GUIDELINES FOR A NIOSH POLICY ON OCCUPATIONAL CARCINOGENESIS

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INTRODUCTION

The Occupational Safety and Health Act of 1970 provides legislative authority for the Occupational Safety and Health Administration (OSHA) of the Department of Labor, "to set standards which most adequately assure, to the extent feasible on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure for the period of his working life."[1] An urgent and essential part of this standard-setting process is the development and preparation of criteria whereby the National Institute for Occupational Safety and Health (NIOSH) can recommend standards to OSHA.

In the case of occupational carcinogens there is need for special, new regulatory approaches for the following reasons.

1. Recent decades have seen a considerable unregulated increase in the number and quantities of synthetic organic chemicals manufactured and used, the human impact of which, in the form of chronic occupational disease, notably cancer, is now becoming manifest.
2. Past regulatory practices, based mostly on *post hoc* epidemiological recognition and regulation, clearly make workers the subjects of involuntary human experimentation.
3. There are recognized inconsistencies between protection afforded the general public through environmental standards, and protection afforded workers through occupational standards.
4. Current regulatory practices for occupational carcinogens often appear to be based on misapplication of scientific concepts.

Most of us here are agreed that some new and viable approaches are needed if we are one day to stem the increasing incidence of occupation-related cancer. Some of us even agree that accomplishment of this goes hand in hand with strong regulatory measures.

I am not here today, however, to speak about details of a viable form of a Toxic Substances Act. Rather, I wish to speak, in the brief time allocated to me, about the outlook on occupational carcinogenesis as perceived by NIOSH. Thus, as a spokesman for NIOSH I wish to present for your information some of the considerations that have gone into the guidelines that are meant to reflect the NIOSH policy on carcinogenesis. These guidelines were formulated on the basis of consultation with experts in the scientific disciplines of carcinogenesis; by review of documents for the safety of drugs and food additives; from recent court rulings concerning ethyleneamine and 3,3-dichlorobenzidine; upon recent regulatory decision-making processes concerning aldrin and dieldrin; and by congressional mandate of the 1970 Occupational Safety and Health Act.

It should be pointed out that these guidelines, as the name implies, are

amenable to alteration commensurate with changes in the state of the art and/or revelation of legitimate facts which, heretofore unknown to us, would cause realignment of our views. Similarly, it is entirely possible that a Conference as all-encompassing as this will reveal still further enlightening data and philosophies that can even strengthen the guidelines.

We know that man is continuingly and increasingly creating most of his environment. Indeed, it has been established that more than 700 new chemicals are introduced into industry each year. During this period of rapid change, the causes of mortality have also changed. In the technically advanced countries, communicable and infectious diseases have been replaced as the principal causes of death by another series of ailments; namely, cancer. The dimensions of environmentally induced diseases are staggering. Boyland states that . . . "Of the causes of cancer in man, chemicals are the most important. Reasonable estimates are that not more than 5 percent of human cancer is due to viruses and less than 5 percent to radiation. Some 90 percent of cancer in man is therefore due to chemicals, but we do not know how much is due to endogenous carcinogens and how much to environmental factors. An expert committee (WHO, 1965) has concluded that half of all cancer in man is due to environmental factors."[2] The past Director of NIH, Dr. Robert Stone, stated that most known environmental carcinogens are a result of our increased agricultural and industrial technology.[3] Dr. Paul Kotin, currently Vice President for Medical Affairs, Johns Manville Corporation, recently projected an annual cost of 35 billion dollars for environmentally induced diseases.[4] This social burden is tolerated only because it is a cost hidden in an ever-increasing annual bill for medical attention of all kinds. We must recognize that this crushing cost will develop further if we continue to rely on the traditional *post hoc*, after-the-fact approach to environmental health. Such consequences are unacceptable, and some alternatives must be found. There is one very important issue we face as a society: i.e., to what extent and by what means should we seek to reduce the burden of environmental factors in cancer causation through increased emphasis on prevention, rather than predominantly on treatment, as is the current mode?

It follows, then, that we ask ourselves the question as to the most realistic and practical approach in the solution of the ever-increasing problem of environmental cancer.

