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TOXICOLOGY AND OCCUPATIONAL MEDICINE

Proceedings of the Tenth Inter-American Conference on Toxicology and Occupational Medicine, Key Biscayne (Miami), Florida, October 22-25, 1978

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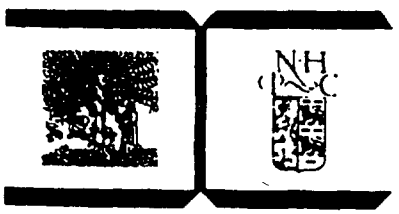

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Preface

The papers in this volume were presented at the 10th Inter-American Conference on Toxicology and Occupational Medicine of the University of Miami, conducted from October 22 to 25, 1978 at the Key Biscayne Hotel, Miami, Florida. This hotel is located on the ocean side of the secluded tropical island of Key Biscayne, 15 minutes by car from downtown Miami.

Each author accepted editorial responsibility for his report.

The purpose of the 10th Conference, as in previous conferences, was the presentation by delegates of research reports on subjects in the broad field of Toxicology and Occupational Medicine, followed by free discussions by all participants.

The Conference met the specific requirements of the American Medical Association, and of the Florida Medical Association for 16 credit hours:

> "As an organization accredited for continuing Medical Education, the University of Miami School of Medicine certifies that this continuing Medical Education Activity meets the criteria for sixteen hours in Category One of the Physician's Recognition Award of the American Medical Association. - Florida Medical Association, mandatory hours - sixteen".

Delegates attended from the United States, from Buenos Aires (Argentina), Porto Alegre, Salvador - Bahia, Sao Paulo, and Rio de Janiero (Brazil), Ottawa, Montreal and Toronto (Canada), London and Manchester (England), Takoradi (Ghana), and The Hague (Netherlands).

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The Conference honored Florida Congressman Dante Fascell who has "vigorously pursued the Good Neighbor Policy with countries of this hemisphere and who has won the admiration and respect of all of us", and Dr. H.G.S. van Raalte "for his pioneering and outstanding contributions in the field of Toxicology and Occupational Medicine".

The Inter-American Conferences on Toxicology and Occupational Medicine would not have been possible without the generous financial contributions of friends in Industry. The 10th Conference was supported by the Ciba-Geigy Corporation, Dow Chemical U.S.A., Exxon Corporation, International Telephone and Telegraph Corporation, Merck, Sharpe & Dohme Research Laboratories, and Shell Internationale Research Maatschappij B.V.

The conferences were organized 22 years ago by faculty members of the University of Miami, Miami, Florida, and the University of Havana, Havana, Cuba. The planners visualized that these conferences would be held every two or three years, and that the site would rotate between Miami and Havana. As fate would have it, all conferences have been conducted in Miami -- but whether in Miami or at another site in this hemisphere, long may they continue!

Wm. B. Deichmann
November 21, 1978.

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MERCHANT MARINE INSPECTORS AND CHEMICALS

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ABSTRACT

A major contribution to the uncertainty inherent in toxicologic data stems from the recognition that exposure to a single substance under carefully controlled conditions is generally most unrealistic. The Coast Guard has a group of approximately four hundred officers and warrant officers who are involved with the inspection of merchant vessels. These individuals, Coast Guard Marine Inspectors, are required to enter cargo tanks, void spaces, and cofferdams as well as normally manned spaces, for the purpose of ascertaining the integrity of the hull, machinery and equipment aboard vessels. A certain number of marine inspectors, estimated to be about 150 persons, spend time inside cargo tanks and are likely to be exposed to many chemicals and other stress factors, in varying combinations and sequences, in the course of a normal day. This presents problems of work practice evaluation with an almost infinite number of variables. Consequently, relatively little is known about synergisms, antagonisms, simple additive and simple subtractive phenomena in producing toxic manifestations.

BACKGROUND

Recently, there has been increasing concern over the effects of chronic exposure to toxic concentrations of chemicals encountered. This concern is not limited only to individual chemical exposure, but to exposure to mixtures. Coast Guard Merchant Marine Inspectors

frequently come into contact with chemicals and must be aware of the hazards of low level exposure.

In LCDR Fred Halvorsen's article in Proceedings, April 1976, he stated that Merchant Marine Inspectors are voicing concern over chronically toxic concentrations.[1] They have had many years of experience in the field and understandably desire to know what the ill effects may be due to this type of exposure. Kent Savage from the National Fire Protection Association, in Boston, Massachusetts, also finds a growing public awareness of the health hazards of atmospheric contaminants which has brought up the problem of appraising low concentration of potentially toxic gases, vapors, and particles.[2]

Outside the Coast Guard, other individuals are raising the same concerns over chronic exposure from hazardous materials and its effect on the human body. For example, medical doctors found that chronic administration of chemical mixtures can induce or inhibit the liver microsomal, drug-metabolizing enzymes. This interaction of chemicals on the liver system can affect the response of the body to drugs.[3]

Throughout these references the problems adressed are chemical-chemical interactions, chemical-drug interactions and drug-drug interactions. Very little work has been done in examining the chronic effects of these interactions. In the literature these problems are examined in the acute exposure range with extrapolation necessary to the chronic levels. In most cases this type of approach is speculative, but useful in assessing the type of interaction which might be encountered.

This paper will attempt to describe the potential effects of chronic exposure to chemicals on the Coast Guard Marine Inspector.

TERMINOLOGY

The terminology in the field of chemical interactions can be

confusing and misleading. A complete and sound knowledge of the terms is essential to the Merchant Marine Inspector when he performs his duties. In addition he should have some knowledge of the individual interaction of the chemicals to which he will be exposed.

