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OSHA Carcinogens

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Executive

Law

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Attached is Appendix C containing NIOSH's responses
to OSHA's questions.

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RHS:rgs

ATTACHMENT

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APPENDIX C

The following are responses to some of those questions received from OSHA. Responses to some questions have not been furnished in this appendix either because they have been discussed in the prepared statement or because of the complexity of the issues and the short amount of time available to gather and evaluate the data, prepare an appropriate response and meet the April 4, 1978 due date for submissions to the OSHA Docket Office.

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Questions 1, 2 & 21

The proposal recommends that animal studies be used to identify potential human carcinogens. This is quite appropriate. In fact, the purpose of the Proposal is to decrease human experimentation, i.e., decrease occupational exposures to carcinogens. Although there might not be 100% correlation between the effects of chemicals on animals and humans, that is not surprising nor should it discourage us from pursuing our goal. It should be noted that of the chemicals and/or classes of chemicals that have been found to cause cancer in humans, including: benzidine; 2-naphthylamine; bischloromethyl ether; chloromethyl methyl ether; 4-aminodiphenyl; N,N-bis(2-chloroethyl)2-naphthylamine; chrysotile; crocidolite; amosite; cadmium compounds; chromium compounds; nickel compounds; arsenic compounds; beryllium compounds; benzene; auramine; diethylstilboestrol; and vinyl chloride, all except possibly benzene have been found to cause tumors in animals (Tomatis, 1976; Newberne, 1975; Bayliss and Wagoner, 1977; Infante, et al., 1977; Oswald and Goerttler, 1971). Thousands of workers have developed cancer as a result of exposures to these agents. They have unwittingly provided scientists with the information needed to make the correlation between animal and human responses to carcinogens.

Another important consideration is the animal species and strain that should be used in the test systems. The degree of correlation between each species and humans as well as the relative cost in performing the studies must be considered before recommendations can be made. Obviously, those species which have been consistently positive when tested with known human

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carcinogens are acceptable. Of the human carcinogens mentioned above, almost all have been shown to be positive in rats and several of them are positive in mice. Fortunately, these are the mammalian species which are least costly to process, and, therefore, their use can be recommended with very few or no qualifications.

Some scientists believe, however, that the mouse is too sensitive to carcinogens, and, therefore, the rat is a better model. Implied in this opinion is that mice will respond to lower doses of carcinogens than will humans. Since quantitative data on carcinogen exposures to humans is almost non-existent, that comparison is impossible to make. The fact that the mouse is slightly more sensitive to carcinogens than the rat is well-known (Tomatis, 1973), however, the model should be designed to protect humans, not rats. Another argument that has been frequently used to exclude mice is that they have a high frequency of spontaneous tumors which might be induced by hormones and/or viruses, and that tumor promotion, but not induction, is measured when that model is used. What the proponents of that argument fail to recognize is that whatever variables are present in mice might also be present in humans. Human tumors might also be induced by yet unrecognized viruses, and hormones certainly play a role in human carcinogenesis (Furth, 1975). It is not unreasonable to expect that the mechanisms of carcinogenesis operative in mice might be identical to those in humans, for example, humans have no zymal gland. It is certainly possible that many carcinogens in humans are in fact co-carcinogens. There is no method to determine this with any degree of certainty in humans.

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Question 4

It has been estimated that occupational cancer represents about one to five percent of the cancer cases reported annually in the United States. We don't know how valid the estimates are of the total incidence of occupational cancer. We know that there are a significant number of occupational cancer cases e.g., from 2-naphthylamine, asbestos, arsenic, vinyl chloride and this alone justifies vigorous preventive action.

Since numerous studies (vinyl chloride - B(a)P, Maltoni and Lefemine, 1975; Bingham and Falk, 1969) etc., have proven that a dose-response relationship is evident in the area of carcinogenesis just as in other areas of toxicology, it is readily apparent that positive results obtained at high doses indicate that lower risks are to be expected at lower doses. The specific limitations in estimating the lower risk factors are inherent in the specific limitations of the data gathering system. Such factors as animal numbers, number of dose levels, confidence limits and other factors must be considered in properly evaluating the dose-response relationship. In addition to a socially acceptable value of risk, the establishment of an absolute value of risk, rather than a relative value of risk (Subcommittee on Environmental Mutagenesis, 1977) is mandated by the OSHA Act in regard to occupational carcinogenesis.