What Is Meant by "Carcinogen"?

In consideration of guidelines we ask ourselves for a definition of a carcinogen and find that a carcinogen is any substance that has been shown conclusively to cause tumors in animals or man.

Relative to this definition, however, there is need for clarification of the often-used distinction between "animal carcinogens" and "human carcinogens," as though evidence existed that these were different kinds of substances. As a matter of fact, all chemical carcinogens, with few notable exceptions, which are shown to be active in man, are also active in animals. Arsenicals are an excepted example still under experimental study. In the absence of solid evidence to the contrary, it is therefore prudent to assume that there is possibility of a carcinogenic effect in the human for any chemical that is conclusively shown to be carcinogenic in at least one other mammalian species.

The question is asked, why at least one mammalian species? Following the

Rome Symposium of the International Union Against Cancer in 1956, the recommended protocol has been to conduct carcinogenesis tests in at least two species. The intent of these recommendations clearly was that of decreasing the chance of false negatives that could result from a test in a relatively resistant species for a given test substance. The recommendation for use of at least two species in testing has, unfortunately, often been misinterpreted to mean that a positive result should be accepted only if it is reproduced in two or more species. If positive carcinogenesis obtains with adequate and reproducible tests in the one species, then these results clearly stand on their own merits and cannot be made less valid by the fact that the results do not obtain with another species. Furthermore, chemicals referred to as being carcinogenic in only one species are usually those which have been tested adequately only in that one species.

The value of animal data in the prediction of carcinogenicity for humans is amply demonstrated and consequently has been repeatedly endorsed by expert national and international committees, as typified by the following quotes:

> Despite wide gaps in our knowledge of the metabolism and ultimate fate of drugs and food additives in man, properly conducted experiments will yield results that can be used to estimate the risk to human populations of long-term exposures.[5]

> In conclusion, animal data can be predictive of carcinogenicity for humans. What are we waiting for? Let's get on with the job and have some faith in the results of our own experimental data.[6]

> Any substance which is shown conclusively to cause tumors in animals should be considered carcinogenic and therefore a potential cancer hazard to man.[7]

These principles have also served as the basis for regulations promulgated by OSHA in the case of ethyleneamine and 3-3 dichlorobenzidine,[8] and the Environmental Protection Agency in the case of aldrin and dieldrin.[9] Regulatory action based upon these have subsequently been upheld by the United States Judiciary.[10]

In summary, then, evidence of carcinogenicity which is conclusive for one species must supercede negative findings in other species as pertains to extrapolation to man, since the state of the art of bioassay as it presently exists will not permit ruling out the likelihood that human beings respond in the same manner as the positive test species.

Distinction between Tumorigens and Carcinogens

Another consideration of guidelines is the declared distinction between tumorigens and carcinogens. It is generally recognized that a wide range of apparently benign spontaneous human neoplasms and induced animal neoplasms may become frankly malignant. In the case of skin carcinogenesis studies with polycyclic hydrocarbons, morphologically benign papillomas first appear. Some of these remain benign, others regress, and others undergo malignant transformation, as evidenced by morphological characteristics, invasiveness, and metastasis.

The invalidity of recently alleged distinctions between tumorigens and carcinogens has been repeatedly and unambiguously emphasized by various expert national and international committees; the terms "tumorigens" and "carcino-

gens" thus have synonymous implications. The following quotations are illustrative:

> In the assessment of carcinogenic risk it is not considered relevant whether the tumor is benign or malignant since the conversion of the first to the second must be considered possible.[11]

> In the thinking of most experimentalists the induction of a benign tumor represents the production of neoplasia. Most would feel that this is an indication of carcinogenicity although it is usual to continue studies until morphologically malignant tumors have appeared. There are few studies on record in which only benign tumors are recorded (the neurofibromas induced by ergot appear to to be such an instance). In the majority of experimental studies with epithelial tissues the induction of a benign tumor is merely a stage in the subsequent occurrence of a malignancy.[18]

