

MUTAGENIC, CARCINOGENIC AND TERATOGENIC EFFECTS OF POLLUTANTS IN RESPECT TO MAN

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ABSTRACT

Although a number of chemicals that occur, or have occurred, in industry have been demonstrated to have carcinogenic activity in man, demonstrations of teratogenic, and especially of mutagenic, activities on man within industrial compounds are rarer or non-existent. Demonstrations in the laboratory of teratogenic and mutagenic activities by industrial chemicals do raise properly the question whether such effects would appear in human populations exposed to these chemicals. The widely variable responses of various species, and even of strains within a given species, to carcinogenic, teratogenic, and mutagenic activities renders extrapolation of the results of tests with experimental animals to man uncertain. The facts that all three types of activity considered here involve probably effects on nucleic acids and that repair of defects in nucleic acids can occur, quite possibly to different extents and at different rates in various species, add to the uncertainty of extrapolations to man for these three sorts of actions by environmental chemicals.

The environment of man has been invaded progressively during the past several centuries by a large number of chemicals that are foreign to the human body or that occur normally within the body in fractions only of the amounts that are available now from the environment. Groups of chemicals that impinge upon the human body in sufficient quantities to be recognized as causes of morbidity or even death comprise medicinal drugs (including hallucinogenic, sympathomimetic, and other types of compounds likely to be used for their psychedelic or even addictive activities), habituating substances (tobacco, caffeine, alcohol, barbiturates, etc), artificial sweetening agents, food additives (including preservatives), food colours, pesticides and other agricultural chemicals, veterinary drugs, cosmetic preparations, pollutants (of air, water, food, soil and land), and compounds used in treating clothing (waterproofing, laundering, dry-cleaning, etc.).

These various chemicals have a wide variety of toxic actions, depending in part on the nature of the chemical and in part on the response of a living organism to the chemical. Because living organisms, even of the same species, usually vary to some degree in their responses to the same chemical,

the effect of some particular compound on a population is commonly of a graded nature even though the response to the chemical of an individual within that population may be of an all-or-none type. This means that a curve of the general nature of that shown in the left-hand section of *Figure 1* is generated.

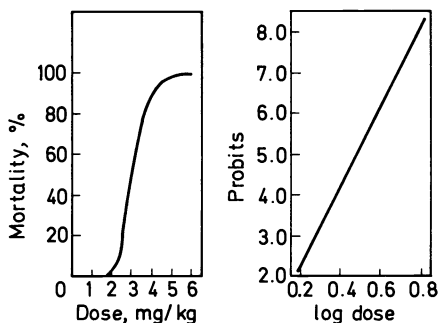


Figure 1. Per cent mortality plotted as such against the oral dose of parathion given to rats (left) and as probits against the logarithm of the dose of parathion (right). Data from Frawley *et al.*, *J. Pharmacol. Exp. Therap.* **105**, 156 (1952).

The curve in *Figure 1* is characterized by having a reasonably linear, sloped central section with fairly sharply curved terminal sections. This shape means that experimental points determining the mid-section of such a curve are poor predictors of responses to doses at the extremities of the dose-response relationship, and vice-versa. One widely used procedure to overcome this disadvantage of the usual shape of a dose-response curve is to convert the percentage response to a unit based on the normal probability curve, the probit, and the dose of compound to the log dose.

The right-hand section of *Figure 1* shows that the probit-log dose transformation of the data used to construct the dose-response curve of the left-hand section of this illustration yields a good straight line, which permits predictions of responses to a wider range of doses to be made from two or three experimentally determined points than is possible with the regular dose-response relationship. In using the probit-log dose transformation, one must keep in mind that validity of this transformation depends upon the responses to the various doses being distributed normally, so that skewness of the dose-response curve renders the probit-log dose transformation progressively less reliable as the skewness increases. On the other hand, we have no indication of failure of the probit-log dose transformation to yield reliable predictions when the criterion of normal distribution of the responses to graded doses is fulfilled, whatever the response may be.