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Question 5

- a. The first direct connection between an occupational exposure and risk of a specific cancer was that of chimney sweeping and cancer of the scrotum pointed out by Pott in 1775. He recognized this association because he saw several affected chimney sweeps but little or none of the disease in persons with other occupations. The disease was exceedingly rare in the general population, and the risk ratio for chimney sweeps was quite high.

About 1880 Hirtling and Kasse showed that "mountain disease" was a lung neoplasm. This condition was recognized as an entity in the Middle Ages because of its frequent occurrence among young miners despite the rarity in the general population. In 1895 the German surgeon, Rehn, published on the hazard of bladder cancer among dye workers. Rehn's association was based not on an exceedingly high risk ratio but rather on the absolute high frequency of the disease among exposed persons.

During the past several decades instances of occupational carcinogens have continued to be recognized both on the basis of an extremely high risk ratio and a high incidence rate among exposed persons.

The following tables show various agents which have been identified as occupational carcinogens on the basis of epidemiologic studies and confirmed and suspected carcinogens by target organ.

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* TABLE 1
Classification of Occupational Carcinogens

A. Organic agents

1. Aromatic hydrocarbons

Agents	Affected organ(s)	Incubation period (years)	Risk ratio	Occupation
Coal soot Coal tar Other products of coal combustion	Lung, larynx, skin, scrotum, urinary bladder	9-23	2-6	Gashouse workers, stokers, and producers; asphalt, coal tar, and pitch workers; coke-oven workers; miners; still cleaners; chimney sweeps
Petroleum Petroleum coke Wax Creosote Anthracene Paraffin Shale Mineral oils	Nasal cavity, larynx, lung, skin, scrotum	12-30	2-4	Contact with lubricating, cooling, paraffin or wax fuel oils, or coke; rubber fillers; retortmen; textile weavers; diesel jet tankers
Benzene	Bone marrow (leukemia)	6-14	2-3	Explosives, benzene, or rubber cement workers; distillers; eye users; painters; etc.

* Philip Cole and Marlene Goldman, Chapter 8-0

"Persons at High Risk of Cancer", edited by J. Fraumeni, National Cancer Institute

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Agents	Affected organ(s)	Incubation period (years)	Risk ratio	Occupation
Auramine	Urinary bladder	13-30	2-90	Dye and textile manufacturers and users; rubber workers (precipitation, filtration, laborers); textile dyers; paint manufacturers
Benzidine				
4-aminodiphenylamine				
6-naphthylamine				
4-aminodiphenyl				
4-nitrodiphenyl				
2. Alkylating agents				
Mustard gas	Larynx, lung, trachea, bronchi	10-25	2-36	Mustard gas workers
3. Others				
Isopropyl oil	Nasal cavity	10+	21	Producers
Vinyl chloride	Liver (angiosarcoma), brain	20-30	200 (liver) 4 (brain)	Plastic workers
A. Organic agents (continued)				
3. Others (continued)				
Agents	Affected organ(s)	Incubation period (years)	Risk ratio	Occupation
Bis(chloromethyl) ether	Lung (oat cell carcinoma)	5+	7-45	Chemical workers
Chloromethyl methyl ether				
B. Inorganic agents				
1. Metals				
Arsenic	Skin, lung, liver	10+	3-8	Miners; smelters; insecticide makers and workers; oil refiners; sprayers; tanners; chemical workers; vinyls
Chromium	Nasal cavity and sinuses, lung, larynx	15-25	3-40	Producers, processors, and users; acetylene and aniline workers; bleachers; glass, pottery and linoleum workers; battery makers

B. Inorganic agents (continued)

1. Metals (continued)

Agents	Affected organ(s)	Incubation period (years)	Risk ratio	Occupation
Iron oxide	Lung, larynx	—	2-5	Iron ore (hematite) miners; metal grinders and polishers; silver finishers; iron foundry workers
Nickel	Nasal sinuses, lung	3-30	5-10 (lung) 100+ (nasal sinuses)	Nickel smelters, mixers, and roasters; electrolysis workers

2. Fibers

Asbestos	Lung, pleural and peritoneal mesothelioma	4-50	1.5-12	Miners; millers; textile, insulation, and shipyard workers
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3. Dusts

Wood	Nasal cavity and sinuses	30-40	—	Woodworkers
Leather	Nasal cavity and sinuses, urinary bladder	40-50	50 (nasal sinuses) 2.5 (bladder)	Leather and shoe workers

C. Physical agents

1. Nonionizing radiation

Agents	Affected organ(s)	Incubation period (years)	Risk ratio	Occupation
Ultraviolet rays	Skin	varies with skin pigment and texture	—	Farmers; sailors

2. Ionizing radiation

X-rays	Skin, bone marrow (leukemia)	10-25	3-9	Radiologists; medical personnel
Uranium Radon Radium Mesothorium	Skin, lung, bone, bone marrow (leukemia)*	10-15	3-10	Radiologists; miners; radium dial painters; radium chemists

3. Other

Hypoxia	Bone	—	—	Caisson workers
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Table 2 Confirmed and suspected occupational carcinogens*
by target organ.

