Mutagens in Our Environment, pages 149–168

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THE PREDICTABILITY OF BIOASSAYS

Diana Anderson, BSc, MSc, PhD. DipEd, MIBiol.

British Industrial Biological Research Association
Woodmansterne Road
Carshalton, Surrey, UK.

INTRODUCTION

Between three and forty percent of cancers are assumed to be due to occupational exposures (Bridbord, et al. 1978; Cole 1977; Cairns 1981; Higginson, Muir 1976; Wynder, Gori 1977) but the unequivocal identification of a human mutagen or carcinogen depends upon epidemiological studies of exposed populations.

Epidemiological approaches for detecting mutagens and carcinogens.

Some industrial agents and processes have been identified as carcinogenic in epidemiological studies but because of mixed exposure to carcinogens and long latency periods for cancer development it is difficult to adapt epidemiological surveys as a means of establishing occupational health policy. Possible long term harmful effects of chemicals are cancer, congenital malformation and spontaneous abortion. The similarities between cancer and teratogenesis have been well reviewed (Harbison 1978; Kalter 1975; Miller 1977) and mutations appear to be a possible common mechanism between them and also a factor in spontaneous abortions (Carr 1977). Many aborted fetuses appear to be malformed (Carr 1977; Kline, et al. 1977; Sentrakul, Potter 1966). The potentialities and limitations of cancer epidemiology have been topics of concern for many years but those of the epidemiology of heritable defects have not and the literature on the subject is greatly lacking. This is probably because until recently there was little evidence to suggest that there was a

sufficient scale of environmental exposure to mutagens for the effects to be detected (Bridges 1980).

Chromosome anomalies are present in about 50% of all aborted fetuses (Bochkov 1977; Stein, et al. 1975) and increased abortion rates are implied in cigarette smokers (Himmelberger, et al. 1978) female anesthetists, operating room nurses (Knill-Jones, et al. 1972; Rosenberg, Kirves 1973; Cohen, et al. 1974) laboratory technicians (Strandberg, 1978) and copper smelter female employees (Nordstrom, et al. 1978; 1979). The claim that wives of vinyl chloride polymerisation workers are similarly affected (Infante 1976; Infante, et al. 1976a-c) has been questioned (Paddle 1976). Spontaneous abortions may form the basis of useful monitoring procedures since they are frequent enough to allow large sample sizes. In the total number of births, childhood cancer is about 0.2%, the incidence of major congenital malformations about 1% (not all genetic in origin (Hakasalo 1973) and spontaneous abortion is up to 15% in retrospective studies (Hemminki, et al. 1979). Table 1 (adapted from Hemminki, et al. 1979) shows the relationship of cancer, abortions and malformations of exposed persons and experimental data of some occupationally important chemicals.

Dominant mutational diseases occur in approximately a further 0.2%, sex-linked diseases in around 0.1% and recessive autosomal mutations become visible only over many generations (Bridges 1980). Dominant and sex-linked diseases are expressed in the first or second generation after induction and as such also may be amenable to human screening. However, only very few dominant changes with unambiguously identifiable phenotypes could be used in monitoring. Suggested marker phenotypes include dominant disorders such as retinoblastoma (frequency 0.05/1000) or achondroplasia (frequency 0.1/1000) (Hemminki, et al. 1979) or sex-linked disorders such as the Lesch-Nyhan syndrome. There is evidence to suggest a rising frequency of chromosomal abnormalities causing such anomalies as Down's syndrome (trisomy 21), and Patou's syndrome (trisomy 13) (Hook 1978). Screening exposed populations for induced genetic effects, may have advantages over screening for cancer in that effects may be manifest earlier since for such changes there would be little or no latent period and they may thus reflect current exposure levels to chemicals.

TABLE 1. (After Hemminki et al. 1979)

RELATIONSHIP BETWEEN EXPOSED PERSONS AND EXPERIMENTAL DATA OF SOME OCCUPATIONALLY IMPORTANT CHEMICALS

INCREASE IN EXPOSED PERSONS	Chromosomal Aberrations	POSITIVE EXPERIMENTAL DATA

TABLE 1. (After Hemminki et al. 1979)

