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INTER-SPECIES COMPARISONS OF CARCINOGENICITY

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Summary.—The carcinogenicity of 250 chemicals in 2 species, usually the rat and the mouse, was obtained from the published literature through 3 independent sources. Of the 250 compounds listed, 38% were non-carcinogenic in both rats and mice, and 44% were carcinogenic in both species. A total of 43 compounds had different results in the two species, 21 (8%) being carcinogenic in mice only, 17 (7%) in rats only and 5 (2%) having differing results from other species. A comparison of the major target organs affected by chemicals carcinogenic in both species revealed that 64% of the chemicals studied produced cancer at the same site.

This comparison of carcinogenic activity in 2 species suggests that extrapolation from results in a single-animal study to man may be subject to substantial errors.

THE RECENT INTEREST in short-term tests for carcinogenicity has focused attention on the predictability of such tests for carcinogenicity as defined by animal studies. Several studies have been undertaken to establish the correlation between short-term test results and animal carcinogenicity (McCann *et al.*, 1975; Purchase *et al.*, 1978). The test systems with the best results (Salmonella microsome assay and cell transformation assay) have correlations with each other and with animal studies of between 85 and 95%. Some reasons for the lack of 100% correlation with animal data, *i.e.* the false negatives and false positives, can be found in the design and execution of either the animal or the short-term tests. In addition, differences in the end-point or differences in metabolism, diffusion and transport barriers and the state of the cellular targets in the two types of test system may contribute to the anomalies generated by the various methods. It is thus not surprising that chemicals can produce effects in *in vitro* tests, with their imposed artificiality, which will not be seen *in vivo*. Also, depending on the criteria used to judge the results of animal carcinogenicity studies, the classification of chemicals as carcinogens or non-carcinogens affects the correlation.

It is conventional to place greater reliance on extrapolating results to man from the results from typical long-term *in vivo* studies in mammals than from *in vitro* studies using mammalian cells or unicellular organisms. The reason for this is partly the differences in end-points described above, but it also derives from a greater experience with mammalian carcinogenicity studies and the greater apparent relevance of the tumours generated in animal studies as a model of carcinogenicity in man. These arguments are not based on systematic study, and therefore provoke the question, "Is the reliance on animal carcinogenicity models warranted?"

Differences in the expression of carcinogenic effects between mammalian species do occur, and these are due not only to details of experimental design, but also to critical differences between species. It is apparent that extrapolation of susceptibility to chemical carcinogenicity from animals to man is just one form of inter-species comparison, and this has

been studied mainly from the converse point of view of demonstrating which human carcinogens have proved to be carcinogenic in animals (Tomatis *et al.*, 1978). This review compares carcinogenicity data from experiments in 2 species of mammals (particularly rats and mice) as a step towards understanding the relevance of such data from one species when predicting the carcinogenicity of that compound in a second species. A similar, but smaller, review was carried out by Tomatis *et al.* in 1973.

METHODS

Source of data.—References and opinions on carcinogenicity were obtained from three sources:

(1) National Cancer Institute Bioassay Programme. In this programme chemicals have been tested in rats and mice using similar protocols. For the purposes of this comparison the opinions on carcinogenicity expressed in the reports of the results appearing in the Federal Register have been taken as definitive. Where equivocal results are reported, these have been omitted.

(2) International Agency for Research on Cancer, Monograph Series (1972–1978). The IARC have convened meetings of experts to consider reports of carcinogenicity and these include opinions on carcinogenicity of chemicals to various species. The opinions of the committees have been accepted as definitive at the times of the respective meetings, and no attempt to revise the opinions has been made. Chemicals which have been tested adequately in at least 2 species have been selected for inclusion.

(3) References to carcinogenicity studies were obtained from U.S. Public Health Service Document No. 149 (Hartwell & Shubik, 1951–1973). By reference to the index, the chemicals which had been tested in more than one species were identified. The most comprehensive study in each species was identified from Hartwell and Shubik's summary tables. The data in the original publication were examined according to the "decision tree" described below. If a positive effect was observed, this was recorded; if the results were negative, all relevant references were examined and the result recorded. Reference to a single study is made in Appendix 3. Chemicals on which the carcinogenicity had already been reported by the IARC Committees were excluded from evaluation.

Decision rules.—After selection of the study, the following idealized decision tree was used. It should be noted that in some cases decisions were not as clear-cut as the decision tree might indicate, and other criteria were used to assist the decision.

(1) Check adequacy of histological examination.
  (a) If Level 1 or 2 (Hartwell & Shubik, 1951), reject.
  (b) If Level 3, proceed.
(2) Establish tumour incidence in treated and control animals.
  (a) If there is a significant increase in treated animals, proceed to (3).
  (b) If there is no increase in treated animals, proceed to (6).
(3) Establish number of animals per group.
  (a) If there are less than 15, reject.
  (b) If there are more than 15, proceed to (4).
(4) Establish route of administration.
  (a) If by repeated s.c. injection or bladder implant, proceed to (5*a*).
  (b) If other route, proceed to (5).
(5) Establish tumour type.
  (*a*) If tumours are at the site of s.c. injection (or in the bladder, in bladder implantation studies) reject.
  (*b*) If tumours are benign and there is a high incidence in controls (*e.g.* pulmonary adenoma or hepatoma in certain strains of mice; mammary fibroadenomas, adenomas or fibromas or Leydig-cell tumours in certain strains of rat) reject.
  (*c*) If other tumours, classify as POSITIVE.
(6) Establish number of animals per group.
  (*a*) If there are less than 25, reject.
  (*b*) If there are more than 25, proceed to (7).
(7) Establish the length of the study.
  (*a*) If less than 80 weeks in mice or 2 years in rats, reject.
  (*b*) If more than 80 weeks in mice or 2 years in rats, proceed to (8).

TABLE I.—*Summary of results from three different sources*

Response in carcinogenicity studies	NCI (Appendix 1)	IARC (Appendix 2)	Other (Appendix 3)	Total (%)
−ve in rat and mouse	26	8	64	98 (39)
+ve in rat and mouse	26	60	23	109 (44)
Rat −ve, mouse +ve	13*	6	2	21 (8·4)
Rat +ve, mouse −ve	8	4	5	17 (6·8)
Differing results from other species	—	5†	—	5 (2)
Total	73	83	94	250 (100)

* Excluding dieldrin, which is reported in Appendix 1. The IARC opinion was given before the NCI bioassay was completed. Both opinions agree and the compound is included in the IARC column.

