcinogenicity to man.

The limited conclusion that emerges from the comparisons given in Table 5 is that if the data from the most sensitive published test on animals are used to predict lifetime human incidence on a dose per body weight basis, the result seems approximately correct for benzidine, chlornaphazine, and cigarette smoking. For aflatoxin, the predicted human incidence is about ten times greater than estimated from existing epidemiologic studies, while for vinyl chloride it is about 500 times higher. For DES, the human incidence predicted from the result of a single dose administered to newborn female mice is about 50 times higher than that estimated from studies of adenocarcinomas in daughters of women given DES during pregnancy.* Thus, as a working hypothesis, in the absence of countervailing evidence for the specific agent in question, it appears reasonable to assume that the lifetime cancer incidence induced by chronic exposure in man can be approximated by the lifetime incidence induced by similar exposure in laboratory animals at the same total dose per body weight. (For a discussion of interspecies scaling factors for dose, see Rall 1974.)

Dose-Response Relationships In the case of suspected environmental carcinogens, we are usually concerned with

*In comparing human and animal sensitivity it is assumed that the response is simply proportional to dose. See the discussion of dose response relationships in the next section.

exposures much lower than those producing a statistically significant increase in tumors in the small number of animals used in laboratory tests. Therefore, we must extrapolate the experimentally measured rate to lower doses. This is the second area in which risk estimation involves a basic assumption, as mentioned earlier.

For estimating the response at doses lower than those tested in laboratory animals, several quite different assumptions have been proposed.

*Threshold hypothesis.* This hypothesis assumes that there is a dose below which cancer induction cannot occur. An examination of published dose-response data for chemical carcinogenesis in laboratory animals provides no clear indication of a threshold for any carcinogen (Craig and Miller 1974). In a review of 151 dose-response curves, none was found to be clearly inconsistent in a manner suggesting a threshold with both the single-event and the probit hypotheses discussed below. Neither is there any adequate theory of chemical carcinogenesis that would require the general existence of thresholds. Thus, even if a threshold is postulated, there is presently no empirical or theoretical basis for determining the dose at which it may occur. Unless and until this can be done, the threshold concept does not provide a practical basis for risk estimation.

*Single-event hypothesis.* This assumes that the induced incidence of cancer is directly proportional to the dose all the way from the lower incidence levels that can be measured in animal experiments of practical size down to zero dose and zero response. In other words, below an induced incidence of about 10 percent, the dose-response curve is, for practical purposes, a straight line. This would result, for example, if cancer is induced by a single cellular event, the likelihood of which is directly proportional to the dose of carcinogen. An essentially linear dose-response relationship can also result under much more general assumptions, so long as the carcinogen in question simply adds its effects to those of other carcinogens already present (Crump et al., in press).

The single-event hypothesis is in agreement with the limited data available for man. The induction of leukemia by ionizing radiation from nuclear explosions is compatible with a linear dose response down to an induced incidence of about 0.1 percent, the lowest incidence for

which the available data can meaningfully be be analyzed.* Other data on the induction of various types of cancer following therapeutic and occupational exposure to ionizing radiation, although less extensive, are likewise compatible with linearity (NAS 1972b). The dose response relating the incidence of lung cancer in men to the average number of cigarettes smoked per day is also compatible with the single-event hypothesis. In this case, the data can be analyzed down to an induced incidence of approximately 2 percent (Doll and Hill 1964, Doll 1967, Kahn 1966).

Animal experiments are not usually conducted on a scale large enough to measure induced incidence below a few percent. For some carcinogens in some investigations, the dose-response relation is compatible with the single-event hypothesis, while in other cases it is not. However, it is quite possible that a dose-response departing from the single-event hypothesis at high induced incidence may nevertheless converge to a linear relation at lower incidence values (Crump et al. 1975).

*The probit and other hypotheses implying a dose-response curve that is concave upwards.* This class of hypotheses assumes that there is no threshold for a population but that the incidence at doses below the lowest tested is less than that implied by the single-event hypothesis. Below a response of a few percent, such a relationship between dose and response is described by a smooth curve that is concave upwards. For example, the incidence of skin tumors produced by surface application of benzo[α]pyrene in the mouse has been found to vary as the square of the amount of chemical applied over the dose range examined (Lee and O'Neill 1971).

Another dose-response relation that is concave upwards at low dose levels is the probit curve. It assumes that the sensitivity of individuals in a population to chemical carcinogenesis is a Gaussian function of the logarithm of the dose. The probit dose-response curve is S-shaped, with a slope that at first increases and then decreases as the dose is lowered. Its use requires the choice of an adjustable parameter, the probit slope, that describes the narrowness of the presumed Gaussian distribution of sensitivity to carcinogenesis in the population

*It has recently been suggested, however, that while the response for neutrons is linear, γ radiation may vary more nearly as the square of the dose (Jablon 1975).

at risk. The probit slope may be estimated from dose-response data at high incidence, as determined in an animal experiment, so long as the experimental data is compatible with a probit curve. For sufficiently low dose levels, the probit extrapolation always predicts a lower incidence than does the single-event hypothesis. However, using a value* for the slope that is well in the range of values found for various carcinogens in animal experiments at high incidence, the probit extrapolation for lower doses does not differ by more than a factor of 10 from the incidence predicted by the single-event hypothesis down to an induced incidence of about 1 per 100,000 exposed individuals.

Estimates of Carcinogenic Hazard Until more is known about the mechanisms of chemical carcinogenesis, any method of extrapolation to predict cancer rates at doses much lower than tested will remain partly a matter of conjecture. However, the single-event hypothesis probably provides an upper limit for induced incidence estimates at low dose levels and is compatible with the very limited human data on carcinogenesis at intermediate response levels. It would therefore seem prudent to employ the single-event hypothesis in making risk estimates, at least for those carcinogens for which the dose-response curve from animal experiments approaches linearity at the lower response levels that can practically be studied. In that case, the estimated total lifetime incidence in man resulting from continuous exposure to an environmental carcinogen would be the lifetime incidence for continuous exposure to the same total dose per body weight found by extrapolation of the animal data under the single-event assumption. For risk assessment, the resulting estimate would then be subject to adjustment to allow for statistical uncertainty in the input data.

## Findings of the Health Hazards Panel

1. For many pesticides in widespread use, it is inevitable that some will appear in the diet of the general population, which may also be exposed, although apparently to a lesser degree, via other routes.

*One standard deviation per log dose (see Mantel, N., and W. R. Bryan 1961).

2. There is no clear indication in U.S. mortality statistics through 1967 reviewed by the Panel of any major deterioration in health attributable to the widespread use of synthetic organic pesticides. This does not preclude the possibility of less-extensive, but still important, effects requiring more detailed evaluation of such statistics for their detection. Such evaluation, including the analysis of the most recent site-specific and age-specific trends and of cancer mortality by county, should be encouraged as a means of detecting previously unsuspected environmental effects on health.

3. Chronic exposure to a chemical carcinogen may not manifest itself as an increase in cancer until many years after the agent is introduced into use. However, the induced cancer incidence may rise sharply thereafter. This seriously limits the assurance that may be drawn from short-term observations of mortality or morbidity statistics for the general population and for smaller groups, exposed to unusually high doses, such as applicators and manufacturers.

4. Although there are major uncertainties in extrapolating the results of animal tests to man, this is usually the only available method for quantitative risk estimation. Despite the uncertainties, enough is known to indicate what dependences on dose and time may operate and to provide rough predictions of induced cancer rates in human populations.