RELATIONSHIP BETWEEN EXPOSED PERSONS AND EXPERIMENTAL DATA OF SOME OCCUPATIONALLY IMPORTANT CHEMICALS

	INCREASE IN EXPOSED PERSONS			Chromosomal Aberrations in Lymphocytes	POSITIVE EXPERIMENTAL DATA		
Chemical Compound	Cancer	Abortions	Malformations		Mutagenesis	Carcinogenesis	Teratogenesis
Acrylonitrile	(+)	..	..	-	+	±	+
Anesthetic gases	(+)	(+)	(+)	..	±	±	+
Arsenic	+	..	..	+	±	±	+
Asbestos	+	..	..	..	±	+	..
Benzene	+	..	..	+	+	±	+
Chloroprene	(+)	+	..	+	+	±	±
Epichlorohydrin	..	..	..	+	+	+	..
Chromium	+	..	..	+	+	+	+
Ethylene Oxide	±	..	..	+	+	..	..
Lead	±	(+)	(+)	±	±	±	+
Styrene	..	..	(+)	+	+	±	(+)
Vinyl Chloride	+	±	±	+	+	+	+

+ = positive data; (+) = limited data; ± = contradictory data; - = negative data; .. = no data.

The public in recent years are becoming more aware of possible threats to health. There are about 25,000 occupational chemicals with potential mutagenic hazard (Loprieno 1977) and to date about 7,000 chemicals have been tested for carcinogenicity in animals and 1,500 are suspected carcinogens. The world capacity for adequate animal testing of chemicals for carcinogenicity is about 500 a year (Maugh 1978 a,b). Obviously many more chemicals could be tested using short term tests for mutagenicity. Whilst cancer is of immediate concern to an individual increased mutational risk may have serious cumulative implications for human genetic health. The majority of known individual animal and human carcinogens are of the classic type giving rise to electrophilic metabolites with mutagenic properties. Even though other factors may affect the metabolism preceding the formation of the electrophiles, accepted models for carcinogensis imply that DNA damage is the initial step in the carcinogenic process. Thus both for mutagenesis and carcinogenesis it might be useful to calibrate human effects in terms of DNA damage and cellular response.

THE PREDICTION OF HUMAN GENOTOXICITY

For genotoxins, Bridges (1980) has suggested that the calibration of human response will involve the linking of epidemiological and laboratory investigations into both the calibration of human response against tissue exposure and the calibration of man against rodents for the same tissue exposures. (Figure 1).

APPLIED DOSE	BIOLOGICALLY SIGNIFICANT DOSE	MARKERS OF GENETIC DAMAGE	GENETIC, CARINOGENIC EFFECT
	Concentration in gonads, blood, urine, etc. Extent of reaction with DNA or markers such as hemoglobin	Chromosome breakage, SCE's or gene mutations in peripheral lymphocytes or other tissues	Epidemiology : Spontaneous fetal loss, congenital abnormalities, perinatal mortality, cancer

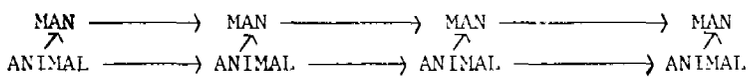

Fig. 1. Suggested linkage of laboratory and epidemiology studies necessary for the calibration of human response to agents which damage DNA.

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Since epidemiological information is generally difficult to obtain, a measure of exposure (i.e. the dose) to a mutagen or carcinogen is needed that can be applied directly for comparative purposes to man, and laboratory animals or in vitro systems. This may take the form of measurements of the concentrations of the agent in body fluids, gonads or in other organs, but presents problems where there is a mixture of agents being investigated or exposure is of low level chronic type. One way is to measure the DNA repair independent phosphotriesters formed when the reaction occurs with the phosphate groups of DNA. Another way is to measure the reaction of electrophilic species with amino acids such as histidine in hemoglobin. Such reactions involve indicators which are themselves not involved in mutagenesis or carcinogenesis but reaction with these molecules may be used directly for interspecific comparative purposes.