The very basic study in this field is the science of poisons. A poison is a substance which can damage biological systems to the extent of serious incapacitation or destruction of body processes and life itself.[4] This way of describing a poison might first appear to be sufficient; however, it fails to establish any guidelines as to concentration or length of exposure in addition to other physical conditions. The toxicity of an agent is more descriptive in assessing the potential of harm from exposure to a chemical substance. Toxicity can be used to set up certain safety limits which can be quantified. This is very important to the Inspector who is concerned whether or not a cargo tank is safe for entry. There are two levels of exposure with which the Inspector must concern himself: acute or chronic. An acute level exposure occurs when a dose is delivered in a single event and absorption into the body is rapid.[5] The concentration level is usually high and effects are immediate. This type of exposure is usually short, but may also lead to long term health effects. Inspectors may be acutely exposed to high levels of chemicals when inspecting a flame screen or when using fresh air blowers to ventilate an enclosed space causing vapors to build up in pockets. Chronic exposures occur when contact with the substance is at some frequency over a period of time[6], usually at low levels of concentrations.

Inspectors seldomly are exposed to acute levels of substances and must be concerned with chronic, low level concentrations found in chemical cargo tanks. The Threshold Limit Values (TLV's), published by the American Conference of Governmental Industrial Hygienists (ACGIH), are limits which represent conditions under which it is

believed that nearly all workers may be repeatedly exposed day after day without adverse effect. They refer to time-weighted concentrations for a seven or eight hour workday and a forty hour work week. It should be noted that certain hypersensitive individuals, may experience discomfort at concentrations at or below the TLV. TLVs should be used as guides in the control of health hazards and should not be used as fine lines between safe and dangerous concentrations.[7]

Threshold limits are based on best available information from industrial experience and from experimental human and animal studies. The TLV is usually regarded at the maximum concentration allowed for safety of health, however, the lowest concentration achievable in the work place is desirable.

Due to his work practices, the Marine Inspector is exposed to a mixture of chemicals. The exposure of the Inspector is sequential. However, "mixing" takes place creating an exposure to a mixture of chemicals. ACGIH states that special consideration should be given to the application of the TLV's in assessing health hazards which may be associated with exposure to mixtures of two or more substances.[8] The TLV for mixtures found in the ACGIH Pamphlet "Threshold Limit Values . . . 1977" should be used when the substances have similar toxicological effects. The assumption made here by the ACGIH is that the chemicals are additive in their action, i.e. one chemical will neither enhance or inhibit the toxicity of the other chemical or chemicals. The formula used is in the ACGIH TLV pamphlet found on pp. 45-49.

This additive or joint toxic action has been examined by Dr. Henry Smyth from the University of Pittsburg using high concentrations. He states that in the occupational, domestic, or ambient environment, encounters with mixtures of chemicals far outnumber encounters with individual chemicals. Judgements of the relative safety or hazards of exposure to these mixtures must often be made, usually in the

absence of the knowledge of the mode of joint toxic action of the components.[9] His results showed that in 95 percent of the cases, a model for additive joint toxicity was followed. However, there are no ongoing studies examining joint toxic action for chemical mixtures encountered at chronic levels.

When the chemicals do not follow the additive action model, the interaction is synergistic. When you have an effect which is greater than the sum of the two chemicals independent effects, potentiation has occurred. This represents the condition whereby one substance is made more potent in the presence of another amount of another substance.[10] When the reverse occurs and inhibits the toxicity, antagonism has occurred. These actions have been examined relative to drug-drug interaction and found that both, potentiation and antagonism, occur with regularity in humans.[11]

One final word must be said concerning concentrations. The most accepted nomenclature for concentrations is the part per million (ppm) volume measurement for low level exposure. The Coast Guard's Vinyl Chloride booklet draws the analogy that one ppm can be illustrated by evaporating an eight ounce cup of liquid vinyl chloride in a room the size of a football field with a sixty foot ceiling. Assuming an equal mixing of air and vinyl chloride, we would have a one ppm concentration.[12]

DIFFICULTIES

The study of the toxicity of the interaction of two or more chemicals at chronic levels is constantly plagued by lack of data. Throughout the literature, studies have been made on the acute and some of the chronic aspects (time and concentrations) of exposure to individual chemicals; the majority of information generated is at acute levels. A Merchant Marine Inspector can refer to the Chemical Hazards Response Information System (CHRIS CG-446) and Chemical Data

Guide for Bulk Shipment by Water (CG-388) to find information about the acute dangers of exposure to an individual chemical.[13] While there are well-known chronic effects from exposure to chemicals such as benzene causing certain blood diseases or vinyl chloride leading to cancer later in life; the only acute data is well documented for a large number of chemicals.

Information can be found concerning drug and drug, drug and chemical, and chemical and chemical inspections. However, the literature reports are deficient with respect to studies done on a chronic level for large numbers of chemicals. The following will give examples of these interactions with an attempt to extrapolate them to chronic levels.

1. Drug-drug interactions are not of primary concern for the Merchant Marine Inspector. However, the number of reports of drug interactions resulting in synergism is increasing rapidly. Drug effects are dependent on concentrations which reach the site of action. Other factors such as metabolism, frequency of administration, distribution, and excretion are important in determining the effects of a drug.

A classic example of drug interaction was seen in patients hospitalized for myocardial infarction (heart attack) and given an oral anticoagulant such as Warfarin plus a sedative such as phenobarbital. Often the sedative was discontinued when the patients were dismissed from the hospital, and bleeding episodes were noted within a few weeks. The phenobarbital had increased the hepatic (liver) metabolism of the anticoagulant, which necessitated a higher daily maintenance dosage. When the phenobarbital was discontinued, the metabolism returned to its slower rate, resulting in higher anticoagulant levels in the plasma - precipitating bleeding.[14]

Therefore, when using various drugs in conjunction, a doctor must be aware of the possible interactions. The chances of drug

interactions is diminished by using as few drugs as possible at a single time.