Types of effects by chemicals that have been of particular concern are teratogenic, carcinogenic, and mutagenic ones. All three of these types of activity seem to involve, at least to an extent, interaction of some sort with

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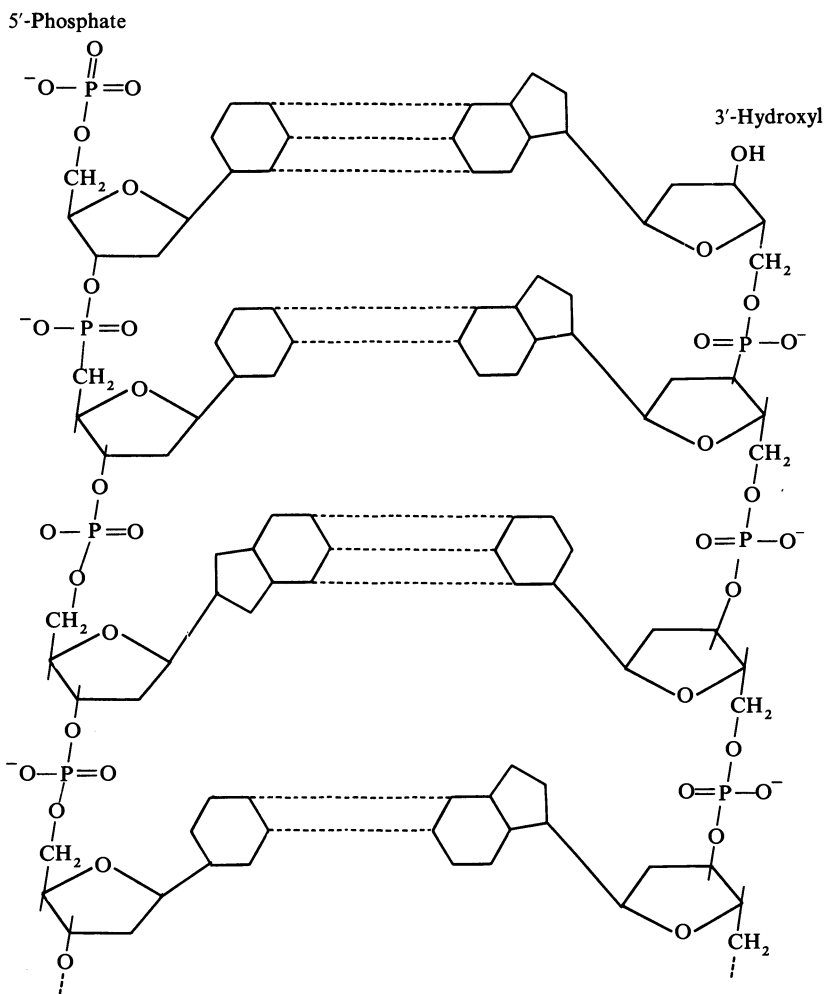


Figure 2. Two-dimensional projection of the hydrogen-bonded anti-parallel chains of the double helix of DNA. From Lewin, *The Molecular Basis of Gene Expression*, Wiley-Interscience: New York (1970).

nucleic acids¹⁻¹⁶. For convenience of discussion, we propose to use the coined word nucleidophile to refer to any chemical that interacts significantly with nucleic acids. A nucleidophile of any type acts by altering the nucleic acids of the genetic material that is shared with daughter cells when cell division takes place, resulting in daughter cells with heritable characteristics different from those of the original parent cell. Because DNA is the genetic

nucleic acid in all mammals, the following discussion will be restricted to effects of environmental chemicals on DNA.

If the nucleidophile affects somatic cells without altering germ cells, the effects are not transferable to progeny. If the result of the action of the nucleidophile on genetic material of somatic cells is to disrupt in some non-foetotoxic way the control over developmental sequencing exercised by the genes, the result will be the production of a congenitally malformed or stunted foetus. This is teratogenesis; this term is used to refer also to death of the conceptus without evident cause (such as, strangulation by the umbilical cord), and to spontaneous abortion unrelated to endocrine upset or trauma. If the result of the action of the nucleidophile on the genetic material of somatic cells is to render certain cells capable of unusually rapid growth and multiplication, the result will be the production of a tumour or tumours. These may be either benign or malignant, depending upon whether they simply displace or invade and destroy normal tissues. The terms tumorigen and carcinogen are applicable to substances that induce the formation, respectively, of benign or malignant tumours.