† These 5 compounds include hydrazine and thioacetamide (+ve in rat and mouse but −ve in hamster) and arsenic (−ve in rat and mouse but considered a human carcinogen).

(8) Examine other aspects of the study, such as abnormal diets, additional chemicals used and unusual route of administration.
   (a) If it invalidates the study, reject.
   (b) If there is no problem identified, classify the compound as NEGATIVE.

Target organ.—The major target organ(s) reported to be affected have been noted for chemicals carcinogenic in 2 species.

RESULTS

The summarized results are presented in Appendices 1, 2 and 3. All chemicals reported in Hartwell & Shubik which were tested in species other than the rat and mouse had been reported in the IARC Monographs. They were therefore not included in Table II. The number of chemicals selected from each of the 3 data sources and the number found to give various combinations of results in rats and mice (and in 5 cases other species) is given in Table I. Of the 250 compounds listed, 98 (38%) were negative in both rats and mice, and 109 (44%) were positive in both rats and mice. A total of 43 had different results from the species tested, 21 (8%) being carcinogenic in mice only, 17 (7%) in rats only and 5 (2%) having results from other species.

TABLE II.—*Organ specificity of chemical carcinogens*

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

When a comparison is made of the major target organs affected in both species, only 64% of chemicals are found to produce cancer at the same site in both species (Table II).

DISCUSSION

The most important reason for testing chemicals for carcinogenicity is to provide information on which an assessment of potential human carcinogenicity can be made. A judgment on the effectiveness of the animal tests in identifying human carcinogens could best be made by identifying which human carcinogens are also carcinogenic in animals. This is not very satisfactory for two reasons: firstly, only 26 specific causes of human cancer have been identified (of which only 19 can be attributed to a single chemical; Tomatis *et al.*, 1978) so that few comparisons can be made. Secondly, most human carcinogens were first identified by clinical or epidemiological methods, and subsequent animal experiments were designed to find a suitable model for studying the carcinogenic effects. This approach is substantially different from that of testing a compound of unknown activity. Nevertheless, there remain 2 compounds considered to be associated with the induction of human cancer (Tomatis *et al.*, 1978) which have not been shown unequivocally to be animal carcinogens, namely arsenic and benzene.

In examining other inter-species com-

parisons of carcinogenicity, certain problems must be recognized. Firstly, the comparison is being made at a certain time, and new data are continually being produced which may alter the opinion on a chemical's carcinogenicity. In order to overcome this problem Hartwell and Shubik's survey and the more up-to-date IARC Monograph Series have been used to provide certain of the data for this review. Since the dates of publication of these references' sources, new data may have been produced on the carcinogenicity of the chemicals. This has not been included, except for that produced by the NCI Bioassay Programme, which has been tabulated separately. In most cases, changes of classification as a consequence of new data on carcinogenicity are from non-carcinogen to carcinogen, because one positive study is often more convincing than several negative studies. These changes in classification are likely to have an effect on all the subdivisions of chemicals used in Tables II and III, except "carcinogenic in all species tested", but it is not possible to estimate the magnitude of the effect.

The second problem is that opinions and interpretations of the same data on the carcinogenicity of chemicals often differ. To reduce the bias likely from this source, several steps have been taken. The IARC Monograph Series, being the opinions of expert committees, are least likely to be affected by bias. The NCI Bioassay Programme reports published in the Federal Register are summaries of the data presented in the full reports, which have been reviewed by the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on Environmental Carcinogens (a U.S. National Cancer Institute committee). The opinion subject to the least review is that expressed in Appendix 3 on the chemicals selected from "Survey of chemicals which have been tested for carcinogenicity". The outline of the method used to classify them is given in the methods section.

The third problem is the difficulty of being satisfied that a chemical is non-carcinogenic on the basis of animal experiments. It is always possible that higher doses, longer survival, greater numbers of dose groups or animals, different strains, species or routes of administration or any of the many factors affecting the outcome of a carcinogenicity study will give a positive result. The opinions of non-carcinogenicity given in Table III refer to the specific studies examined. Similarly, the IARC and NCI reports confine themselves to statements such as, "under the conditions of this study photodieldrin was not carcinogenic to Osborn–Mendel rats or B6C3F1 mice".

It is clear from the information obtained from three separate sources that there are a substantial number of compounds which, although carcinogenic in one species, have not been shown to be carcinogenic in a second species. There are differences in the number of chemicals falling into the various categories depending on the source of the data. Thus, very few chemicals which are non-carcinogenic in 2 species are seen in the IARC series, probably reflecting the philosophy of selection of chemicals for review. There are few chemicals in Appendix 3 which are negative in one species and positive in the second; this is because most of the chemicals in this category selected from the "Survey of chemicals which have been tested for carcinogenicity" had been reported on in the IARC Monographs and were therefore omitted from Appendix 3. For these reasons the most significant figures are those which combine the information from all three sources. Of the 250 chemicals for which data in 2 species are available, 109 (44%) were carcinogenic in both species, 98 (39%) were non-carcinogenic in both species and 43 (17%) were carcinogenic in one species and non-carcinogenic in the other.

Another way of expressing this information is that of 126 chemicals found to be positive in the rat, 109 (87%) were positive in the mouse; and of the 119 chemicals found to be negative in the rat 98 (82%)

were negative in the mouse. Similarly, of the 130 chemicals found to be positive in the mouse, 109 (84%) were positive in the rat: and of the 115 chemicals negative in the mouse 98 (85%) were negative in the rat. This suggests that a chemical positive in one species has about an 85% chance of being positive in a second species. A similar figure was obtained in the review by Tomatis *et al.* (1973).

Cooper *et al.* (1979) have provided a method of expressing the usefulness of short-term tests for carcinogenicity which involves calculation of the specificity and sensitivity of a test. Similar calculations can be made for these long-term animal studies. As a predictor of carcinogenicity in the mouse, the rat carcinogenicity study has a specificity of 85·2% and a sensitivity of 83·8%. The mouse carcinogenicity study has a specificity of 82·4% and a sensitivity of 86·5% as a predictor of rat carcinogenicity. These figures taken on their own can be misleading, as the overall predictive value of a test result is also dependent on the prevalence of carcinogens among the chemicals tested. If the chemicals tested had a 10% prevalence of carcinogens the predictive value for both rat and mouse results would be 27%.

The reasons for differences in carcinogenicity and organ specificity between the results in the 2 species, when they occurred, are not readily apparent. Factors such as differences in metabolism and metabolic products may well contribute to these differences. Where the route of administration has been different in the 2 species tested, this may also contribute to differences in response, though there are many examples in Appendices 1, 2 and 3 where this is not so.