The measurement of some change in the cells of exposed persons resulting from DNA damage provides other information and confirms dosage or exposure and takes into account human metabolism. Peripheral lymphocytes from exposed work forces have been used to measure chromosome damage both as conventional aberrations and sister chromatid exchanges (e.g. Purchase et al. 1978 a,b; Anderson, et al. 1980 and 1981) and also for the measurement of gene mutation using the radioautographic method (Strauss, Albertini 1979; Strauss, et al. 1979) to detect hypoxanthine-guanine phosphoribosyl transferase (HGPRT) deficient variants. The detection of HGPRT mutants in cultured cells is well established for screening purposes (e.g. Arlett 1977). Seminal fluid can be used for detecting sperm abnormalities in human populations and the mouse (Wyrobek, Bruce 1978). Sperm abnormalities may be inherited (Topham 1980) and reflect the action of mutagens but can also occur as a response to physiological differences. The measurement of human fetal loss detects dominant lethals arising from male and female exposure and also teratogenic effects as a result of exposure in utero. Dominant lethality is thought to result from gross chromosomal aberrations although it is known that it can arise from non-genetic events and is thus not a heritable hazard for man (Bateman , Epstein 1972). However, it is a germ line effect which may be an indicator for less easily detectable serious heritable chromosome abnormalities. Changes in the sex ratio may arise due to a preferential loss of male conceptuses resulting from recessive lethal mutations on X chromosomes but this method was of little use in detecting

radiation effects among Hiroshima descendants (Bridges 1980).

The measurements described above are best suited to substances where electrophilic reactive species are systemically distributed throughout the body and for direct acting carcinogens it might be possible to proceed in a similar way to that described above for mutagens. Some populations are systemically exposed to carcinogens and mutagens e.g. cigarette smokers who inhale have a mutagenic urine (Yamasaki , Ames 1977) with carcinogenicity of organs remote from the lung and this indicates the likelihood of distribution throughout the body. Cigarette smoke mutagens reach the testes (Wyrobek, Bruce 1978) and chromosomal exchanges (Obe, Herha 1978) and sister chromatid exchanges (Lambert et al. 1978) are found in peripheral blood lymphocytes. There is a dose-related increase in perinatal mortality and the incidence of congenital abnormalities in the children of smoking fathers (Mau, Netter 1974). The linking of all these factors could provide the calibration of response of human spermatogonia to chemical mutagens. The already existing information about cancer incidence in cigarette smokers could also be linked with estimates of tissue reaction and cellular response particularly for data (other than bronchial carcinoma) for cancers at sites remote from the lung which can then be attributed to the carcinogens carried in the blood (Bridges 1980).

Human mutagenicity?

Infante and co-workers reported an increase in fetal wastage amongst vinyl chloride exposed workers (Infante 1976; Infante, et al. 1976 a-c). This study was thought to provide evidence of human chemical mutagenicity. It compared pre- and post-employment reproductive history of vinyl chloride workers and compared them with workers in other parts of the chemical industry. However no dose-response relationship was established since no exposure history was available. The survey was carried out as a consequence of questioning the fathers which produces less than accurate data on reproductive history, the data were corrected for paternal age when maternal age has the biggest effect on fetal wastage, and only a small number of workers were interviewed amongst the total available for interview. Congenital abnormalities did not increase alongside fetal wastage. Because of these considerations it is not proven definitively that vinyl chloride is causally associated with such effects

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in man (Purchase 1980b). Exposure to lead (Rom 1976) and anesthetic gases (Cohen, et al. 1974) has been reported to increase the abortion rate in wives of exposed workers. In these cases also the evidence cannot yet be considered as conclusive.

There are a wide variety of test systems available for detecting mutagenic and carcinogenic potential but the situation for carcinogenesis can be more complex than for mutagenic effects, however, not only because of the influence of promotors or other non-mutagenic substances but because of the phenomenon of organ specificity.

Human carcinogenicity?

The method of assessment of potential human carcinogenicity other than by epidemiologically relies on data generated from laboratory studies such as the production of mutations or the induction of tumors in rodents which are thought to be indicators of potential human carcinogenicity. Answers that the tests might provide are whether the chemical is a carcinogen, the potency of that carcinogen and its organ specificity (Purchase 1980a).

Carcinogen or not? A qualitative answer can be provided as to whether the chemical is or is not a carcinogen (as opposed to quantitative answer which implies that the chemical will produce a carcinogenic effect at a particular dose). It is possible to classify a chemical as positive or negative in a short-term test or long-term test in a given species and either as a human carcinogen or non-carcinogen. The efficiency of the testing systems in assessing potential carcinogenicity can be judged using various criteria (Purchase, et al. 1978c, 1980a; Cooper, et al. 1979): a) Reproducibility: the ability of the test to produce qualitative and quantitative results during repeat tests on a chemical; b) Sensitivity: the ability of the test to detect carcinogens i.e. the proportion of positive results among the carcinogens tested; c) Specificity: the ability of the test not to detect non-carcinogens or the proportion of negative results among the non-carcinogens; d) Predictive value: this is the proportion of carcinogens among the chemicals positive in the test. It depends on both the sensitivity and the specificity of the test and on the proportion of carcinogens in the group of chemicals being tested. Because of such dependence, predictive values