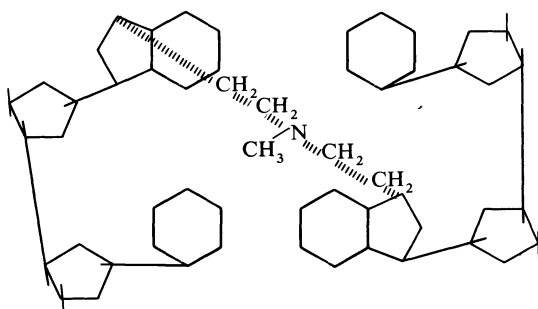


Figure 3. Inter-strand crosslinking in DNA following exposure to a nitrogen mustard. From Lewin, *The Molecular Basis of Gene Expression*, Wiley-Interscience: New York (1970).

If the nucleidophile affects germ cells rather than, or in addition to, somatic cells, there will be alterations transferable to succeeding generations in accord with the usual rules of genetics, depending upon whether the new characteristics are transmitted as dominant or recessive traits, sex-linked or non-sex-linked, etc.

The alterations of DNA caused by nucleidophilic chemicals may result from simple chemical substitution on the purine or pyrimidine bases of the hydrogen-bonded anti-parallel chains that make up the double helix of DNA (Figure 2), guanine being the most common point of attack, from crosslinking between adjacent guanine residues, as by sulphur or nitrogen mustards (Figure 3) and mitomycin C, by alteration of the sequenced bases in the chain by processes of either substitution, deletion, or insertion (Figure

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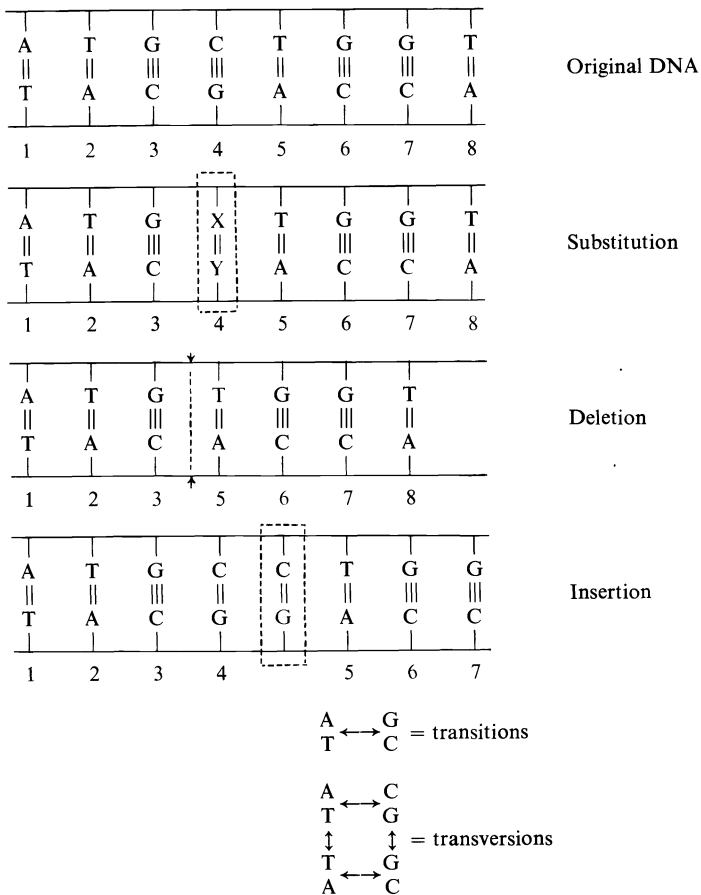


Figure 4. Types of point mutations (upper) and base-pair substitutions (lower) that can be caused in DNA by nucleidophilic chemicals. From Freese in *Chemical Mutagens: Principles and Methods for Their Detection*, A. Hollaender, ed. Plenum: New York (1971).