2. Drug-chemical interactions could become a problem for the Merchant Marine Inspector. Phenobarbital, a commonly used barbituate, has been shown to potentiate the toxicity of carbon tetrachloride and chloroform, typical halogenated hydrocarbon solvents.[15] It is recognized that in general, barbituates are used by a considerable segment of the working population; thus the increase of solvent toxicity by phenobarbital represents a potential hazard that must be recognized.[16] When inspecting tanks, which carried an organic solvent such as tetrachloride, inspectors taking medication such as phenobarbital should take precautions such as consulting a physician. Other studies show that alcohol increases the effects of most tranquilizers, morphine, and barbituates.[17]

3. Chemical-chemical interactions are of the utmost concern for the Inspector. Many studies have shown that there are effects between some of the chemicals which the Inspector routinely comes into contact.[18]

Studies have demonstrated the potentiation of carbon tetrachloride by ethanol and isopropanol at various concentrations.[19,20] This potentiation of toxicity of carbon tetrachloride by ethanol has been known for many years. It was reported in 1925 that the ingestion of alcohol increased the hepatoxic (liver destruction) action of carbon tetrachloride. Later reports described the ethanol potentiation of trichloroethylene toxicity.[21] Further studies by Dr. Cornish (University of Michigan) in 1967 showed that various high carbon number aliphatic alcohols potentiated the toxicity of carbon tetrachloride.[22]

Carbon tetrachloride, benzene, trichloroethylene, and alcohol are some of the more common types of chemicals to which an Inspector is exposed. The anesthetic effect of alcohol may compound the already

narcotic effect of these solvents. Therefore the Inspector may be in trouble if he goes to inspect after a "few". Therefore, not only the individual chemical effects, but the interaction between chemicals, which may be more damaging, must be considered when inspecting various cargo tanks.

THE MARINE INSPECTOR

The types of chemicals to which a Merchant Marine Inspector may be exposed are listed in Subchapter O and D in Title 46 of CFR. CHRIS and CG-388 have these chemicals listed with some of their common acute exposure effects. However, most Merchant Marine Inspectors feel they are "in the dark" about the effects of chemicals. They are not aware of possible accumulation or interaction effects of chemicals in their bodies.

New Orleans and Baton Rouge, in the 8th Coast Guard District, and along the Ohio River are probably the areas where a Merchant Marine Inspector comes into contact with chemicals more than any other location. One Warrant Officer who has served four years in New Orleans and two years in Baton Rouge stated that an Inspector working in the Eighth Coast Guard District can expect to come in contact with benzene, various nitriles, methanol, caustic soda, carbon tetrachloride, vinyl chloride and anhydrous ammonia. He could possibly be in one tank for up to two hours on one barge or could inspect many tanks in a relatively short period of time. The tanks on the barges may have had different cargoes onboard and the Inspector is exposed to all of the chemicals.

While performing his job the Inspector works closely with the Marine Chemists. In LCDR Halvorsen's article "The Marine Chemist and the Marine Inspector", he stated there is a professional respect held between the two parties.[23] The Marine Chemist insures that the tank or barge is safe for men and safe for fire. The Marine Chemist

Certificate states, "standard safety designations for men . . . . means that in the compartment or space so designated:

a. The oxygen content of the atmosphere is at least 18.0 percent by volume;

b. Toxic materials in the atmosphere are within permissible concentrations; and

c. In the judgement of the Marine Chemists, the residues are not capable of producing toxic material under existing atmospheric conditions while maintained as directed on the Marine Chemists' Certificate." (NFPA 306)[24]

According to Tom Wolf, a Marine Chemist in Baton Rouge, the permissible levels used are the established TLV's for the material which was in the tank. He went further to attest that when a Coast Guard Inspector enters a tank that he has certified, the atmosphere is at the safest level achievable. In order to have it safe, he must know what the last cargo was, and then take an atmospheric reading for oxygen and toxic atmosphere with an oxygen, carbon monoxide and combustible gas indicator or other suitable device. For particularly hazardous materials such as benzene he will check for the levels of that specific chemical to make his determination. There are problems; a lack of odor does not guarantee safety and a Marine Chemist Certificate is not the last word. The certificate must be current, as conditions at the time of certification may change causing the tank to be unsafe. For many chemicals no TLV's are listed; in addition, there is no reference to the problems of possible interactions of the chemicals when exposed to different kinds. Each tank must satisfy the TLV for the individual chemical (if TLV is known). No mention is made about the need to achieve a lower TLV due to the subsequent exposure to the Inspector by other chemicals during that day--he must be aware of possible interactions and the possibility of needing a lower exposure limit! The Marine Chemist Certificate is very

important to the Inspector, and he should be aware of all aspects of the gas tests made and the results. Further, appropriate instructions, discrepancies, and dates and times of tests should be examined prior to entry.

The Merchant Marine Inspector usually is not exposed to high concentrations of chemicals. When he must check a flame screen he may be subjected to acute concentrations of the chemical which may cause dizziness or nausea, however, most of his exposure will be limited to low concentrations. The problems of interactions or accumulations of chemicals may surface here. In addition, sensitive individuals may have problems working in atmospheres of chemicals at or slightly below TLV levels. For example, one Warrant Officer interviewed had experienced a type of paralysis while working on an inspection in a "safe" atmosphere. He stated that the tank was certified by a Marine Chemist. This after he had been working around chemical carriers for six years. Could he have been accumulating chemicals in his body and the latent response have surfaced with the cargoes encountered during the last inspection? It is impossible to retrace the types of chemicals, exposure concentrations, exposure times and the sequences of exposure, but there seems to be some correlation between the work around chemical carriers and future medical problems. Other Warrant Officers, who after retiring, have been found to have liver dysfunctions which may be indicative of the kind of work they previously performed.