One important feature of the results is that where differences in carcinogenicity between 2 species are obtained, the chemicals concerned may share certain structural characteristics. Thus, there are several chlorinated pesticides which are positive in mice but negative in rats; 1,1,2-trichlorethane and 1,1,2,2-tetrachlorethane are negative in rats but positive in mice. In these cases metabolic pathways and mechanisms of action may account for the difference in response. As has been suggested for short-term tests (Ashby & Purchase, 1977) this may be a useful way of improving extrapolation of results to other species, particularly when appropriate positive and negative control data are available to assist in the extrapolation. Accurate extrapolation to man requires an intimate knowledge of the metabolism and mode of action of the chemical in the species selected for laboratory tests and knowledge of whether the key features established in the laboratory animal are also present in man.

In most cases, knowledge of the metabolic fate of a chemical in man is imperfectly understood, and it is against this background that extrapolation is frequently made. Possibly the only additional evidence that can be used in the extrapolation is the lack of inter-species variability in laboratory tests (or consistency). Thus a chemical carcinogenic in all species tested and in all *in vitro* mutagenic assays could be considered to be more likely to be carcinogenic in an untested species. Another chemical, negative in all but one test, would be less likely to be carcinogenic in an untested species. Using this argument, N-nitrosodiethylamine, carcinogenic in 8 species, is more likely to be carcinogenic in man than isonicotinic acid hydrazide, which is carcinogenic in mice but not in rats and hamsters. As in all simple rules, there will be exceptions (*e.g.* 2-naphthylamine, a potent carcinogen in man, is carcinogenic in 3 laboratory species but negative in rats and rabbits). Nevertheless, information on the mode of action, metabolism and pharmacokinetics, and on the results from chemicals with similar critical structural features, together with data on consistency, will provide a better basis for extrapolation than the simple assumption that a carcinogenic response in one species indicates carcinogenic hazard in man.

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APPENDIX 1

Summarized carcinogenicity results from NCI Bioassay Programme

1. Rat and mouse negative. p.o. administration

Compound	Federal Register Reference
Anilazine	49055 **43** (1978)
p-Anisidine hydrochloride	47793 **43** (1978)
Anthranilic acid	14130 **43** (1978)
1H-Benzotriazole	40061 **43** (1978)
2-Chloro-p-phenylenediamine sulphate	46382 **43** (1978)
Chlorpropamide	64444 **42** (1977)
3-Chloro-p-toluidine	49574 **43** (1978)
Clonitralid[1]	47793 **43** (1978)
Diarylanilide Yellow	11760 **43** (1978)
Dichlorvos	43132 **42** (1977)
Dimethoate	15140 **42** (1977)
Dioxathion	45645 **43** (1978)
Iodoform	46382 **43** (1978)
Lindane	58791 **42** (1977)
Malathion	12385 **43** (1978)
Methoxychlor	11760 **43** (1978)
Mexacarbate	49574 **43** (1978)
4-Nitroanthranilic acid	49055 **43** (1978)
1-Nitro naphthalene	26139 **43** (1978)
3-Nitro proprionic acid	21737 **43** (1978)
1-Phenyl-3-methyl-5-pyrazolone	49055 **43** (1978)
Photodieldrin	61316 **42** (1977)
2,3,5,6-Tetrachloro-4-nitro-anisole	50741 **43** (1978)
Triphenyltin hydroxide	49574 **43** (1978)
Tolbutamide	62212 **42** (1977)
2,5-Toluenediamine sulphate	49055 **43** (1978)

2. Rat and mouse positive. p.o. administration, except * (i.p.).

Compound	Site affected: Rat	Site affected: Mouse	Federal Register Reference
2-Aminoanthraquinone	Liver (m)	Liver	51451 **43** (1978)
3-Amino-9-ethylcarbazole	Liver	Liver	47289 **43** (1978)
1-Amino-2-methylanthraquinone	Liver, kidney (m)	Liver (f)	97289 **43** (1978)
0-Anisidine hydrochloride	Bladder, kidney (m), thyroid (m)	Bladder	43074 **43** (1978)
Chlordecone	Liver	Liver	14914 **41** (1978)
Chloroform	Kidney	Liver	23449 **41** (1978)

Compound	Site affected: Rat	Site affected: Mouse	Federal Register Reference
3-(Chloromethyl)pyridine hydrochloride	Stomach (m)	Stomach	47289 **43** (1978)
4-Chloro-m-phenylenediamine	Adrenal glands (m)	Liver (f)	39431 **43** (1978)
4-Chloro-o-phenylenediamine	Urinary bladder, forestomach	Liver	30356 **43** (1978)
2,4-Diaminoanisole sulphate	Skin (associated glands), thyroid	Thyroid	16417 **43** (1978)
Dibromochloropropane	Stomach, mammary gland (f)	Stomach	8189 **43** (1978)
1,2-Dichloroethane	Stomach, mammary gland (f)	Mammary gland, uterus, bronchi	43564 **43** (1978)
1,4-Dioxane	Liver (f), nasal turbinates	Liver	41285 **43** (1978)
Hydrazobenzene	Liver, Zymbal's gland, mammary gland	Liver (f)	40548 **43** (1978)
*Isophosphamide	Uterus, mammary gland (f)	Haemopoietic system (f)	2942 **43** (1978)
1,5-Naphthalenediamine	Uterus, clitoral gland (f)	Thyroid, liver, lung (f)	51451 **43** (1978)
Nitriloacetic acid NTS tri-sodium salt, monohydrate	Urinary tract	Urinary tract	25534 **42** (1977)
Nitrofen	Pancreas (f)	Liver	8854 **43** (1978)
5-Nitroacenaphthene	Ear canal, lung, clitoral and mammary glands (f)	Liver, ovary (f)	50741 **43** (1978)
5-Nitro-o-anisidine	Integumentary system, clitoral glands (f)	Liver (f)	49574 **43** (1978)
Phenazopyridine HCl	Colon	Liver (f)	45645 **43** (1978)
Tetrachlorvinphos	Thyroid, adrenal gland	Liver (f)[2]	12951 **43** (1978)
4,4′-Thiodianiline	Thyroid, ear canal, liver, colon (m), uterus (f)	Liver, thyroid	20562 **43** (1978)
*Thio-tepa	Skin, ear canal, haemopoietic system (m)	Skin, associated glands	43074 **43** (1978)
Trimethylphosphate	Subcutaneous tissue (m)[2]	Uterus (f)	42043 **43** (1978)
Tris (2,3-dibromopropyl)phosphate	Kidney	Liver, lung, stomach (f), kidney, lung, stomach (m)	19463 **43** (1978)