can only be estimated if a knowledge of the composition of the group of chemicals in terms of proportion of carcinogens is available. When testing chemicals of unknown activity this information is not available and therefore weight must be given to the comparison of the structure of the chemical with established carcinogens or non-carcinogens. It can be assumed, however, that there is a particular value for the proportion or percentage of carcinogens in the group of chemicals being tested (e.g. 10%) and the predictive value (PV) can be expressed at that proportion. Thus the PV_{10} would be the proportion of carcinogens among the chemicals found to be positive when 10% of the group submitted for testing are carcinogens.

There are many short-term tests available for carcinogenicity and these are based on end-points other than the production of cancer. Many of them are tests for mutation e.g. when considering reproducibility the international collaborative study (de Serres, Ashby 1981) revealed that there are a number of chemicals with differing results in the Ames test in different laboratories. When considering quantitative reproducibility where the same doses of the same compound were used in reference and 'in-house' strains in the international Genetic Drift study (draft in preparation) variability in 38 interlaboratory comparisons was revealed even with standardisation of details in techniques. (A significant difference in mutability was found between 'in-house' and reference cultures in a number of cases suggesting genetic drift. These effects, however, were less significant overall than the lack of reproducibility with the reference culture). The sensitivity, specificity and PV_{10} values for the six tests used by Purchase, et al. 1978 are shown in Table 2 and it is seen that the Ames and cell transformation tests have the greatest sensitivity and specificity. Further increases in these parameters can be obtained by using both tests together when they give the same result but predictions of carcinogenicity become less accurate when the tests do not give the same result. This has also been demonstrated for microbial assays by Rosenkranz and Mermelstein (1980) who point out that chemical choice and carcinogenicity criteria greatly influence the description of the validity of a study. Sensitivity is presumably most important in a screening programme designed to identify potential carcinogens even at the risk of scoring false positives. However, from an industrialist's point of view this poses a problem. A text devoted wholly to the predictive value of short-term screening

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TABLE 2.

THE SENSITIVITY, SPECIFICITY AND PREDICTIVE VALUE OF SHORT-TERM TESTS FOR CARCINOGENICITY

TEST	SENSITIVITY	SPECIFICITY	PV_{10}
Ames	91	94	63
Cell transformation	91	97	77
Degranulation	71	71	21
Sebaceous gland suppression	67	64	17
Tetrazolium reduction	40	73	14
Subcutaneous implant	37	95	45
Ames and cell transformation			
1. Chemicals for which both tests gave same result	96	100	100
2. All chemicals – one test positive	99	91	55

Long-term animal studies provide the main data base on which potential carcinogenicity for man is judged. The definition of a human carcinogen depends upon epidemiological studies. To validate long-term animal studies the results are compared with known human carcinogens. For mutagenicity, due to the lack of known human mutagens, animal studies cannot be validated in the same way. There are 26 agents which are known to produce cancer in man of which 19 chemicals are also animal carcinogens; examples are as shown in Table 3. This information is insufficient to calculate the predictive value and suffers because the majority of the carcinogenic chemicals were identified as carcinogens firstly by epidemiology and only later tested in animals. Rats and mice are the most commonly used animals for carcinogenicity studies and there are a number of chemicals which have been tested in both species. Extrapolation to man is by an interspecies comparison of man with the test animal. An idea of the effectiveness of animal carcinogenicity studies may be obtained by comparing the results from the two species i.e. the ability of carcinogenicity studies in rats to predict the outcome in mice and vice versa can be considered. The information under consideration is from

TABLE 3.

SOME CHEMICALS ASSOCIATED WITH CANCER INDUCTION IN HUMANS AND RODENTS (IARC 1978)

	MAN		RAT		MOUSE		Prediction of human target organ by rat or mouse
Compound	Route	Target organ	Route	Target organ	Route	Target Organ	
Aflatoxins	Dietary	Liver	ip/co	Liver	(No good positive study)		Yes
Benzene	ih top po	Hemopoietic system	(No good animal model)				
Diethyl-stilboestrol	po	Uterus, vagina	sc	Mammary gland, pituitary	po sc	Mammary gland cervix, vagina, testis	Yes
2-Naphthyl-amine	ih top po	Bladder	(no positive study)		po sc	Liver local (dog, monkey, hamster bladder	No
Vinyl chloride	ih top	Liver, brain, lung	ih	Liver, brain Zymbal gland kidney	ih	Lung, mammary gland, liver	Yes

ip = intraperitoneal; po = oral; sc = subcutaneous; ih = inhalation; ib = intrabronchial; top = topical

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that of Purchase (1980a) and the data were obtained from three sources; the IARC monograph series, the NCI Bioassay programme and by assessing information in the literature through the "Survey of Chemicals which have been tested for carcinogenicity". The results are shown in Table 4.