Merchant Marine Inspectors must always be aware of the possibility of harmful effects from their exposure to chemicals, both acute and chronic. Guidelines (Occupational Safety and Health Administration and Coast Guard regulations) must be followed for safety. Entry into confined spaces should be kept at a minimum and only when necessary. The Inspector must have an awareness and an appreciation of the materials with which he comes in contact. There is a need for

"cargo compatibility" of the chemicals within the body. Certain chemicals should not be mixed. This means the Inspector should not drink alcohol before or after (for a specific period of time) working in a chemical atmosphere, any chemical atmosphere. Further examples and safety precautions should be given to the Inspectors in the field. The new Marine Safety Manual to be published soon will be a good up to date reference guide. The Inspectors must not be left "in the dark". The biggest concerns echoed by Inspectors is "what is it?, how does it affect me?, and how can I protect myself?."

Medical monitoring is necessary to flag any problems before they surface into disease or impairments.

There should not be a blind reliance on the gas free certificate. The time of day, temperature, and other parameters must be taken into account before entry into the tank. The tank might be void of toxic vapors at 0800, but at the temperature increases any liquid could vaporize and concentrations above the TLV could appear in the tanks. The individual Inspector must take each situation as a new one and protect himself from possible injury.

Throughout this discussion it has been noted the lack of data exists in the field of interactions of substances on a chronic level of exposure. Information at the acute exposure level may be extrapolated to the chronic levels, making many assumptions; however, this leads to many inaccuracies. Further studies must be made.

Personal safety should be the main concern of the Merchant Marine Inspector. Chemical interaction could become an invisible enemy to the health and welfare of the Inspector. Do not fall victim to the psychology, "If I can't see it, it won't hurt me." Treat chemicals with respect.

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THE PREDICTIVE VALUE OF TESTS FOR CARCINOGENIC AND MUTAGENIC ACTIVITY

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ABSTRACT

Mutagenic, carcinogenic and epidemiological data are compared between known human carcinogens, probable human carcinogens and compounds which produce tumours in mice but not in other species. It is concluded that tumours of the lung or the liver, produced in the mouse but not in other species, are an unvalidated criterion for prediction of a hazard in man.

INTRODUCTION

A concerted research effort to identify the main factors associated with the incidence of human cancer has recently become a real possibility and challenge. This is due mainly to the convergence of three developments.

INVESTIGATIVE TOOLS

Cancer Registries. Increasing numbers and more comprehensive cancer registries in several countries and close international co-operation between epidemiologists has enabled the hypothesis to be derived that perhaps as much as 70 or even 90% of human cancer may be due to extraneous factors and might therefore be preventable. These epidemiological developments have been well presented in reviews by e.g. Higginson[1], Weisburger et al.[2], Wynder [3] and Doll[4]. It may be noted that these estimates crucially depend upon the accuracy of cancer registries in underdeveloped countries. In view of the difficulties involved in running a satisfactory registry, the higher percentage may be unduly optimistic. But even if the real percentage was nearer to, say, 60%[5], this would fully justify a great effort to lower exposures to identified carcinogens.

Genetic and cytogenetic research. Enormous strides have been made in these fields, largely independent from the main stream of cancer research. This work has led to the development of a number of easily performed short-term methods for testing chemicals for mutagenic or cell-transformation activity[6]. The growing realisation of a close (but certainly not absolute) correlation between mutagenic and carcinogenic activity has led to the feasibility of systematically screening the carcinogenicity of the foreign factors to which we are exposed (the majority of which may be expected in our normal daily

food[3,4]). These methods have also proved of value in identifying active carcinogenic metabolites of indirect carcinogens[7].

Animal carcinogenic studies. The number of animal tests for carcinogenicity has been greatly expanded and standardized protocols have enabled an objective comparison to be made of qualitative and quantitative differences in response between species.

Consequently, the number of potential tools for screening has been magnified over the last few years. Few of these have been developed to the point that they can be relied upon to predict the existence of a human hazard when used on their own. However, confidence in these methods, alone or in combination, will grow or diminish when subjected to a continuous and critical validation process. The difficulty of the validation process is illustrated by a recent validation effort of the Ames test and a test on saccharomyces cerevisiae against the known animal data on several mycotoxins[8]. The authors concluded that except for aflatoxin B1 and sterigmatocystin, "a positive correlation between the other mycotoxins reported to be carcinogenic and the two in vitro test systems employed was not demonstrated". It is not clear whether the discrepancy was due to a deficiency of the mutagenic test systems or to a deficiency of the animal tests which proved carcinogenic activity in mice but not in rats for those mycotoxins which were found to be non-mutagenic in these tests.

VALIDATION

This process involves several steps:

1. Most but no all short-term tests assay mutagenic activity. The genetic effects in man are expected to be rare events, indistinguishable from the relatively frequent natural background mutations. Consequently, validation of the capacity of mutagenic tests to predict a demonstrable mutational hazard in man is unlikely in the near future. This particular prediction, of course, may be proven wrong by the first comprehensive epidemiological investigation[10].

2. Due to an observed correlation between mutagenic and carcinogenic activity of many (but not all) chemicals, mutagenic tests are held (often) to predict carcinogenic activity. Indeed, several mutagens have subsequently been found to be carcinogenic in experimental animals[9], although obvious exceptions remain. Therefore most mutagenic testing procedures are currently "validated" in terms of correlations with long-term cancer-investigations in animals.

3. The only fully relevant validation of any toxicological test can be obtained from man. Thus, a continuing critical effort must be made to check

the validity in man of all laboratory data including animal data.

For logistic reasons, it is clear that the second phase of the validation process will progress more rapidly than the third phase. Progress in the first phase has still to take place until the first clearly confirmed epidemiological data become available[10].

As to be expected with any toxicological test method, predictability of each short-term test depends upon the class of compounds examined[11,12].