Target Organ/Tissue	Occupational Carcinogen	
	Confirmed	Suspected
Bone		Beryllium
Brain	Vinyl Chloride	
Gastroenteric Tract	Asbestos	
Hematopoietic Tissue (Leukemia)	Benzene Styrene Butadiene and other Rubber Manufacture Substances	
Kidney	Coke Oven Emissions	Lead
Larynx	Asbestos, Chromium	
Liver	Vinyl Chloride	Aldrin Carbon Tetrachloride Chloroform DDT Dieldrin Heptachlor PCB's Trichloroethylene Beryllium Cadmium Chloroprene Lead
Lung	Arsenic Asbestos Bis (chloromethyl) ether Chloromethyl methyl ether Chromates Coke Oven Emissions Mustard Gas Nickel Soots and Tars Uranium Vinyl Chloride	
Lymphatic Tissue		Arsenic Benzene
Nasal Cavity	Chromium, Isopropyl Oil, Nickel, Wood Dusts	
Pancreas		Benzidine PCB's
Pleural Cavity	Asbestos	
Prostate		Cadmium
Scrotum	Soots and Tars	
Skin	Arsenic Coke Oven Emissions Cutting Oils Soots and Tars	Chloroprene
Urinary Bladder	4-Aminobiphenyl Benzidine B-Naphthylamine	Auramine 4-Nitrodiphenyl Magenta

*Occupational Diseases - A Guide to their Recognition - U.S. Department of Health Education and Welfare - NIOSH

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Table 3 Suspected carcinogens based upon structural similarity to vinyl chloride.

Suspected Carcinogen	Structure
Vinyl Chloride	$\text{H}_2\text{C}=\underset{\text{Cl}}{\text{CH}}$
Bromoprene	$\text{H}_2\text{C}=\text{CHCH}_2\text{Br}$
Chloroprene	$\text{H}_2\text{C}=\text{CHCH}_2\text{Cl}$
Epibromohydrin	$\text{H}_2\text{C}-\underset{\text{O}}{\text{CH}}-\text{CH}_2\text{Br}$
Epichlorohydrin	$\text{H}_2\text{C}-\underset{\text{O}}{\text{CH}}-\text{CH}_2\text{Cl}$
Perbromoethylene	$\text{Br}_2\text{C}=\text{CBr}_2$
Perchloroethylene	$\text{Cl}_2\text{C}=\text{CCl}_2$
Tribromoethylene	$\text{Br}_2\text{C}=\underset{\text{Br}}{\text{CH}}$
Trichloroethylene	$\text{Cl}_2\text{C}=\underset{\text{Cl}}{\text{CH}}$
Styrene (Vinyl Benzene)	$\text{H}_2\text{C}=\underset{\text{C}_6\text{H}_5}{\text{CH}}$
Vinyl Bromide	$\text{H}_2\text{C}=\underset{\text{Br}}{\text{CH}}$
Vinylidene Bromide	$\text{H}_2\text{C}=\underset{\text{Br}}{\text{CBr}}$
Vinylidene Chloride	$\text{H}_2\text{C}=\underset{\text{Cl}}{\text{CCl}}$

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- b. No one study approach can provide all or even most of the needed health information. While epidemiologic studies in the occupational setting have the potential to determine effects of long term low level exposures, the difficulty in making quantitative estimates of present exposures and the even greater problem in determining past exposures makes it hard to obtain accurate dose response data. On the other hand, while more accurate dose response data can be derived from toxicological studies using experimental animals, one is always faced with the difficulty of extrapolating results from experimental animals to humans and often with the additional problem of extrapolating from observed higher dose levels to lower dose levels. However, when the two study approaches are utilized in a coordinated way, benefits of each approach can be maintained and many of the individual methodological weaknesses can be overcome.

The following table shows these strengths and weaknesses.