Class of agent	Number of agents				
	Prophage induction	Mutagenic	Carcinogenic	Carcinostatic	Teratogenic
Radiation	5	4	4	2	2
Alkylating	21	17	15	17	7
Microbial metabolite	35	5	4	29	10
Miscellaneous	28	13	2	15	10
Total	89	39	25	63	29

Figure 5. Summary of mutagenic, carcinogenic, carcinostatic, and teratogenic activities of 89 compounds having the ability to induce conversion of prophages of lysogenic bacteria into phages. From Heinemann in *Chemical Mutagens: Principles and Methods for Their Detection*, A. Hollaender, ed. Plenum: New York (1971).

4), and by alteration of the ribose phosphate backbone of the nucleic acid. *Figure 4* shows also two ways (lower part of the figure) in which base-pair substitutions may alter the chains of DNA.

Because teratogenic, carcinogenic, and mutagenic compounds all operate by altering DNA in some way, it is not surprising that some nucleidophilic chemicals have overlapping activities. Thus, of 31 compounds for which both teratogenic and mutagenic activities were estimated, 9 of the 27 that had at least one of these kinds of nucleidophilic activity definitely had both kinds of activity; another 6 were found to exert both sorts of influences in various trials but in a rather unpredictable way. A group of 89 compounds studied by Heinemann¹⁸ (*Figure 5*) contained 29 compounds that were teratogenic, 25 that were carcinogenic, and 39 that were mutagenic; 63 of the chemicals were carcinostatic rather than carcinogenic. Of 6 compounds that had mutagenic activities, 4 induced the formation of monsters and 3 caused the development of tumours classified as carcinomas¹⁹. The most carcinogenic of these 6 compounds had no activity in 3 of 7 tests for mutagenicity but was active in others; it was not tested for teratogenicity. The most teratogenic of three compounds examined for this type of activity was also the most carcinogenic of the three but was not the most mutagenic.

Figure 6 gives a comparison between the effective doses for mutagenicity and teratogenicity of 8 compounds. Of the 6 compounds for which both

Chemical	Mutagen		Teratogen	
	Mice	Rats	Mice	Rats
HN2	2.4, 3.2 (29)		1-2 (73)	0.5-1 (71)
Cyclophosphamide	60, 210 (95)		20 (109)	7-10 (27)
TEM	0.2 (33)	0.2, 0.4 (47)	1.5-1.65 (125)	0.5-0.75 (80)
ThioTEPA	5 (122)		3-5 (135)	3-5 (80)
Busulphan	10-40 (149)	4-10 (147)	25 (158)	18-34 (80)
MMS	50 (161)			100 (158)
EMS	240 (163)			200 (158)
IMS		50 (147)		50 (158)

Figure 6. Comparison of the mutagenic and teratogenic doses (mg/kg) of 8 nucleidophilic compounds. From Kalter in *Chemical Mutagens: Principles and Methods for Their Detection*, A. Hollaender, ed. Plenum: New York (1971).

sorts of activity were estimated in the same species, 3 were more potent as teratogens than as mutagens; the other 3 were either equally potent in these two ways or more potent as mutagens than as teratogens. Busulphan, tested in both the mouse and the rat, was equally potent in both activities in the mouse but more potent as a mutagen in the rat than as a teratogen. TEM, the other compound tested in the two species, was a more potent mutagen than a teratogen in both species.