TABLE 4.

CARCINOGENICITY STUDIES IN RATS AND MICE

NUMBER OF CHEMICALS	RESULT IN MOUSE	RESULT IN RAT
109	Positive	Positive
98	Negative	Negative
21	Positive	Negative
17	Negative	Positive
5	Negative	Positive other species
250		

Using these data the reproducibility, specificity, sensitivity, and predictive value can be considered as shown in Table 5.

TABLE 5.

THE SENSITIVITY SPECIFICITY AND PREDICTIVE VALUE OF RAT OR MOUSE STUDIES AS PREDICTORS OF CARCINOGENICITY IN RATS OR MICE

	SENSITIVITY	SPECIFICITY	PV_{10}
Mouse study	87	82	35
Rat study	84	85	38

The short-term tests actually appear to have a higher sensitivity and specifity than animal studies and have a correspondingly higher PV_{10}. However, in the case of animal studies results are defined in terms of one species but for the short-term tests any species was taken as the end-point.

Since the predictive value of a test is partly dependent on the proportion of carcinogens in the chemicals being tested as the proportion of carcinogens decreases so it has a greater influence on the PV. For a single chemical

Vinyl chloride	ih top	Liver, brain, lung	ih	Liver, brain Zymbai gland kidney	ih	Lung, mammary gland, liver	Yes

ip = intraperitoneal; po = oral; sc = subcutaneous; ih = inhalation; ib = intrabronchial; top = topical

the PV is difficult to estimate but structural comparisons with known carcinogens and non-carcinogens provide an opinion which effectively replaces the need to estimate the PV provided a sensitive and specific test is utilised.

The potency of the carcinogen. Potency correlations have been attempted with short-term tests. Meselson and Russell (1977) presented a comparison of the potency of a number of chemicals in the *Salmonella* plate incorporation assay and animal carcinogenicity studies. They deduced a fixed relationship between the mutagenicity to *Salmonella* and the potency of carcinogens in animals. The relationship is dependent, however, on the values obtained for a few chemicals at either end of the potency scale and there are notable exceptions to the relationship. A fixed quantitative relationship is improbable for several reasons. Small modifications in the protocol of the *Salmonella* test can have a considerable influence in the quantitative results obtained (Ashby, Styles 1978). Comparison of the dose-response relationships requires expression both of the response at a given dose and the slope of the dose response curve. When the slopes are omitted as in this correlation, slope divergence could make a difference to the quantitative expression of the relationship. In the Ames assay generally Aroclor induced rat liver S-9 is used and is probably unlikely to be quantitatively representative of the metabolism for all carcinogens in vivo at all target organs. False positive and negative results belie a quantitative relationship between in vitro and in vivo results. The studies of Coombs, et al. (1976) and Kameswar Rao, et al. (1979) evaluated the polycyclic aromatic hydrocarbons and aliphatic nitrosamines respectively by comparing *Salmonella* results with in vivo data and did not confirm the relationship. More comparative data would be needed before a quantitative relationship can be proven.

The use of animal carcinogenicity data for quantitative extrapolation to man should be more satisfactory for potency considerations than the use of short-term tests because of the greater similarity of the laboratory model to the human.

However, a number of assumptions are made to allow quantitative extrapolation of animal carcinogenicity data to man 1) it must be assumed that there are only small species differences in susceptibility. However of the 250 chemicals shown in Table 4 there is evidence that in 43 there