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Table 4*

DISCIPLINARY APPROACHES TO HEALTH EFFECTS OF AIR POLLUTION

Discipline	Population studied	Strengths	Weaknesses
Epidemiology	Communities Diseased groups	Natural exposures Observation in man No extrapolations Vulnerable groups included Long term, low-level effects evaluated Study many people	Quantifying exposure difficult Many covariates Minimal dose response data Association vs. causation Can only make few health measurements Long latent periods for disease a problem
Toxicology	Animals Biochemical systems Cells	Easy to obtain dose-response data Rapid data-acquisition Cause-effect more definite Mechanisms of response Predict shapes of dose response curves Administer toxic materials Study acute and chronic effects	Realistic models of human disease? Extrapolation from animals to man Threshold of human response? Artificial exposures

*Dr. Carl Shy, "Strengths and Weaknesses of Epidemiological, Clinical and Toxicological Study Approaches," Chemist/Meteorologist Workshop 1975, U.S. Energy Research and Development Administration

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c. The impact of epidemiologic studies in cancer research, such as the studies on cigarette smoking and lung cancer, prompted a recent Nobel Laureate to proclaim these studies as the major scientific finding of the 20th century.

It is doubtful that the impact of smoking on lung cancer incidence would have been known if research had been limited solely to cellular and whole animal studies. Although agents contained in cigarette smoke have been shown to induce cancer in laboratory animals, the sum of the carcinogenic effects of the known agents does not equal that of the cigarette smoke condensate. Particular difficulty has been encountered in inhalation studies of cigarette smoke on laboratory animals because the animals, particularly smaller species such as the rat, frequently die from the acute toxic effects of the nicotine and carbon monoxide in tobacco smoke. Another problem stems from the fact that the upper respiratory tract of experimental animals, particularly the nose, is much different from analogous human structures resulting in a more efficient filtration of smoke in the upper respiratory tract of these animals.

There is mounting epidemiologic evidence from a series of occupational health studies incriminating benzene as a possible leukemogenic agent. Thus far, no animal studies have been able to demonstrate this effect. Similarly, the carcinogenic activity of

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arsenic has been demonstrated through epidemiologic but not by toxicologic studies. If reliance were placed solely on cellular and animal tests, then the importance of benzene and arsenic as carcinogenic agents would presently be unrecognized.

According to Sir Austin Bradford Hill, more weight must be given to positive as opposed to negative studies. Negative epidemiologic studies, particularly in cancer, cannot be construed as providing firm evidence of safety. This is because of the problems of latency and the small number of people often observed in epidemiologic carcinogenic studies which often preclude demonstration of statistically significant differences.

- d. If the appropriate steps are used in epidemiologic research, then descriptive studies have the potential to identify unusual clusters and high risk individuals for subsequent study which should then limit the number of negative studies.

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Question 6

It has been customary to rely upon animal studies in the absence of human evidence for a carcinogenic assessment of chemicals. An examination of the literature and of the experience in this method of approach reveals that animal data can be satisfactorily used as a predictor of human response.

The development of the vinyl chloride study, the coal tar/coke oven emission studies and various other examples illustrate the predictive value of animal bioassay methods.

In addition, the correlation between species with certain carcinogens such as benzo(a)pyrene, bischloromethylether, aminodiphenyl, benzidine, vinyl chloride, etc., have been in excellent agreement, even though the target tissue may differ among the species tested. In the case of benzo(a)pyrene, nine species of animals have been tested and all found to respond to this widely tested ubiquitous carcinogen. (Survey of Compounds Which Have Been Tested for Carcinogenic Activity - NCI).

If the responses of animals to known human carcinogens are examined it becomes obvious that all human carcinogenic chemicals, with the possible exception of arsenic and benzene, are also carcinogenic for animals.

The inhalation and percutaneous routes of exposure are the obvious routes of choice in experimental carcinogenesis studies when considering occupational exposure to chemical carcinogens. These routes are also the

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choice when considering experimental design of studies to investigate other toxic agents. However, it is well known that clearance from both the upper airways and the deep lung involves the mucociliary escalator in which materials are cleansed from these areas and usually find their way into the alimentary tract, in lieu of expectoration. Therefore, the oral route of administration via either stomach intubation, for purposes of exact quantitation of dose, or through consumption of food or water containing contaminants, is a perfectly adequate route of administration to test the carcinogenicity of chemicals and complex mixtures found in the occupational environment.