We should not be misled into thinking that validation will be easy or quick: There are only a few pure compounds which are established carcinogens in man, probably less than two dozen. In contrast, generally, mixtures are of greater importance in man, such as cigarette smoking, nickel refining or exposure to mixtures such as soot, coaltar or some cutting oils. If rational action is to be taken in these cases, identification of the responsible carcinogen is necessary. If not, then it is as likely that such factors are unwittingly introduced into a process as they were equally unwittingly removed from e.g. the nickel refining process in a particular plant[13]. Another example is the Japanese work on factors in the basic fraction of cigarette smoke-tar which might well be much more potent than the polynuclear aromatic fractions [14,15]. Since the basic fraction largely stems from the protein component, lowering this fraction might be quite feasible[2]. Intelligent application of such findings to the development of less dangerous cigarettes might well lead to a greater reduction in the future lung cancer incidence than reliance on educational programmes alone[16].

PREDICTABILITY OF ANIMAL TESTS

Unfortunately, the scientific analysis of the subject of validation of test methods has been postponed because initially the discussion was largely limited to the subject of occupational carcinogenesis[17]. Although this subject is highly important in its own right, this circumstance, especially in the USA, transferred the necessary critical discussion between the many different scientific disciplines involved into the adversary fields or regulatory authorities and pressure groups. The scientific discussion was distorted out of all recognition by legal considerations[18], politics, emotions and dogmatic assertions. This situation only delayed the necessary insight of single scientific disciplines into the strength and limitations of related disciplines.

Because of this unfortunate intermingling of "political oncology"[19], emotions and legal constraints, the questions asked have been in terms of legal requirements[20] but not in terms which are helpful to the aim of identify-

ing the most important environmental carcinogens and lowering exposure to established carcinogens.

Thus the question has been debated whether animal tests are predictive for a human hazard. Of course, they are in certain circumstances the best we have, Also, it is well proven that they can be predictive[21]. However, the real questions should be:

(a) do particular animal tests reliably predict the existence of a human hazard?

(b) if so, can they also predict that a hazard exists under particular conditions of use and exposure of populations?

To illustrate the validation process which will be necessary, the available data will be reviewed on some:

- known human carcinogens,
- probable human carcinogens,
- mouse-specific carcinogens.

The above classification requires some clarification. The selection of compounds in the second and third class is to some extent arbitrary. In addition, separate problem areas are well-known but will not be discussed here. Some are: carbontetrachloride, chloroform, saccharin and many other compounds of which the carcinogenic hazard in man at normally occurring exposures is unknown, and thought by many to be non-existent. Therefore, the classification is certainly neither exhaustive nor final.

However, purpose of this division is to illustrate how data from different sources must be combined in order to come to a reasonable estimate of whether a human carcinogenic hazard is expected to exist at any level of exposure. Different (biochemical and pharmacokinetic) investigations are needed in order to investigate whether a hazard might exist at low exposure levels.

Mutagenic activity of compounds is not a simple yes or no statement. Chosing plus or minus denotations for inclusion in the Tables is to some extent a subjective effort; in general, the outcome of the Ames-test has been taken as the decision point for plus or minus, unless convincing data were available from other tests. Each such sign in the following Tables has to be confirmed or rejected after full quantitative assessment of each compound.

However, I hope to illustrate that the obvious differences between these classes should lead to further research and more directed epidemiolo-

gical work in order to verify in how far the noted differences should be regarded as important in the ongoing validation effort. Especially epidemiological investigations are of the greatest importance in validation because the direction of future cancer research may depend upon their outcome[22].

DIFFERENCES BETWEEN ANIMAL CARCINOGENS

Confirmed human carcinogens. The first class (see Table 1) is a small class of some chemically defined known carcinogens in man.

TABLE 1
KNOWN HUMAN CARCINOGENS

Compound	Species tested					Mutagenic Activity
	Mouse	Rat	Hamster	Rabbit	Monkey	
β-Naphthylamine[23]	+?	+?	+	+?	+	+[25,26]
Benzidine[24]	+	+	+			+[25]
4-Aminobiphenyl[24]	+	+		+		+[25]
Vinylchloride monomer[30]	+	+	+			+[25]
Bis(chloromethyl) ether[31]	+	+				+[25,31]
Asbestos[32]	+	+	+	+		chromosome aberr.[27]
Arsenic[32]	-	-				+[28]
Benzene[33]	-	-		-		chromosome aberr.[29]
Diethylstilbestrol[32]	+	+	+		+	-[34]

+ positive for carcinogenicity or mutagenicity
- negative for carcinogenicity or mutagenicity

Apart from diethylstilbestrol all members of this class are mutagenic. When tested in animals known carcinogens were either entirely negative (i.e. up till now: arsenic and benzene) or positive in most or all species tested.

Probable human carcinogens. The second class (see Table 2) consists of some compounds for which the evidence strongly suggests a human carcinogenic hazard under certain conditions of exposure. All are carcinogenic in all or most species tested and all are mutagenic. In effect, mutagenic tests have been used as a help in identifying the ultimate carcinogens in these classes[7].

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3,4-Benzo(a)pyrene has been put into this category because, although the human carcinogenicity of soot, coaltar, and some mineral oil fractions is beyond doubt, the contribution by each member of the large class of polynuclear hydrocarbons is unknown. Some members of this class have been found not to be carcinogenic in animal tests. Aflatoxin has been put into this category because - although there are good epidemiological correlations with the incidence of liver cancer, aflatoxin is still not a proven human carcinogen and some (very limited) evidence exists that it may not be (strongly) carcinogenic in man on its own[35,36]. The insistence upon scientific proof is not only of academic importance because it may help in discovering the real role of aflatoxin in producing liver cancer in man (conceivably only or mainly in combination with some other factor[37]). Such knowledge is essential if those countries where aflatoxin contamination is unavoidable are going to deal effectively with the problem of liver cancer.