> The response of test animals in carcinogens may take one of several forms: (a) an increased incidence of one or more of the tumor types noted in the controls; (b) the occurrence of tumors earlier than in the controls, without increased incidence; (c) the development of types of tumor not seen in the controls (this may or may not be associated with an overall increase in the number of tumors seen in the controls); and (d) a multiplicity of tumors in individual animals, the incidence in terms of tumor-bearing animals being the same. Furthermore, the tumors seen may be benign or malignant, or tumors of both categories may be present.[12]

> The Panel is unaware of the existence of any chemical which is capable of producing benign tumors only, which is to say, in the light of present knowledge, all tumorigens must be regarded as potential carcinogens: . . . (a) No adequately tested chemical has been found to produce only benign neoplasms and, (b) a substantial percentage of benign-appearing tumors in mice has been demonstrated ultimately to eventuate in cancer.[18]

> In the first instance benign tumors may cause death in man and animals without even undergoing malignant transformation. The induction of a benign tumor is, itself, therefore, an indication of a serious adverse reaction. There can be no doubt from a survey of experimental studies that benign neoplasms are often precursors of malignancies.

> Under these circumstances, it would be wise to take serious note of the occurrence of benign neoplasms in experimental studies, although this alone is not sufficient for conclusion of carcinogenesis. The occurrence of metastases provides an unequivocal demonstration of malignancy. There are, however, many tumors induced experimentally that are invasive and are classified as malignant, that metastasize only rarely during the average experiment. The absence of metastasis, in the view of most pathologists, does not rule out the diagnosis of malignancy.

> Transplantation has been used by some investigators as additional proof of malignancy. This method is employed infrequently and has certain drawbacks. There are, for example, some tumors such as the mammary fibrademona of the rat that are benign in all respects and yet may be transplanted readily.[14]

"Safe" Levels

Still another aspect of guidelines to be considered is that of the so-called "safe" levels of carcinogens. Apart from the insensitivity of animal test systems and the impossibility of accurately assessing human sensitivity from animal tests, substantial data on interaction between individual carcinogens and a wide range

of noncarcinogenic agents further confirm that it is not possible to predict safe levels of carcinogens based on an arbitrary fraction of the lowest effective animal dose in a particular experimental situation. As HEW Secretary Fleming stated in 1960,[15] "Scientifically, there is no way to determine a safe level for substances known to produce cancer in animals."

Such considerations underlie the 1958 Delaney Amendment, which imposes a zero tolerance for carcinogenic food additives. The Amendment states, in part, that:

". . . No additive shall be deemed to be safe if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animals. . ."

These conclusions were further emphasized, as follows, by an expert committee of the World Health Organization: [11]

". . . It is agreed that no assuredly safe level for carcinogens in human food can be determined from experimental findings at the present time."

The scientific basis of the Delaney Amendment has been consistently endorsed by qualified independent expert committees, such as the 1966 Symposium of the International Union Against Cancer and the 1970 Ad Hoc Committee Report to the Surgeon General [7] which states:

"The principle of a zero tolerance for carcinogenic exposures should be retained in all areas of legislation presently covered by it and should be extended to cover other exposures as well. Only . . . where contamination of an environmental source by a carcinogen has been proven to be unavoidable should exception be made (and then) only after the most extraordinary justification is presented. . . Periodic review. . . should be made mandatory."

It is noted that no such instance of "extraordinary justification," necessitating open societal consideration of the benefit-risk calculus, appears to have yet been presented or documented for any carcinogenic industrial chemical the use of which might result in widespread environmental contamination. The scientific basis of the Delaney Amendment and of the absence of threshold or "no-effect" levels for carcinogens, which has been recently further detailed,[16, 17] was overwhelmingly endorsed at a workshop on this subject convened by The New York Academy of Sciences, on January 15–16, 1973. Strong support was also expressed for extending "Delaney-type" legislation to carcinogens in water, particularly from point-source industrial discharges, and also to occupational carcinogens.

Conclusions

Given the above, the course of action for development of NIOSH policy on occupational carcinogenesis is relatively clear. As a matter of fact, we have not set the course at all; rather, it has been set for us as evidenced by the above numerous quotations representing the collective thinking of the experts, many of whom are participants in this Conference.