3. Rat result negative; mouse positive. p.o. administration

Compound	Rat	Mouse	Federal Register Reference
Aldrin		(m)	2450 **43** (1978)
3-Amino-3-ethoxyacetanilide		(m)	40062 **43** (1978)
Captan			59120 **42** (1977)
Chloramben		(f)	56805 **42** (1977)
Chlordane			48394 **42** (1977)
Chlorbenzilate			47793 **43** (1978)
Dicofol		(m)	44890 **43** (1978)
Dieldrin[4]		(m)	2450 **43** (1978)
Heptachlor			48395 **42** (1977)
Hexachloroethane			27238 **43** (1978)
5-Nitro-o-toluidine			43074 **43** (1978)
1,1,2,2-Tetrachloroethane	[2]		9360 **43** (1978)
1,1,2-Trichloroethane			30365 **43** (1978)
Trifluralin		(f)	12385 **43** (1978)

4. Rat result positive; mouse negative. p.o. administration

Compound	Rat	Mouse	Federal Register Reference
4-Amino-2-nitrophenol	(m)		45645 **43** (1978)
Aniline hydrochloride			50741 **43** (1978)
Chlorothalonil			46382 **43** (1978)
m-Cresidine		[1]	44890 **43** (1978)
Dapsone	(m)		61631 **42** (1977)
2,4-Dinitrotoluene	[3]		21737 **43** (1978)
Picloram	(f)[3]		5076 **43** (1978)
Pivalolactone			50741 **43** (1978)

Abbreviations:

p.o.—administration by gavage or by addition to diet.
m—male.
f—female.
[1]—Negative in the female mouse; male not evaluated because of poor survival.
[2]—two hepatocellular carcinomas observed; not statistically significant.
[3]—benign tumours.
[4]—also included in the IARC tabulation.

Footnote

Most reports in the Federal Register up to 24 October 1978 have been examined. For various reasons, such as inadequacy of the data or only one species being tested, the following compounds listed in the Federal Register have not been included in the tabulation:

Aroclor 1254
5-Azacytidine
Chloropicrin
Diaminoxide
1,1-Dichloroethane
Emetine
Hexachlorophene
3,3′-Iminobis-1-propanol dimethane sulphonate
Lasiocarpine
2-Methyl-1-nitroanthraquinone
Phenformin
N-phenyl-p-phenylene diamine
Proflavin
Tetrachloroethylene
1,1,1-Trichlorethane
Trichloroethylene
Trichlorofluoromethane

APPENDIX 2

Summarized data from IARC Monograph Series

1. Rat and mouse negative

Compound	Route (rat)	Route (mouse)	Reference
Aniline	p.o.	s.c.	27 **4** (1974)
γ-Butyrolactone	p.o.	p.o.	231 **11** (1976)
	s.c.	s.c.	
Cis-9, 10-Epoxystearic acid	s.c.	s.c. top	153 **11** (1976)
Maleic hydrazide	p.o.	p.o.	173 **4** (1974)
	s.c.	s.c.	
Norgesterol	p.o.	p.o.	201 **6** (1974)
Ponceau SX	p.o.	p.o.	207 **8** (1975)
	s.c.	s.c.	
Yellow AB	p.o.		279 **8** (1975)
	s.c.	s.c.	
Yellow OB	p.o.		287 **8** (1975)
	s.c.	s.c.	

2. Rat and mouse positive

Compound	Rat		Mouse		Reference
	Route	Site affected	Route	Site affected	
Amitrole	s.c., p.o.	Thyroid, liver	p.o.	Thyroid, liver	31 **7** (1974)
o-Aminoazotoluene	p.o.	Liver, bladder	i.p., s.c., p.o.	Liver, lung	61 **8** (1975)
4-Aminobiphenyl	s.c.	Mammary gland, intestine	p.o.	Bladder, liver	74 **1** (1972)
Aramite	p.o.	Liver	p.o.	In 1 of 4 strains tested: liver	39 **5** (1974)
Asbestos	i.pl, i.h.	Lung	i.h.	Lung	17 **2** (1972); 14 **2** (1977)
Benzidine	s.c., p.o.	Liver	s.c.	Liver	80 **1** (1972)
Benzo(a)pyrene	top., i.t., i.v., p.o.	Mammary gland, forestomach	top., i.p., p.o.	Forestomach	91 **3** (1975)
N,N-bis(2-chloroethyl)-2-naphthylamine	s.c.	Local tumours	i.p.	Lung	119 **4** (1974)
Bis(chloromethyl)ether	s.c., i.h.	Lung, nasal cavities	s.c., top., i.h.	Lung	231 **4** (1974)
β-Butyrolactone	s.c., p.o.	Tumours at site of admin.	top., s.c.	Tumours at site of admin.	225 **11** (1976)
Cadmium salts	s.c.	Interstitial-cell tumours of testis	s.c.	Interstitial-cell tumours of testis	74 **2** (1973)
Carbon tetrachloride	s.c., i.h.	Liver	p.o.	Liver	53 **1** (1972)
Chlorambucil	i.p.	Lymphomas	i.p.	Ovary, lung	125 **9** (1975)
Chromium salts	i.b.	Lung	i.h.	Lung	100 **2** (1973)
Calcium chromate					
Citrus Red No. 2	p.o.	Bladder	s.c., p.o.	Bladder	101 **81** (1975)
Cycasin	p.o.	Liver, kidney	top., p.o.	Liver, lung, kidney	157 **1** (1972)
Cyclophosphamide	s.c., i.p.	Lung, liver, reproductive organs	i.v., i.p.	Mammary gland	135 **9** (1975)
Diazomethane	i.h.	Lung	s.c., i.h., top.	Lung	223 **7** (1974)
Dibenz(a,h)anthracene	s.c., i.t.	Lung	top., p.o.	Forestomach	178 **3** (1973)
7H-Dibenz(C_{19}) carbazole	s.c.	1 expt: sarcomas, no details	top., s.c., p.o.	Forestomach, liver	260 **3** (1973)
1,2-Dibromo-3-chloropropane	p.o.	Forestomach, mammary gland	p.o.	Forestomach	139 **15** (1977)
Diethylstilboestrol	s.c.	Mammary gland, pituitary	p.o., s.c.	Mammary gland, cervix, vagina (f), testis (m)	55 **6** (1974)
Dihydrosafrole	p.o.	Oesophagus	p.o.	Liver (m), lung	231 **10** (1976)
1,2-Dimethylhydrazide	s.c., p.o.	Intestine, lung	s.c., p.o.	Liver, lung, muscle	145 **4** (1974)
Ethinyloestradiol	p.o.	Liver	p.o.	Pituitary, mammary gland	77 **6** (1974)
Ethylene dibromide	p.o.	Forestomach	p.o.	Forestomach	195 **15** (1977)
Ethylmethane sulphonate	i.p.	Lung	s.c., i.p.	Lung, kidney	245 **7** (1974)
Ethynodiol diacetate	p.o.	Mammary gland (benign) (m)	p.o.	Mammary gland (castrated) (m)	173 **6** (1974)
2[2-Formylhydrazino]-4-(5-nitro-2-furyl)thiazole	p.o.	Mammary gland, gastrointestinal tract	p.o.	Stomach, lung	151 **7** (1974)
Isosafrole	p.o.	Liver	p.o.	Liver	231 **10** (1976)
Melphalan	i.p.	Peritoneum	i.p.	Lung	167 **9** (1975)