The results summarized above show that, although it is possible for a single compound to possess all three of the nucleidophilic activities, there is no absolute parallelism between activities in the usual tests for these

three kinds of potency. These tests are uncertain of interpretation because they are commonly performed with the mouse or the rat, both these species, and especially the mouse, being rather unlike man in their responses to many nucleophilic chemicals. Thus, we and other investigators have found that the mouse fed diets containing such chlorinated hydrocarbon compounds as DDT²⁰⁻²⁹, Dieldrin^{23, 26, 30-32}, and Mirex forms tumours in its liver that are not mimicked in the livers of other species, including the rat; there is no evidence that prolonged exposure of man to such compounds has increased the incidence of tumours of the human liver³³⁻³⁵.

Similarly, although a fairly large number of chemicals has been found to be mutagenic in a variety of tests, including the use of viruses, bacteria, fungi, animal and human cells in cultures, and intact animals, only a comparatively small group of compounds is known to be mutagenic for man. This group includes, of course, compounds like the sulphur and nitrogen mustards, the cyclophosphamides, the purine and pyrimidine analogues, the alkyl sulphonic acid esters, the ethyleneimine derivatives, the folic acid antagonists and other types of compounds used for reducing the severity of tumorigenic activities, and also such miscellaneous compounds as Thalidomide, measles vaccine, and benzene.

With respect to teratogenesis, there is a similar general situation: many compounds tested in such species as the mouse, the rat, the hamster, and the rabbit have been reported to be teratogenic; only a few compounds are known to be teratogenic in man. The monkey is coming to be considered as a particularly useful species for judging teratogenicity because of the general similarity of its menstrual cycle and reproductive processes to those of man. It does have the distinct advantage over non-primate species of responding to experimental rubella infection, a known teratogen in man, in much the same way as man. The monkey responds by teratogenesis also to Thalidomide and to testosterone, as does man, and fails to respond in this way to Aspirin, rubeola, and Meclizine, as does man also. Meclizine and Aspirin have been found to be teratogenic in the rat.

The attack of nucleophilic compounds upon DNA may depend upon preparatory metabolism of the compound, as is true for the herbicide 3',4'-dichloropropionanilide³⁶, dimethylnitrosamine³⁷, and the insecticide DDT³⁸. The intensities of the effects of nucleophilic substances on DNA depend on their affinities for the target molecule, their effectivenesses in altering it, and their stabilities within the body. Thus, ethyl methanesulphonate, which is hydrolysed rapidly *in vivo* and is only about 1/5 as active in alkylating biological molecules as methyl methanesulphonate, was found in the testis of the rat 8 hours after its intraperitoneal injection to the extent of only 18.9 per cent of its peak concentration there whereas methyl methanesulphonate was still present in testicular tissue to the extent of more than 50 per cent of its peak concentration; the nucleic acid of the testis took up 5.3 times as much methyl methanesulphonate within 15 minutes after the administration as it did of ethyl methanesulphonate although by 8 hours after the injection the nucleic acid of the testis held only 1.5 times as much of methyl methanesulphonate as of ethyl methanesulphonate³⁹.

The precise alteration of development caused by a teratogenic nucleophile depends on the time after fertilization at which the chemical impinges

upon the embryo or foetus. In general, chemicals rarely produce malformations when they affect the embryo before gastrulation but, rather, usually cause its death whenever they have any effect. The most critical period for the embryo commences at gastrulation and lasts throughout the phase of organogenesis; that is, from about the 13th to the 56th day after fertilization in man. In the rat, the corresponding period is from about the 8th to the 13th day after fertilization. In both species, nervous structures are affected the most by nucleidophiles administered fairly early in the critical period (the 9th day in the rat and the 19th day in man) whereas skeletal deformities are most likely to be induced when the nucleidophile is given comparatively late in the vulnerable period (the 11th or 12th day in the rat or the 39th day in man).

When nucleidophilic chemicals cause some alteration in the structure of DNA, that alteration is not necessarily permanent (*Figure 7*). Moseley

Structural:	Cell membrane, only certain molecules can enter
	Nuclear membrane, protects during DNA replication
	Condensation of DNA into chromosomes, avoids tearing of DNA during segregation
	Precision of chromosomal segregation
Enzymic:	Destruction of dangerous chemicals
	Specificity of nucleotide kinases and replicases, avoids incorporation of wrong nucleotides
	Excision of wrong bases + repair
	Repair of single-strand lesions by copying of complementary strands and sealing of gap
	Repair of double-strand breaks by stickiness and joining of broken ends
	Maintenance of pH, ion concentration, etc.