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is no qualitative agreement between rat and mouse which suggests that there are probably large quantitative differences in susceptibility. There are examples in the literature of differences in susceptibility of men and laboratory animals e.g. to diethylstilboestrol man is 50-fold more suceptible, to aflatoxin 50-fold less susceptible, 500-fold to vinyl chloride and several 100-fold to ethylene dibromide (Ramsey, et al. 1979). Cigarette smoke is an example where man is similar to the laboratory animal (Bridges, et al. 1979). 2) It must also be assumed that data produced in high dosage experiments in animals can be used for extrapolation to very low doses in man i.e. there is no threshold. It is usual to assume that there is no threshold for chemically induced carcinogenesis based on several concepts: a) that mathematical expression of dose response data show no threshold b) that this is a conservative way to respond to the data and c) somatic or germ cell mutations can be induced by a single lesion in the DNA and are then fixed in the genome. The mathematical models are based on a one-hit model which is linear at low dosages or on probit/log dose extrapolation. Neither allows for a threshold and thus do not take account of a basic biological property. However a conservative approach to the data is a proper approach with the current lack of knowledge to provide a suitable basis for extrapolation. The ED_{01} study (Cairns 1980) re-examination reports now present models which might take account of possible thresholds (Members of the SOT. ED_{01} Task force 1981). As low doses as 1 rad of X-rays can induce genetic damage which lends support to the dogma that a single lesion can cause mutation (Gaulden, Read 1978 and references therein). Such a dogma is difficult to reconcile with two stage models of carcinogenesis and the reversibility or redifferentiation of some neoplastic cells. Also for those chemicals which act through a different mechanism of action other than the DNA a threshold can usually be established (Kroes 1979). 3) It has also to be assumed that the same mechanism of cancer induction applies in animals and humans over a wide dose range i.e. they have the same pharmacokinetics etc. The quantitative differences in susceptibility (Berg 1979; Cairns 1981) and lack of organ specificity shows this not to be the case.

Since these three assumptions have obvious limitations and are not well substantiated by experimental observations, extrapolation by current methods should really be restricted to those situations when the biological assumptions are known

PREDICTION OF THE TARGET ORGAN

Short-term tests are not yet able to predict organ specificity but the use of S-9 homogenates other than from the liver hold promise. Preliminary investigations using this approach with the oesophageal carcinogen N-nitroso-N metnylaniline (NMA) however have not shown oesophageal S-9 mix to activate this compound when rats were pretreated with Aroclor or NMA (Anderson, et al. unpublished). The data are shown in Table 6 after NMA pretreatment.

TABLE 6.

ORGAN SPECIFICITY STUDIES WITH *SALMONELLA* STRAIN TA 98 TREATED WITH NITROSOMETHYLANILINE (NMA) (rats pretreated with 100 mg/kg NMA i.p.)

COMPOUND		REVERTANTS PER PLATE			
NMA	NORHARMAN	LIVER		OESOPHAGUS	SALIVARY GLAND
(μmoles/ml incubate)		(50 μl 25% S-9 mix)			
0	0	40			
5	0	99*		41	39
5	1.2	75		38	37
		(100μl)	(25 μl)		
0	0	27	29		
0.5	0	39	32		
1	0	48	38		
2	0	60*	110*		
5	0	21	200*		

* = +ve result (Anderson D., Craddock V.M., Blowers S.D.)

Comparison of carcinogenicity data in rat and mouse allows a determination of whether carcinogenic chemicals have the same organ specificity in these two species (Table 7). A few carcinogens have exactly the same target organs in both species and many carcinogens affect more than one organ. There is a common target organ in rat or mouse of only 11 out of the 19 human carcinogens i.e. 58% Of the 109 carcinogens from the various sources 70 have at least one or more organs as a common site in both rat and mouse. Vinyl chloride is an example of a chemical with a common

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target organ in man and animals but in general the belief that organ specificity can be predicted from animals is not well substantiated.

TABLE 7.

THE ORGAN SPECIFICITY OF CHEMICAL CARCINOGENS

	NCI DATA	IARC DATA	LITERATURE	TOTALS
No. of chemicals positive in rat and mouse	26	60	23	109
No. of chemicals with at least one common site in both species	15 (58%)	40 (67%)	15 (65%)	70 (64%)

CONCLUSION

The models available for assessing human mutagenicity and carcinogenicity have many inadequacies. To extrapolate quantitatively to man from experimental data from these systems is not generally feasible. Such extrapolation would require a full appreciation of the mechanism of action in the laboratory model and man by understanding the metabolism and distribution of the chemical and how it interacts with the receptor organ. For man such information is not always available and information from laboratory models is all that is possible. Thus it is important to understand the variability of these models. Chemicals which behave similarly accross species would be of more concern to man than those that do not since they are more likely to behave the same way in man. Therefore the limitations of model systems should be understood and taken into consideration in the extrapolation process.

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