Inhalation is usually the preferred route of administration in animal studies for judging the carcinogenicity of airborne substances. Because of the expense of this type of study and methodologic difficulties, other routes, especially per oral, are used. In the usual case, this route gives valid, extrapolatable information, but each case has to be considered individually. Similarly, other routes, e.g., topical application, give useful information. Injection site sarcomas by themselves, probably do not indicate carcinogenicity by other exposure routes. They may indicate specific hazards in the event of accidental implantation of the substances.

The validity of using the maximum tolerated dose in rodent bioassays has been discussed and debated for a number of years. It is appropriate to mention that the National Cancer Institute as well as other agencies such as NIOSH, FDA and EPA continue to consider this as an appropriate approach in experimental bioassays. The reasons for this choice are obvious when considering economics and the probability of response.

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Question 10

Present knowledge does not permit development of a consistent and rational basis for decisions on additive and synergistic effects. Complicating this problem is the question of promoting agents and co-carcinogens, widely and variously used terms without the same meanings to everyone.

Additive effects should be assumed when two agents cause cancer at the same site, especially when the two agents also have chemical similarities, such as PN's or aromatic amines. Synergistic effects should be assumed only when there are data or principles suggesting in the specific case that potentiation is likely. Similarly, co-carcinogenicity and promotion should not be assumed except in a specific case where there are data or principles that apply. In clearcut areas involving personal habits such as smoking, counseling of workers should be called for. Other areas of personal habits, such as diet or lifestyle, should not be considered in this proposed standard, at least until the issues are clearer.

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Questions 15 & 16

Questions 15 and 16 are closely related and will be answered together. The problem of additive and synergistic effects is extremely difficult to assess with available scientific methodologies, either toxicology or epidemiology. To date, the scientific community has not adequately dealt with this problem. Toxicology and epidemiology both provide valuable information about carcinogenic risk. The problems of additive (or antagonistic) and synergistic effects do not make dose-response data in test animals irrelevant. Epidemiology and toxicology have both strengths and weaknesses. However, by combining two methodologies, in this case toxicology and epidemiology, it is often possible to overcome some of the weaknesses of each individual methodology, yet retaining their strengths. From this point of view, corroborating data on carcinogenic risk from both epidemiology and toxicology provides the most defensible data as to carcinogenic risk. Most toxicology studies assess effects of single exposures. It is virtually impossible to artificially generate an exact replica of the complex workplace environment in any toxicologic experiment. One of the greatest strengths of the epidemiology approach is to observe the effects of this complex environment directly in man. However, unless the possible synergistic or additive effect is specifically tested either epidemiologically or toxicologically, it is impossible to assess the importance of such interactions. In the final analysis, though, health may still be protected even if precise information on interactions is not available. This is because a given compound in a complex mixture may often serve as an index, which when controlled, will also result in decreased exposure to all compounds in the complex mixture. The situation with coke oven emissions is an excellent example in this regard.

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Question 19

Latency refers to the long period of cancer induction. Because of the uncertainties in identifying the specific time or event in the genesis of the cancer and the uncertainties in identifying the cancer itself, the term latency is not precise. It usually is taken to be that interval between the first known exposure to the cancer-causing substance and the first evidence of the consequent cancer, which is often at autopsy.

Whether the cancer process is initiated by the first exposure is not known; it is generally thought that the process is initiated by the effect of repeated exposures, but there are rational bases for suggesting that any one of these repeated exposures may have been the initiating event. It is conceivable that both ideas are correct, for example, it might be that the cancer is initiated by one exposure and is enhanced sufficiently by subsequent exposures to progress to enough overt cases to constitute a statistically significant excess (whether in an epidemiologic survey or an experimental animal investigation). However, this speculation should not obscure the point that latency is an imprecise term referring to the many years required for the development of most cancers to the point they are observed and is defined more precisely in specific investigations or surveys for the purpose of that study.

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Question 28

According to a report from the DHEW Subcommittee on Environmental Mutagenesis (1977), mutagenesis (short-term or in vitro) testing, in addition to providing valuable information on the risk to future generations, can provide valuable information regarding other toxicological manifestations. Examples are cited stating that there is an "apparent relationship between carcinogenicity and mutagenicity" (McCann, et al., 1975; McCann and Ames, 1976). However, the predictive value of short-term mutagenicity tests for carcinogenicity is currently under investigation, involving numerous efforts to assess the use of short-term mutagenicity tests.