Figure 7. Cellular mechanisms that protect DNA from alteration by nucleidophilic chemicals and physical influences. From Freese in *Chemical Mutagens: Principles and Methods for Their Detection*, A Hollaender, ed. Plenum: New York (1971).

and Laser⁴⁰ reported that the bacterium *Micrococcus radiodurans* is able to repair DNA damaged by irradiation with either ionizing radiation (x-rays or γ -rays) or u.v. light. Other bacteria have been found to be capable of repairing not only DNA damaged by radiation but also that altered by nucleidophilic chemicals⁴¹⁻⁴⁴. Human and other mammalian cells also have been found to have the ability to repair damage to DNA caused by either irradiation⁴⁵ or nucleidophilic chemicals^{46,47}. The alteration of DNA that results in the inherited cutaneous disease known as xeroderma pigmentosum reduces the ability of the cell to repair damage to DNA induced by radiation⁴⁸ or *N*-acetoxy-2-acetylaminofluorene⁴⁹, but not that induced by methyl methanesulphonate⁵⁰. There seem to be, therefore, at least two different cellular systems for repair of lesions in DNA.

An ostensibly interesting example of an effect attributable possibly to repair processes has been reported⁵¹ in a study in which male RF mice were given dimethylnitrosamine in their drinking water. Two groups of mice

given practically identical total doses of the nitrosamine in concentrations in the drinking water that differed by a factor of 4.5 had haemangiosarcomas in the liver of only the group that had received the higher concentration of the nucleidophile. The explanation advanced for this finding is that the lower rate of delivery produced damage that could be repaired whereas the higher rate caused damage to DNA that was sufficiently extensive that it could not be repaired completely, with the consequent production of tumours. There is a difficulty with this explanation, however, in that the livers of the group of mice that developed haemangiosarcomas contained no hepatomas whereas those of the mice that drank the lower concentration of dimethylnitrosamine did contain hepatomas. This latter result can hardly be explained by overwhelming of repair processes. Because only 10 livers from the group of mice that drank the lower concentration of the nitrosamine were examined for hepatomas and 17 for haemangiosarcomas, compared with 68 livers examined for both tumours from the group ingesting the higher concentration of the nitrosamine, there is considerable question about the significances of these apparent differences in the incidence of tumours of the liver. The incidence of haemangiosarcomas in the livers of the mice that drank the higher concentration of dimethylnitrosamine was only 9/68, so that a group of 17 livers containing no tumours of this type could occur in the same group of mice by chance fairly readily.

Other factors that influence the outcome of experimental studies with nucleidophilic chemicals are:

(1) The manner of caging of the animals. For example, C3H mice caged singly developed mammary tumours earlier and in higher proportion than litter mates living in a cage with 7 others⁵².

(2) The species of animal, as 2-amino- and 2-acetylaminofluorene produced tumours of the intestine in the rat but not in the mouse, the rabbit, the cat, or the dog⁵³.

(3) The strain of an animal species. As examples, Slonaker rats were found to have more tumours of the bladder and fewer of the intestine than Wistar rats treated similarly with 3,2'-dimethyl-4-aminodiphenyl⁵⁴, and diethylnitrosamine induced haemangiosarcomas of the liver in BALB/c mice and hepatomas in RF mice⁵⁵.

(4) The endocrine status of the test organisms, as illustrated by the finding that hydrocortisone enhances the induction by insulin of tyrosine transaminase in hepatoma cells⁵⁶. Indirect effects may be important here; for example, treatment of rats with the antihistaminic drug, perphenazine, has been found to result in elevations of the concentrations of several steroids in the plasma⁵⁷, so that this compound may have an indirect influence on responses to nucleidophilic compounds.