Compounds	Rat		Mouse		Reference
	Route	Affected organ	Route	Affected organ	
Mestranol	p.o.	Mammary gland (f)	p.o.	Mammary gland, pituitary	87 **6** (1974)
Methyl methanesulphonate	i.p. s.c.	Nervous system	i.p. p.o.	Lung; thymic lymphomas	253 **7** (1974)
N-methyl-n-nitro-n-nitrosoguanidine	i.p. p.o.	Stomach, forestomach, liver	top. i.p. p.o.	Stomach	183 **4** (1974)
Methylthiouracil	s.c. p.o.	Thyroid, kidney (f)	p.o.	Thyroid	53 **7** (1974)
Metronidazole	p.o.	Mammary gland	p.o.	Lung	113 **13** (1977)
Nickel salts					75 **11** (1976)
Nickel subsulphide	i.h.	Lung			
Nickel subsulphide, nickel oxide	i.m.	Local tumours	i.m.	Local tumours	
5-Nitroacenapthene	p.o.	Intestine, mammary gland (f)	i.p.	Leukaemia, reticulum cell sarcoma	319 **16** (1978)
N-[4-(5-nitro-2-furyl)-2-thiazolyl] acetamide	p.o.	Mammary, salivary glands, lung, renal pelvis	p.o.	Forestomach	185 **7** (1974)
Nitrogen mustard	i.v.	Variety of tumours	s.c. i.p. i.v.	Lung, thymus	193 **9** (1975)
Nitrogen mustard n-oxide hydrochloride	i.v.	Lymphoreticular tumours	s.c.	Lung, thymus, Harderian gland	209 **9** (1975)
N-nitrosodiethylamine	i.h. i.p. p.o.	Liver	top. i.p. s.c. p.o.	Liver, forestomach, oesophagus, lung	107 **1** (1972)
N-nitrosodimethylamine	i.p. i.h. p.o.	Liver, kidney	s.c. i.p. p.o.	Liver, lung	95 **1** (1972)
Nitrosoethylurea	s.c. i.v. p.o.	Brain, peripheral nervous system	i.p.	Multiple tumours, including intracranial, neurogenic	135 **1** (1972)
Nitrosomethylurea	top. i.p. i.v. p.o.	Brain, peripheral nervous system	top. s.c. i.p.	Lung; thymic lymphomas	125 **1** (1972)
Norethisterone	p.o.	Liver (m) (benign)	s.c. p.o.	Liver (m, benign) pituitary (f)	179 **6** (1974)
Norethynodriel	p.o.	Liver, pituitary	s.c. p.o.	Pituitary	191 **6** (1979)
Oestradiol 17β	s.c.	Mammary gland, pituitary	s.c.	Mammary gland, pituitary, reproductive system	99 **6** (1974)
Oestrone	s.c.	Pituitary, mammary gland	s.c. p.o.	Mammary gland	123 **6** (1974)
Phenobarbitone	p.o.	Liver, benign	p.o.	Liver, benign/malignant	157 **13** (1977)
Ponceau MX	p.o.	Liver	p.o.	Liver	189 **9** (1975)
β-Propiolactone	p.o.	Forestomach	top. i.p.	Liver (m), lymphomas	259 **4** (1974)
Propylthiouracil	p.o.	Thyroid	p.o.	Thyroid, pituitary	67 **7** (1974)
Safrole	p.o.	Liver	p.o.	Liver	231 **10** (1976)
Sterigmatocystin	top. p.o.	Liver	p.o.	Lung	245 **10** (1976)
Streptozotocin	i.v. i.p.	Kidney, liver	i.p.	Lung, kidney	337 **17** (1978)
Thiouracil	p.o.	Thyroid	p.o.	Liver	85 **7** (1974)
Uracil mustard	i.p.	Peritoneum, pancreas, ovary, mammary gland	i.p.	Lung, liver, ovary	235 **9** (1975)
Urethane	i.p. p.o.	Liver, uterus etc.	i.h. i.p. s.c.	Lung, liver etc.	111 **7** (1974)
Vinyl chloride	i.h.	Liver, Zymbal gland, kidney	i.h.	Lung, mammary gland. liver	291 **7** (1974)

3. Rat results (all p.o.) negative, mouse positive

Compound	Mouse Route	Reference
1,4-Butanediol dimethane sulphonate	i.v.*	247 **4** (1974)
DDT	p.o.	83 **5** (1974)
Dieldrin	p.o.	125 **5** (1974)
Isonicotinic acid hydrazide	s.c., i.p., p.o.	159 **4** (1974)
2-Naphthylamine	p.o.	**97 4** (1974)
Trichlorethylene[1]	p.o.	263 **11** (1976)

[1] Trichloroethylene also included in NCI list. IARC opinion based on early report of NCI data.
* p.o. negative.

4. Rat results positive, mouse negative

Compound	Rat Route	Mouse Route	Reference
Daunomycin	i.v.	p.o.	145 **10** (1976)
p-Dimethylamino-azobenzene	top., i.p., p.o.	top.	125 **8** (1975)
Thiourea	p.o.	p.o.	95 **7** (1974)
Aflatoxin B_1	i.p., p.o.	p.o.	51 **10** (1976)

5. Different results from various species

Compound	Neg. Species	Neg. Route	Pos. Species	Pos. Route	Reference
Arsenic compounds	Rat, Mouse	p.o.	Man	top.	48 **2** (1973)
Chlormadinone acetate	Rat, Mouse	p.o.	Dog	p.o.	149 **6** (1974)
3,3′-Dimethylbenzidine	Hamster	p.o.	Rat	s.c., i.p.	87 **1** (1972)
Hydrazine	Hamster	p.o.	Rat Mouse	p.o. i.p. p.o.	127 **4** (1974)
Thioacetamide	Hamster	p.o.	Rat, Mouse	p.o.	77 **7** (1974)

Routes: In addition to the usual abbreviations are the following:
p.o.—gavage or in diet.
top.—topical.
i.h.—inhalation.
i.pl.—intrapleural injection.
i.b.—intrabronchial pellets.