The Subcommittee Report goes on further to state that the utility of mutagenicity test procedures for screening of chemicals for somatic effect, for example, carcinogenicity is not predicated on the assumption that the effect is due to mutations in somatic cells; but "the empirical demonstration of a high correlation between mutagenicity and the effect of concern (carcinogenesis) is a sufficient basis for establishing a role for mutagenicity testing as a predictive tool regardless of the mechanism involved."

There is widespread belief among investigators in the cancer area that DNA damage is involved in the induction of cancer. This is the basis for the supposition that carcinogens might be detected by the consequences of DNA damage in simple systems (Bridges, 1976).

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Short term or in vitro tests that have had some testing for validation purposes included those referenced by Bridges (1976). Many other validation tests are ongoing (DeSerres, 1977; Dunkel, 1978). Reports are available commenting on the state of the art status of in vitro testing for carcinogenesis (Casto, 1977; Kouri and Schechtman, 1977; Conservation Foundation, 1977).

For scientific purposes, justification of the use of short-term tests for the purpose of screening thousands of chemicals for their suspected carcinogenic activity and for the purpose of prioritizing these chemicals for long-term animal bioassay, appears to be adequate. However, the original intent for utilization of these tests was only for these two objectives and not for use as a confirmational test for long-term animal bioassay.

It is inappropriate at this time to attempt to substitute a short-term test for a long-term animal bioassay for at least two reasons:

- (1) Validation procedures are not complete and correlations between the test systems have not been adequately performed; and
- (2) The outcome of the short-term tests as compared to the long-term bioassay are not biological equivalents. In one case the end point is mutagenesis, in the other case, carcinogenesis. However, one (mutagenesis) may often cause the other (carcinogenesis).

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It has also been observed that a carcinogen does not always produce tumors in the same organs in all species. The mouse liver responds more readily than most other tissues with most of the carcinogens that have been tested. Yet it is still predictive for cancer at other sites in other species, including man (Tomatis, 1973; Newberne, 1975).

Another consideration in evaluating a predictive model for human carcinogens is the route of administration. Although the route of administration might not be important in determining whether or not an agent is carcinogenic for research purposes, it is important from a preventive health standpoint. To properly evaluate carcinogenicity, the suspect agents should be administered to animals by the same routes as humans are exposed, namely, via the lungs, gastrointestinal tract, dermally and in some cases intramuscularly, intradermally and subcutaneously. The latter conditions would apply, for example, to those agents such as metal fragments that might become embedded in skin or muscles. In industrial exposures to particulates, oral exposures are frequently as important as pulmonary exposures in as much as the particulates that are trapped in the upper respiratory tract are usually swallowed.

Although in the above discussions chemicals have been given primary consideration as carcinogens, some consideration should also be given to physical agents, e.g., ultraviolet and infrared irradiation and heat. To exclude physical agents from consideration in the regulatory process is unwarranted. To exclude any agent on the basis of its proposed mechanism of action is also unwarranted, since the mechanism is not being regulated, but instead the agent. It is, therefore, recommended that paragraph (1) in section 1990.111 be deleted from the Proposal.

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Question 31

In the attempts to develop models for predicting human carcinogens prolonged debates have centered around the type of lesion in animals that must be induced before a chemical can be called a carcinogen. Particular attention has been given to the mouse hepatoma (Butler and Newberne, 1975). Some scientists believe that most mouse hepatomas are not cancers because they do not metastasize, and imply that the mouse hepatoma is, therefore, not predictive. This argument is illogical. In the first place, not all hepatocellular carcinomas metastasize in any species studied, yet they are frequently responsible for the death of the hosts. Of 33 mice that died subsequent to chronic exposures to 4-dimethylaminoazobenzene, 71% died as a result of hepatocellular carcinoma (with ascites and/or anemia) yet pulmonary metastases were infrequently observed (Gallatly, 1975). Metastases are observed in humans in only approximately one-half of patients with hepatocellular carcinomas (Robbins, 1975). In the second place, even the spontaneous hepatocellular carcinomas in mice seldom metastasize. In fact, very few of any of the spontaneous neoplasms in mice or rats ever metastasize. In this way, rodents are more resistant than humans and possibly are not sensitive enough to the induction of cancer as we know it in humans. The reasons for that might also be explained on various factors that modify the ability of tumors to metastasize (Fidler, 1975). Thirdly, for predictive purposes there is no reason why the rodent tumors need metastasize. There need only be a correlation between cancer in man and a neoplasm in animals, and this has already been demonstrated many times.

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