(5) The composition of the diet. Thus, rats fed a diet containing 0.75 per cent of butylated hydroxytoluene were protected from the lethal effect of ethyl methanesulphonate⁵⁸; another sort of possible action depending upon the composition of the diet is exemplified by the finding that the insecticide carbaryl reacts with sodium nitrite (as in corned meats) in the presence of either hydrochloric acid (normal gastric juice) or organic acid (as found in the gastric juice of a person with gastric cancer) to yield *N*-nitrosocarbaryl, a potent mutagen⁵⁹.

(6) The presence of infectious agents in target tissues or organs. For example, specific-pathogen-free mice exposed to an atmosphere of artificial smog developed only adenomas and adenocarcinomas of the lung⁶⁰, whereas previous investigators had reported that colony mice of the same strain exposed to similar smog developed squamous metaplasia and squamous cell carcinoma.

(7) The humoral immunity of the test organisms. Thus, splenectomy of the Syrian hamster before initiation of periodic topical application of 7,12-dimethylbenz(a)anthracene to the skin decreased the latencies of appearance of both papillomas and carcinomas⁶¹.

The comparatively large number of factors that determine the responses of an entire organism to nucleidophilic chemicals render most uncertain the extrapolation of findings with such substances in experimental animals to man (*Figure 8*). Studies of the effects of chemicals on experimental

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- A. Variation in absorption, distribution, and excretion.
 - B. Differences in detoxication mechanisms
 1. Presence or absence of enzymes.
 2. Rates of inactivation.
 3. Enzyme induction by environmental chemicals.
 - C. Receptor differences
 1. Qualitative.
 2. Sensitivity.
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Figure 8. Difficulties in extrapolating data obtained in studies using experimental animals to prediction of probable effects in man.

animals can demonstrate possible toxic effects in man but cannot guarantee either that these effects will be seen in man or that the toxic actions exerted upon man will be restricted to those found in experimental animals. Nucleidophilic substances found to be teratogenic, carcinogenic, or mutagenic, or to combine these actions, in experimental animals may prove to be completely innocuous in man because of qualitatively or quantitatively different metabolic conversion, excretion from the body, storage within the body, penetration into cells within the body, intrinsic sensitivity of DNA to alteration by the nucleidophile, or any of the factors that modify the actions of nucleidophilic compounds on cellular activities.

Demonstration of a potential for having a teratogenic, carcinogenic, or mutagenic action in cellular or tissular systems is even further away from furnishing a basis for predicting effects of these types on man than similar findings in intact animals. Such demonstrations do indicate the need for careful study in experimental animals to detect nucleidophilic activity in intact organisms as similar to man as possible. We see no practical alternative at present to eventual study in man if a new material seems to have sufficiently useful properties to justify the risk of such trials.

The benefit-risk relationship is the only reliable guide for judging, first whether a new compound should be studied in man to obtain more pertinent

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data on the actual hazard of the material for man and later, using that data, whether the new material should be allowed for use by either the general public or a restricted fraction of the public in its proposed pattern of use. Unless benefit-risk considerations as outlined above are applied to compounds found to be nucleophilic in either *in vitro* studies or trials with experimental animals, man may be denied the use of many newly-synthesized, advantageous, but somewhat toxic, chemicals. Banning a new compound from use because it has been found to be carcinogenic, teratogenic, or mutagenic in research by *in vitro* methods or the use exclusively of small animals (mouse, hamster, rat, etc.), without regard to the possible benefits from its use by man, does not seem to us to be a reasonable procedure.

As an example of the value to be derived from careful consideration of the risk-benefit relationship, we would like to end with a brief discussion of the schistosomacidal compound, hycanthone. This substance was discovered as a fungal metabolite of an earlier synthetic schistosomacidal chemical, lucanthone, from which it differs by having a methylenol group in place of a methyl group at the 4-position of the thioxanthone nucleus. Hycanthone was found to be both less toxic to mammals and more schistosomacidal than its parent, lucanthone.