APPENDIX 3

Summarized carcinogenicity results from references derived from U.S. Public Health Service Publication No. 149

1. Compounds negative in both rat (R) and mouse (M) (excluding compounds in Appendix 2)

Compound	M/R	Route	Reference
(Acetato) phenylmercury	M	i.vag.	Boyland & Roe (1964) *Br. Emp. Cancer Campaign*, **42**, 22.
	R	p.o.	Fitzhugh *et al.* (1950) *AMA Arch. Ind. Hyg.*, **2**, 433.
Acetone	M	top.	Roe *et al.* (1970) *Br. J. Cancer*, **24**, 788.
	R	top.[2]	Glucksmann & Cherry (1968) *Br. J. Cancer*, **22**, 545.
Adipic acid dioctyl ester	M, R	top., s.c., p.o.	Hodge *et al.* (1966) *Tox. Appl. Pharmacol.*, **9**, 583.

Compound	M/R	Route	Reference
Aniline (or aniline hydrochloride)	M	s.c.[2]	Hartwell & Andervont, *In* Hartwell & Shubick (1951) 50.
	R	p.o.	Druckrey (1950) *Arch. Exp. Path. Pharmakol.*, **210,** 137.
Anthracene	M	s.c.	Steiner (1955) *Cancer Res.*, **15,** 632.
	R	s.c.[2]	Schmahl (1955) *Krebsforsch.*, **60,** 697.
Arabinose	M	s.c.	Hueper (1965) *Cancer Res.*, **25,** 440.
	R	s.c.	
Arachis oil	M	s.c.	Boyland & Sims (1967) *Int. J. Cancer*, **2,** 500.
			Carter *et al.* (1969) *Fd. Cosmet. Tox.*, **7,** 53.
	R	s.c.	Dickens & Jones (1964) *Br. Emp. Cancer Campaign*, **42,** 141.
			Dickens & Jones (1965) *Br. J. Cancer*, **19,** 392.
Azobenzene	M	s.c.[2]	Shear & Stewart (1941) *In* Hartwell & Shubick (1951)
	R	s.c.	Spitz *et al.* (1950) *Cancer*, **3,** 789.
Benzene-1-azo-2-naphthol	M	p.o.	Clayson *et al.* (1965) *Br. J. Cancer*, **19,** 297.
	R	p.o.[2]	Hackmann (1951) *Krebsforsch.*, **57,** 530.
Benzene hexachloride (γ isomer)	M	top.	Orr (1948) *Nature*, **162,** 189.
	R	p.o.	Fitzhugh *et al.* (1950) *J. Am. Pharm. Assoc.*, **40,** 583.
Benzoyl peroxide	M	p.o.	Sharrat *et al.* (1964) *Fd. Cosmet. Toxicol.*, **2,** 527.
	R	p.o.	
2-Biphenylol	M	p.o.	Innes *et al.* (1969) *J. Natl Cancer Inst.*, **42,** 1101.
	R	p.o.	Hodge *et al.* (1952) *J. Pharmacol. Exp. Therap.*, **104,** 202.
3,6-Bis(dimethylamino)acridine (Acridine Orange)	M	s.c.	Van Duuren *et al.* (1969) *Br. J. Cancer*, **23,** 587.
	R	s.c.[2]	
Camphor	M	i.p., top.	Stoner *et al.* (1973) *Cancer Res.*, **33,** 3069.
			Graffi *et al.* (1953) *Arch Geschwulstforsch*, **5,** 110.
	R	s.c.	Ezeyza (1952) *Semana Med.*, **100,** 663.
Carboxymethylcellulose	M	p.o.	McElligott & Hurst (1968) *Fd Cosmet. Toxicol.*, **6,** 449.
	R	p.o.	Teller *et al.* (1970) *Cancer Res.*, **30,** 179.
2-Chloro-4,6-bis(ethylamino)-s-triazine (Simazin)	M	p.o.	Innes *et al.* (1969) *J. Natl Cancer Inst.*, **42,** 1101.
	R	s.c., p.o.	Pliss & Zabezhinsky (1970) *Vopr. Onkol.*, **16,** 81.
Cholesterol	M	s.c.	Bischoff (1957) *J. Natl Cancer Inst.*, **19,** 977.
	R	i.p.	Koch (1963) *Arzneimittelforschung*, **13,** 1116.
CI Acid Blue 9, diammonium salt (Brilliant Blue)	M	s.c.	Hansen *et al.* (1966) *Tox. Appl. Pharmacol.*, **8,** 29.
	R	p.o.	
CI Acid Green 5, disodium salt (Light Green SF Yellowish)	M	p.o.	Hansen *et al.* (1966) *Fd Cosmet. Toxicol.*, **4,** 389.
	R	p.o.	
CI Acid Red 26, isodium salt (Ponceaux MX)	M	p.o.	Waterman & Lignac (1958) *Acta Physiol Pharmacol. Neerl.*, **7,** 35.
	R	p.o.	Ikeda *et al.* (1966) *Fd Cosmet. Toxicol.*, **4,** 485.
CI Food Blue 1, disodium salt (FD & C Blue No. 2)	M	s.c.	Hansen *et al.* (1966) *Tox. Appl. Pharmacol.*, **8,** 29.
	R	p.o.	
CI Food Green 3, disodium salt (Fast Green FCF)	M	p.o.	Hansen *et al.* (1966) *Fd. Cosmet. Toxicol.*, **4,** 389.
	R	p.o.	
CI Food Red 1, disodium salt (Ponceaux SX)	M	p.o.	Davis *et al.* (1966) *Tox. Appl. Pharmacol.*, **8,** 306.
	R	p.o.	
CI Solvent Yellow 5 (phenylazo-2-naphthylamine)	M	s.c.[2]	Hansen *et al.* (1963) *Tox. Appl. Pharmacol.*, **5,** 16.
	R	s.c., p.o.[2]	
CI Solvent Yellow 6 (I-(2-methylphenyl)azo-2-naphthalenamine)	M	s.c.	
	R	s.c., p.o.[2]	
Cyclohexanesulfanic acid, monosodium salt	M	p.o.	Rudali *et al.* (1969) *C. R. Acad. Sci.*, **269,** 1910.
	R	p.o.	Grasso *et al.* (1971) *Fd Cosmet. Toxicol.*, **9,** 463.
Cyclohexene hydroperoxide	M	s.c.	Van Duuren *et al.* (1966) *J. Natl Cancer Inst.*, **37,** 825.
	R	s.c.	
D-glucose	M	s.c.	Hueper (1965) *Cancer Res.*, **25,** 440.
	R	s.c.	
2,6-Dichloro-4-nitroaniline	M	p.o.	Innes *et al.* (1969) *J. Natl Cancer Inst.*, **42,** 1101.
	R	p.o.	Hadidian *et al.* (1968) *J. Natl Cancer Inst.*, **41,** 985.
Dicyclohexylamine	M	s.c.	Pliss (1958) *Vopr. Onkol.*, **4,** 659.
	R	p.o.	
3,3′-Dihydroxybenzidine	M	s.c.	Bonser *et al.* (1956) *Br. J. Cancer*, **10,** 533.
	R	s.c.	Pliss (1961) *Vopr. Onkol.*, **7,** 33.
p-Diethylaminoazobenzene	M	s.c.	Kirby (1947) *Cancer Res.*, **7,** 333.
	R	s.c.[2]	
17α,21-Dihydroxypregn-4-ene-3,11,20-trione (Cortisone)	M	s.c.	Della Porta *et al.* (1970) *Tumori*, **56,** 121.
	R	p.o.	Field (1959) *Cancer Res.*, **19,** 870.