TABLE 2
PROBABLE HUMAN CARCINOGENS

Compound	Species tested				Mutagenic Activity
	Mouse	Rat	Hamster	Monkey	
Aflatoxin[38]	- (only newborn)	+	+	+	+[25]
Dimethylnitrosamine (and many but not all nitrosamines)[39]	+	+	+	+	+[25]
3,4-Benzo(a)pyrene (and several but not all polynuclear aromatic HC's)[40]	+	+	+	+	+[25]

+ Positive for carcinogenicity or mutagenicity
- Negative for carcinogenicity or mutagenicity

Mouse-specific carcinogens. Thirdly (see Table 3) there is a steadily increasing category of compounds which after oral or inhalational exposure produces tumours of the liver or the lung in mice but not in other species. These compounds are not mutagenic or only weakly mutagenic (DDT).

On current evidence none of these compounds is known to present a carcinogenic hazard to man. For some, this merely reflects the absence of epidemiological data. For phenobarbitone, two epidemiological surveys from different countries were both negative[60,61]. For isoniazid, the epidemiological studies

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are all negative, but may have covered too short a period of exposure[62,63]. For DDT and dieldrin, a number of studies is available which are all criticized because of the small populations studied for too short a period [64,65,66,67]. However, all of them were negative. For trichloroethylene, one epidemiological study did not find any carcinogenic effect in humans[68]. On current epidemiological evidence the data in mice may all be false positives and, in view of the recurrent discussions on the significance of tumours in mice only, it is gratifying to see that for isoniazid, phenobarbitone and trichloroethylene ongoing epidemiological work has been reported[69]. Such work may clarify a legitimate scientific controversy which by its nature cannot be settled in the laboratory alone.

TABLE 3
MOUSE-SPECIFIC CARCINOGENS

Compound	Species tested				Mutagenic Activity
	Mouse	Rat	Hamster	Monkey	
Dieldrin[41]	+	-	-[42]	-[43]	-[46,47,48]
DDT[41]	+	-	-	-	weak or -[26,25]
Heptachlor[44]	+	-			-[48]
Chlorobenzilate[41]	+	-			-[48]
Phenobarbitone[45]	+	-?			-[25]
Tetrachloroethylene[49]	+	-			-[50]
Trichloroethylene[51]	+	-			-[51]
Isoniazid[52]	+	-	-		-[53≡,54,55]
Griseofulvin[56]	+	-			-[8,34]
Rifampicin[57]	+	-			-[58,59]

\+ Positive for carcinogenicity or mutagenicity
\- Negative for carcinogenicity or mutagenicity
≡ Positive in host-mediated assay, probably not relevant to human situations

Certainly, further research will change the data. Some compounds may be found positive in another or better developed mutagenic test system, such as happened in the past with vinylchloride monomer[25]. Others may be found non-mutagenic after purification of the compound as happened with trichloroethylene[51].

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Some may be found carcinogenic in additional species when tested under appropriate conditions. Finally, one or more may be found to present a human carcinogenic hazard under certain conditions of exposure. But it should be stressed that all data necessary to resolve the problem can be obtained with currently available techniques. A better understanding of this fundamental problem would greatly influence the future course of cancer research and the interpretation of the results of the current validation efforts of short-term tests.

CONCLUSIONS

The following conclusions are in accord with the presently available evidence:

a. No chemical, known to be carcinogenic to man, produce tumours in mice only but not in other species. There is no evidence that the production of tumours in mice only is predictive of a human hazard[*].

b. On the basis of the currently available evidence, the absence of carcinogenic activity in rats and of (potent) mutagenic activity of mouse-specific carcinogens seems more predictive of the uniformly negative epidemiological data than the mouse data.

c. Because of the large ongoing programmes to validate mutagenic test systems [70,71], further epidemiological studies of humans occupationally exposed to mouse-specific carcinogens should be promoted as a matter of urgency. Such studies are essential when a conflict exists between prediction of a human hazard based on mouse data and the contrary prediction from rat and mutagenic data.

d. It would seem that the increase of only those tumours which commonly occur in the unexposed mouse is an entirely unvalidated criterion for predicting a health hazard in man.

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[*] This conclusion does not contradict Tomatis et al.'s conclusion[21] of a general correlation between data in mice and in other species because most carcinogens in rats and other species (apart from aflatoxin) will also produce tumours in mice.

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Deichmann: Toxicology and Occupational Medicine

SUSPICION AND CONFIDENCE IN TOXICOLOGY AND OCCUPATIONAL MEDICINE

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ABSTRACT

With the possible exception of one or two compounds all known human industrial chemical carcinogens have been detected by an alert physician who suspected the chemical. In certain cases of reduced exposure, the industrial physician may have confidence that the risk of the exposed may not be greater than that of the non-exposed.

It is a historical fact that, with one or perhaps two exceptions, all industrial chemical or occupational carcinogens which are recognised today, have been identified in workers in the workplace. This has been accomplished through the suspicion of an observant physician, more often than not in association with an industry. It is a lesson of history - even as recent as a decade ago - that in the industrial setting chemical or industrial process carcinogens can be identified in small populations after a relatively short latency period and at a comparatively early age of onset. These compounds include:

- radon and radium compounds
- certain polynuclear aromatic hydrocarbons (PAH) in soot, pitch, shale oil, paraffin, cutting oils
- arsenic
- chromates
- certain aromatic amines and related compounds (auramine, benzidine, alpha- and beta-naphthylamines, 4-aminodiphenyl)