Based upon this guidance, NIOSH will pursue its recommendations of standards to OSHA, but with altered procedure where possible. The intelligence system for recognition and priority setting of occupational carcinogens will utilize all available input, including the NIOSH Toxic Substances List, the data from the NCI Bioassay Program, and, when necessary, the decision process of a joint NIOSH-NCI-sponsored committee for the development of criteria for

carcinogenesis. A second joint NIOSH-NCI-sponsored effort of a committee for the screening of agents can be resorted to in those instances for decision as to whether an agent is, in fact, carcinogenic, on the basis of criteria already established by the first-mentioned joint committee. It should be noted at this point that should a viable form of a Toxic Substances Act come to fruition, it would be a great boon toward the development of such systems whereby early warning of toxicity, and most importantly, carcinogenecity, would become standard procedure.

Once the decision is made on basis of a priority need to develop criteria for recommendation of a standard, there would be (as there is now) an intensive evaluation of crucial gaps in available data. Gaps can sometimes be so critical as to delay significantly the standard recommendation process. Other evaluation studies may be resorted to by NIOSH if deemed necessary, and, providing resources were available, would be those pertaining to the societal needs and availability of substitute materials for carcinogenic chemicals. This aspect could be greatly facilitated with cooperative input from industry, as well as from funded studies in academia.

The most important feature of the NIOSH policy for carcinogenic substances in the future will be recommendation of the use-permit and the registration system. These, combined with recommendation for no detectable exposure, can add a highly significant dimension toward a much-needed cancer-prevention program as pertains to the occupational environment.

An OSHA requirement for a permit in use of carcinogenic substances, combined with a registration procedure, would aid immeasurably not only in prevention measures, but also in the facilitation of scientific management. By this is meant the assured mechanisms to perform surveillance and epidemiologic research for purposes of continued safety of the working populace. Within this framework of a concerted NIOSH-OSHA effort, the surveillance and study of established, as well as newly discovered, carcinogenic substances could be effectuated with maximum assurance of the best available safety commensurate with current state of the art.

The NIOSH policy to push for a permit-registration system and no detectable exposure levels for proven carcinogenic substances will be considered by many as unattainable and much too idealistic. Even the suspect carcinogens should be submitted to such control, and admittedly, in rare instances they are. The obvious intent of this form of control, however, the prevention of possible future episodes and, hopefully, eventual erradication of occupationally related cancer sources. Inasmuch as there are still too many unknowns, we choose to utilize the well-worn cliché relative to purposeful, directed erring on the side of conservatism when it comes to carcinogenesis.

A somewhat somber closing note is added, but those of us in attendance at this Conference cannot afford to ignore it. In this connection, certain of the comments made below do not necessarily reflect NIOSH policy. These have to do with the apparent incongruities between philosophies observed in the United States and in other countries. Most of us are aware, for example, that many countries have seen fit to ban certain carcinogens for which we still attempt to set a "safe" level. We are, supposedly, about the most advanced in the category of technically advanced nations (if one chooses to use our standard of living as a rating criterion), yet we tend to misconstrue the motives of others who have attempted to accomplish preventive programs against chronic occupational and environmental diseases by attendance to the unregulated increase in the

number of quantities of chemicals used and manufactured. For example, we, as a collective citizenry, are somewhat surprised when told that regulation of toxic substances is ongoing in the Soviet Union. Indeed, it has been my observation that the Soviet system, at least in philosophy and probably in practice, regarding prevention methodologies, is somewhat advanced over the United States. It is not an unawareness of the disdain with which some of our scientists behold Soviet technology that prompts the above statement, but, perhaps, more of an eye-opening awareness on my part. At least in theory, as well as in some form of practice, the Soviets already attempt to provide surveillance, screening, and research programs that approach a type of action not greatly unlike what we envision as a Toxic Substances Act.

It follows, then, that we ask ourselves about the realism of the various philosophies and approaches for the prevention of environmental cancer. We cannot afford to fail in the development of at least some form of a viable program, and we can do no less than try. NIOSH has a charge of moral and ethical obligation to provide a safe and healthful working environment, and toward this end we must persevere.

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