Compound	M/R	Route	Reference
a,a-Dimethylbenzyl hydroperoxide	M	s.c.	Van Duuren *et al.* (1966) *J. Natl Cancer Inst.*, **37**, 825.
	R	s.c.[2]	Van Duuren *et al.* (1967) *J. Natl Cancer Inst.*, **39**, 1213.
o,o-Dimethyl-1-hydroxy-2,2,2-trichlorethylphosphonate (Dipterex, Trichlorphon)	M	top.	Gibel *et al.* (1971) *Arch. Geschwulstforsch*, **37**, 303.
	R	s.c.	
2-(2-(2-(dodecyloxy)ethoxy)ethoxy) ethanol	M	top.	Tusing *et al.* (1962) *Tox. Appl. Pharmacol.*, **4**, 402.
	R	p.o.	
3-(Dodecyloxy)-1,2-propanediol-1-(hydrogen sulphate), sodium salt	M	top.	
	R	p.o.	
9,10-Epoxystearic acid	M	s.c.	Van Duuren *et al.* (1966) *J. Natl Cancer Inst.*, **37**, 825.
	R	s.c.	
Ergosterol	M	top.	Barry *et al.* (1935) *Proc. R. Soc. Lond.* [*Biol.*], **117**, 318.
	R	i.p.[2]	Pizzolato & Beard (1945) *Exp. Med. Surg.*, **3**, 95.
Ethanol	M	p.o.	Kuratsune *et al.* (1971) *Gann*, **62**, 395.
	R	p.o.[2]	Yamamoto *et al.* (1967) *Int. J. Cancer*, **2**, 337.
(Ethylenebis(dithiocarbamato))	M	p.o.	Innes *et al.* (1969) *J. Natl Cancer Inst.*, **42**, 1101.
Manganese (Maneb)	R	p.o.	Andrianova & Alekseev (1970) *Vopr. Pitan.*, **29**, 71.
(Ethylenebis(dithiocarbamato))	M	p.o.	Innes *et al.* (1969) *J. Natl Cancer Inst.*, **42**, 1101.
Zinc (Zineb)	R	p.o.	Smith *et al.* (1953) *J. Pharmacol. Exp. Therap.*, **109**, 159.
Hexamethylenetetramine (Urotropin)	M	p.o.	Della Porta *et al.* (1968) *Fd Cosmet. Toxicol.*, **6**, 707.
	R	p.o.[2]	Della Porta *et al.* (1970) *Tumori*, **56**, 325.
4-Hydroxy-3-nitrobenzenearsonic acid	M	p.o.	Prier *et al.* (1963) *Tox. Appl. Pharmacol.*, **5**, 526.
	R	p.o.	
Indole	M	s.c.	Felistovich (1964) *Vopr. Onkol.*, **10**, 70.
	R	p.o.	McDonald *et al.* (1962) *J. Urol.*, **87**, 381.
Isopropyl-N-(3-chlorophenyl) carbamate	M	p.o.[2]	Innes *et al.* (1969) *J. Natl Cancer Inst.*, **42**, 1101.
	R	p.o.	Larson *et al.* (1960) *Tox. Appl. Pharmacol.*, **2**, 659.
Lactose	M	s.c.	Hueper (1965) *Cancer Res.*, **25**, 440.
	R	s.c.	
Lauroyl peroxide	M	s.c.	Van Duuren *et al.* (1966) *J. Natl Cancer Inst.*, **37**, 825.
	R	s.c.[2]	Van Duuren *et al.* (1967) *J. Natl Cancer Inst.*, **39**, 1213.
Maltose	M	s.c.	Hueper (1965) *Cancer Res.*, **25**, 440.
	R	s.c.	
1-Naphthyl-N-methylcarbamate (Crag Sevin)	M	p.o.[2]	Innes *et al.* (1969) *J. Natl Cancer Inst.*, **42**, 1101.
	R	p.o.	Andrianova & Alekseev (1970) *Vopr. Pitan.*, **29**, 71.
N-dodecylguanidine acetate	M	p.o.	Innes *et al.* (1969) *J. Natl Cancer Inst.*, **42**, 1101.
	R	p.o.	Levinskas *et al.* (1961) *Tox. Appl. Pharmacol.*, **3**, 127.
N,N-diphenylnitrosamine	M	p.o.	Innes *et al.* (1969) *J. Natl Cancer Inst.*, **42**, 1101.
	R	i.p.	Boyland *et al.* (1968) *Eur. J. Cancer*, **4**, 233.
Ochratoxin A	M	s.c.[2]	Dickens & Waynforth (1968) *Br. Emp. Cancer Campaign*, **46**, 108.
	R	s.c., p.o.[2]	Purchase & Van der Watt (1971) *Fd Cosmet. Toxicol.*, **9**, 681.
Piperonyl butoxide	M	p.o.	Innes *et al.* (1969) *J. Natl Cancer Inst.*, **42**, 1101.
	R	p.o.	Sarles & Vandegrift (1952) *J. Trop. Med. Hyg.*, **1**, 862.
Piperonyl ether butoxide	M	p.o.[2]	Innes *et al.* (1969) *J. Natl Cancer Inst.*, **42**, 1101.
	R	p.o.[2]	Sarles & Vandergrift (1952) *J. Trop. Med. Hyg.*, **1**, 862.
Polyethylene glycols	M	p.o.	Roe *et al.* (1970) *Fd. Cosmet. Toxicol.*, **8**, 135.
	R	i.p.	Boyland *et al.* (1968) *Eur. J. Cancer*, **4**, 233.
Polyvinyl pyridine-n-oxide	M	i.v.	Schmähl (1969) *Arzneimittelforschung*, **19**, 1313.
	R	i.v.	
Procaine penicillin	M	i.m.	Gilman & Ruckerbauer (1962) *Cancer Res.*, **22**, 152.
	R	i.m.	
1,2-Propanediol (propylene glycol)	M	top.	Fujino *et al.* (1965) *J. Natl Cancer Inst.*, **35**, 907.
	R	s.c.	Hine *et al.* (1958) *Arch. Ind. Hlth*, **17**, 129.
Sorbose	M	s.c.	Hueper (1965) *Cancer Res.*, **25**, 440.
	R	s.c.	
Sucrose	M	s.c.	
	R	s.c.	
Sulfosuccinic acid, 1,4-bis-(2-ethylhexyl)ester, sodium salt	M	p.o.	Klein (1963) *Cancer Res.*, **23**, 1701.
	R	p.o.	Fitzhugh & Nelson (1948) *J. Pharmacol. Exp. Therap.*, **93**, 147.