Test System	Dose	Results
Salmonella	0.2 mg/plate	Frameshift mutations
T ₄ Bacteriophage	100 µg/ml	Frameshift mutations
Saccharomyces	2.7 × 10 ⁻⁴ M	Gene Conversion
Neurospora	0.05-0.30 mM	Positive
Drosophila	3-400 mg/kg	Recessive, sex linked lethal mutations
Habrobracon	0.01-0.1 M in sucrose	Negative

Figure 9. Tests of mutagenicity of hycanthone with microbiological preparations and invertebrate species.

Unfortunately, however, studies of the effects of hycanthone on several microbiological preparations and on fruit flies (*Figure 9*) disclosed a potential for reacting with DNA. In the wasp, habrobracon, there was no mutagenic action. In the mouse, hycanthone was not mutagenic in a dose of 100 mg/kg

Species	Assay	Dose	Result
Rat	Chromosomes in bone marrow cells	20, 40, 80, 100 mg/kg i.p.	Increased chromosome abnormalities above 40 mg/kg
Mouse	Host-mediated with Saccharomyces	100 mg/kg i.m.	Negative

Figure 10. Tests (*in vivo*) of mutagenicity of hycanthone for the mouse and the rat.

(Figure 10); in the rat, doses above 40 mg/kg did produce some abnormalities of chromosomes but no visible changes in the animal or its behaviour. Hycanthonc has been reported to exert also hepatotoxic⁶² and teratogenic⁶³ actions. The facts that it has been found to alter DNA within somatic cells and that it has antineoplastic activity⁶⁴ have raised a question about its carcinogenic potential.

Despite the disadvantages enumerated, the advantages of hycanthonc have been judged to outweigh its risks. A single intramuscular injection of 3 mg/kg of the thiaxanthone base in the form of its methane sulphonate salt renders an average of 69 per cent of patients free of ova for 2 to 3 months after treatment; side effects appear in from 25 to 50 per cent of those given hycanthonc.

The majority of the side effects are mild: vomiting, headache, dizziness, weakness, muscular aches, anorexia, nausea, abdominal pain, and diarrhoea. About 1 out of every 770 patients may be expected to have persistent vomiting lasting for up to 48 hours and damage to the liver. About 1 in 17650 of patients treated with hycanthonc have died of damage to the liver.

The risks for the individual patient in using hycanthonc to treat his schistosomiasis are that he may suffer nausea and vomiting and the other acutely toxic effects mentioned previously. Risks to both the patient and to his societal group are the small chance of death from damage to the liver and the incompletely-evaluated possibilities that use of the compound may induce terata, tumours, and mutations within treated human populations (Figure 11) and may result in the production of schistosomes resistant to

Benefits	Risk
High efficacy	Hepatotoxicity
Single-dose treatment	Mutagenic?
Low incidence of side effects	Carcinogenic?
Mass therapy	Tolerance?

Figure 11. Summary of risk-benefit considerations for hycanthonc.

the compound, apparently by a process of mutation⁶⁵. These risks seem to be outweighed by the advantages to both the person and his societal group of the decreased morbidity from his parasitic infection, at least in the short term. If the report of Rogers and Bueding should turn out to be correct in the field, an end result of widespread use of hycanthonc in treating schistosomiasis could be that the parasite would become resistant not only to hycanthonc and lucanthonc but also to aminoalkyl tetrahydroquinolines, another group of schistosomacidal compounds.

In spite of the possibilities that hycanthonc is a carcinogen, a teratogen, and even a mutagen, a committee of experts assembled in Geneva, Switzerland, under the auspices of the WHO decided in 1972⁶⁶ that the current need to treat approximately 400000000 people infested by schistosomes, to restore them to a condition of being able to care for themselves and to perform useful work, is sufficiently great that the risk of future harm had to be

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taken. In the case of hycanthone, as in other benefit-risk considerations, it was essential to establish that the benefit expected to flow from use of the material was greater than the probable hazard or risk to man or animal. This is not a particularly new concept, but it is a valuable one. If it is followed carefully, serviceable chemicals will continue to be discovered and put to use in a beneficial way for the betterment of mankind.

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