- asbestos
- benzene
- phenacetin
- BCME

Theophrastus von Hohenheim (1567)[1], the famous Paracelsus, a junior contemporary of Columbus described as "malum metallorum" a disease in his Saxon Schneeberg miners an invariably fatal disease caused by exposure to something in the mines. Three hundred years later this disease was diagnosed as lung cancer by Härting and Hesse[2]. At that time the group numbered 262 miners and could not have been much greater at the time of Paracelsus. In 1932 Pirchan and Sikl[3] described similar cases in miners from Joachimsthal. They reported 9 cases from 13 autopsies in 19 miners, dying from the disease, out of a group of 323 miners and 83 retired miners. The carcinogenic effect of other radium derivatives was also identified in a relatively small occupational population in New Jersey. In 1929 Blum[4], a dentist detected the cause of the "radium jaw" which led to osteosarcomas in radium watch-dial painters. A few years later Martland (1929 and 1931)[5,6] found nine cases occurring between 1914 and 1924 in a group of 800 "girls" of whom no more than 500 were working in the luminous dial paintshop at any one time.

In 1775 Percivall Pott[7] detected cancer of the scrotum in chimney sweeps as an occupational disease and noted that the disease was probably due to soot. It is estimated that at the time Pott identified the carcinogen, the population at risk in London would not have numbered more than 200 boys, since during the 15 year period, 1911-1935, the exposed population in the whole United Kingdom numbered 5274 (Goldblatt and Goldblatt,1956)[8]. Twenty years later, Benjamin Bell (1794)[9] agreed with Pott that soot obviously was the cause of scrotal cancer and we now know that soot may contain a considerable amount of

benzo (a) pyrene and other polynuclear aromatic hydrocarbons (PAH). About a century after Pott's discovery, Volkmann [10,10a] described scrotal cancer in workers employed in the separation of paraffin from the destillates of German brown coal. The year thereafter another Bell (1876) [11] also from Edinburgh first described scrotal cancer in a Scottish shale-oil worker also producing paraffin. Wilson (1927) [12] reported the carcinogenic action of shale-oil and some mineral oils. The case of cutting oil cancer provides a similar story (Cruickshank and Squire, 1950; Mastromatteo, 1955; Rivoire et al., 1965; Thony et al., 1970, 1970a) [13,14,15,16,16a]

In 1820 Ayrton Paris [17] who for a few years practised in Penzance, a small town in the Cornwall (England) mine district reported scrotal cancer in copper smelters which he ascribed to arsenic. In 1887, Sir Jonathan Hutchinson [18] in London described five cases of skin cancer following prolonged administration of arsenicals. Robson and Jeliffe (1963) [19] described six similar cases of yatrogenic arsenic skin cancer, all of whom developed cancer of the lung. Again, a specific cancer, identified in a comparatively small group (Middlesex Hospital). One of the patients was a female only 31 years old.

Liver and lung cancers from occupational exposure to arsenic-containing pesticides used by small groups of applicators in small areas of wine-growing, in Germany and France, were reported by Liebegott (1952) [20] and Galy et al., (1963) [21]. Thus in the case of arsenic, like with the PAH's, the carcinogenicity for man was detected by observant physicians in relatively small groups of exposed people without the co-operation of predicting laboratory rodents and epidemiologists with computers. It is interesting to notice that in later

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≡ Some people now believe that some or even many of these latter cases were rather caused by arsenic.

years, scientists have never succeeded in eliciting cancer in laboratory rodents by arsenic which suggests the occurrence of a species specificity.

In 1890 Newman[22] detected the carcinogenicity of chromates, later confirmed in Germany by Pfeil (1935)[23] who detected seven lung cancers in chromate workers in a comparatively small plant. Chromates have not been shown to be inhalation carcinogens in animals, although tumors have been produced by intrapleural administration (Hueper and Payne, 1959; Payne, 1960)[24,25].

One of the most striking examples of the identification of a chemical human carcinogen by an observant physician associated with industry is the famous case of the aromatic amines, 83 years ago. In 1895 Rehn[26] detected the carcinogenic action of aniline derivatives in a worker population of only 45 men in the "Fuchsine (Magenta) room" of a coaltar plant. Once he had been alerted, Rehn[27] reported 10 years later twenty further cases in one factory. Even at that time he mentioned naphthylamine as the possible culprit among the aromatic amines. Leuenberger (1912)[28] reported 18 cases in dye-workers in Basle in a total population of only 840 workers over one decade. Much later, the carcinogenicity was confirmed by animal experimentation, and some other aromatic amines and allied compounds were also shown to have carcinogenic activity.

Another good example is the well-known case of asbestos. Excellent epidemiological studies in large populations have been carried out in England and in the United States (e.g. Doll, 1955; Selikoff et al., 1972,1973)[29,30,31]. Later (i.e. Gross et al., 1967)[32] positive experiments with animals were reported. However, twenty years before the first epidemiological study, Gloyne (1935)[33] in England, together with Wood (1934)[34] reported two lung cancers and one pleura malignancy in a relatively small group of asbestos workers.

A similar situation exists with benzene. In 1928, Dalore and Borgomano[35] first reported on the occurrence of leukemia in relation to exposure to benzene. A confirmation followed four years later (Émile-Weil, 1932)[36] Penati and Vigliani (1938)[37] demonstrated that it is not always so difficult to detect in industry - with the necessary alertness - a carcinogenic agent. Laboratory studies in mice with benzene were initiated after the first clinical report had appeared but it has not been possible to demonstrate a leukemogenic activity of benzene in laboratory rodents. The first clinical observations were confirmed 25 years later by an epidemiological study (Révol et al., 1954)[38].

An additional example, showing that it is possible to identify a human chemical carcinogen in a small industrial population is the case of bischloromethylether. In 1962, the suspicion arose that an excessive number of workers with lung cancer were being reported in one area of one plant (Figueroa et al., 1973)[39] : three cases among 50 operators in one building.

A similar early suspicion arose in Germany (Thiess et al., 1973)[40] who eventually found eight cases among 68 workers. One of them was a young man of 31 years old with 12 years between onset of exposure and death. Again, suspicion and identification occurred earlier than could be shown by animal experimentation and epidemiological studies.

Interesting for several reasons is the case of phenacetin and renal pelvis tumors. The observant physician who identified the causative chemical was Grimlund (1963)[41]. He was a medical officer at a small-arms factory in the small Swedish town of Huskvarna employing 1800 workers, many of whom regularly took phenacetin-containing "Hjorton's powder". Hultengren et al., (1965)[42] and Bengston et al., (1968)[43] confirmed Grimlund's findings.

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Studying the original reports, it appears quite often in these industrial settings that the latency period was not always long, at times even as short as a few years, and the age at onset was by no means always as late in life as is usually purported; young people were often afflicted.

Thus in Martland's[5,6] series of exposure to radium a derivative, a latency period of one year was seen, and the patients were "girls". Sir James Earle (1808)[44] editing Percivall Pott's publications remarked that the interval between first exposure of chimney sweeps and the appearance of scrotal cancer (at puberty) was often 8-10 years. He himself observed a case in a child, eight years old. Patients among Thony's[16,16a] cutting oil workers sometimes had a latency period of only 4 years (Graves and Flo, 1940[45] observed a latency of 3-$^{1}/_{2}$ years); some patients were in their forties.

In the case of the chromate workers, Gross and Kölsch (1943)[46] reported a latency of 7 years, one case was in a man of 32. In Manusco's (1951)[47] study the gecmetric mean of the latency was 10.6 years. As regards the aromatic amines, Hueper (1966)[48] found in 11-$^{1}/_{2}$ per cent of the bladder tumors a latency period of 1-5 years and Goldblatt (1949)[49] mentioned a case of papilloma after only six months of exposure.

Even with asbestos, the classic example of a carcinogen with long latency periods, cases occur even in small populations, where exposure times and latent periods are only intermediate (Wood and Gloyne, 1934: 8 years in 35 year old man; Selikoff, 1972: 10 years; Nordmann, 1938: patients of 25-41 years old)[33,31,50]. In the case of benzene, the latency may be as short as 2 years or less (Girard et al., 1970)[51], and Mallory (1939)[52] described a case in a boy age 12.

Today, to the alert physician in industry, some substances should come under suspicion of carcinogenesis.

The cancer death rate in the U.S. is now 170 per 100,000 population, i.e. 18.6 per cent of total deaths (Anon., 1977)[53]. Yet, Higginson (1976)[54] stated that cancers identified as due to occupational factors form a relatively small proportion of all cancers (less than one per cent). That is, of course, one per cent too many and everything possible should be done to reduce the number of cases of occupational cancer. Efforts in this respect include technical refinements to reduce exposure. It is well known that the law of diminishing returns applies here and works in both directions. More and more technical refinements involve ever higher costs and ever lesser effects. Since eventually it is society, the public, and not the manufacturer who has to realize the extra cost and effort, the question will be raised of whether or not, at a certain moment, the extra cost and effort raised for considerations of health should not rather be used in a different area of health promotion. And this raises the question of whether or not an absolute no-effect level of exposure to a carcinogen, an absolute "safe dose" exists. In the context and limitation of this article it is not possible to go further into the philosophy and intricacies of this question. It is,however, suggested that today, in the occupational setting, the question of the existence or not of an absolute no-effect level, an absolute safe level may not be relevant.

It is suggested that absolute safety or zero-risks are not obtainable. Every human activity carries a risk, and inactivity carries perhaps, a greater risk. The specious concept of "socially acceptable risk" is not more than a siren song. It is usually not possible to predict the incidence of occupational cancer associated with a certain defined level of exposure. For many reasons extrapolation from animals to man quantitatively is unjustified. Among these reasons are the great variations in susceptibility within and between species

and the differencies between species in response. It is simply not possible, based on an incidence of cancer occurring in groups of rodents at certain levels of exposure, to arrive at the prediction of a risk of incidence in man at a much lower level of exposure. Therefore, it is equally impossible to philosophize or to consider whether such a risk is "socially acceptable".

It is impossible, however, for existing compounds already in use, to compare incidence in a group at low level exposure to incidence in an unexposed group. Sometimes, one will find that the incidence in the low-level exposed group is no greater than it is in the unexposed group. At these low levels of exposure one cannot guarantee that nobody will get cancer, but the risk is not greater than in those not so exposed. A similar situation exists with radiation. Notwithstanding predictions based on assumptions and mathematics, the cancer incidence in mile-high Denver is not greater and is, on the contrary, lower than elsewhere in the United States (Fraumeni, 1975)[55].

Cancer of the scrotum in wax pressmen has disappeared and it does not occur in machinists with low-level exposure to cutting oils in the United States and the Netherlands (Pruyn, 1972)[56]. No hemangiosarcomas have occurred in vinyl-chloride workers who had a comparatively low-level exposure (De Boer, 1978)[57]. The incidence of renal pyelum carcinoma in occasional users of phenacetin-containing painkillers is not increased, and lead workers have no higher cancer risk than other workers (Dingwall et al., 1963; Robinson, 1974; Hernberg, 1977)[58,59,60].

The reason that no excess cancer appears in these low-exposure groups may well be that at these low levels of exposure the latency period exceeds the lifespan. In cases such as phenacetin, the necessary antecedent tissue injury, the papillary necrobiosis, does not occur. This tissue injury itself has a no-effect level.

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After having reviewed the above historical facts we may conclude that, today, the industrial physician must not ever lay aside the good habit of a healthy suspicion. At the same time, he may be confident that reasonably thorough efforts to reduce exposure will effectively reduce risks to the level of the non-exposed.

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