Compound	M/R	Route	Reference
Tricaprylin	M	s.c.	Van Duuren *et al.* (1966) *J. Natl Cancer Inst.*, **37**, 825.
	R	s.c.	
1,1,1-Trichloro-2,2-bis(p-methoxyphenyl)ethane (methoxychlor)	M	top.	Hodge *et al.* (1966) *Tox. Appl. Pharmacol.*, **9**, 583.
	R	p.o.	Deichmann *et al.* (1967) *Tox. Appl. Pharmacol.*, **11**, 88.

2. Compounds positive in both rat and mouse

Compound	M/R	Route	Affected organ	Reference
2-Acetylaminofluorene	M	p.o.	Liver, bladder	Wood (1969) *Eur. J. Cancer*, **5**, 41.
	R	p.o.	Liver, mammary gland	Peraino *et al.* (1971) *Cancer Res.*, **31**, 1506.
2-Amino-2,5-azotoluene	M	p.o.	Liver	Crabtree (1948) *Br. J. Cancer*, **3**, 387.
	R	p.o.	Liver	
2-Amino-fluorene	M	top.	Liver	Bielschowsky & Bielschowsky (1960) *Br. J. Cancer*, **14**, 195.
	R	top.	Liver	Goodall (1965) *Endocrinology*, **76**, 1027.
2-Anthramine	M	top.	Mammary gland	Lennox (1955) *Br. J. Cancer*, **9**, 631.
	R	p.o.	Skin	Griswold *et al.* (1968) *Cancer Res.*, **28**, 924.
Bis(acetato)dihydroxytri-lead	M	p.o.	Kidney	Van Esch & Kroes (1969) *Br. J. Cancer*, **23**, 765.
	R	p.o.	Kidney, brain	Oyaswi *et al.* (1970) *Cancer Res.*, **30**, 1249.
Carbon tetrachloride	M	p.o.	Liver	Unakar (1966) *Arch. Path.*, **82**, 170.
	R	s.c.	Liver	Reuber & Glover (1970) *J. Natl Cancer Inst.*, **44**, 419.
2,7-Diacetylaminofluorene	M	p.o.	Liver	Takayama (1968) *J. Natl Cancer Inst.*, **40**, 629.
	R	p.o.	Mammary gland, liver, intestine	Yamada *et al.* (1971) *Gann.*, **62**, 471.
p-Dimethylaminobenzene-1-azo-2-naphthalene	M	top.	Skin	Mulay & Saxen (1952) *J. Natl Cancer Inst.*, **13**, 1259.
	R	p.o.	Liver	Mulay & Longdon (1953) *J. Natl Cancer Inst.*, **14**, 571.
7,12-Dimethylbenz(a)-anthracene	M	i.v.	Leukaemia, ovary	Uematsu & Higgins (1969) *Gann.*, **60**, 545.
	R	i.v.	Mammary gland	Geyer *et al.* (1953) *Cancer Res.*, **13**, 503.
4′-Fluoro-4-aminodiphenyl	M	p.o.	Liver	Clayson *et al.* (1965) *Br. J. Cancer*, **19**, 297.
	R	s.c.	Kidney, liver	Matthews & Walpole (1958) *Br. J. Cancer*, **12**, 234.
Imuran	M	i.m.	Thymus etc.	Casey (1968) *Blood*, **31**, 396.
	R	p.o.	Zymbal gland	Frankel *et al.* (1970) *Tox. Appl. Pharmacol.*, **17**, 462.
3-Methylcholanthrene	M	top., s.c.	Leukaemia, local	Rubin (1971) *Progr. Exp. Tumor Res.*, **14**, 138.
				Matsuyama *et al.* (1963) *Nature*, **197**, 805.
	R	p.o., s.c.	Mammary gland, local	Gruenstein *et al.* (1966) *J. Natl Cancer Inst.*, **36**, 483.
				Matsuyama *et al.* (1963) *Nature*, **197**, 805.
7-Methylbenz(a)-anthracene	M	s.c.	Local	Miller & Miller (1963) *Cancer Res.*, **23**, 229.
	R	s.c.	Local	Pataki & Huggins (1969) *Cancer Res.*, **29**, 506.
N-Fluoren-2-yl acetohydroxamic acid	M	p.o.	Mammary gland, stomach, liver	Miller *et al.* (1964) *Cancer Res.*, **24**, 2018.
	R	p.o.	Liver, bladder	Weisburger *et al.* (1970) *J. Natl Cancer Inst.*, **45**, 29.
N-Isopropyl-a-(2-methyl-hydrazino)-p-toluamide monochloride	M	i.p.	Leukaemia, lung	Kelly *et al.* (1969) *J. Natl Cancer Inst.*, **42**, 337.
	R	i.p.	Mammary gland	Kelly *et al.* (1968) *J. Natl Cancer Inst.*, **40**, 1027.
N-nitrosobutylethylamine	M	p.o.	Stomach	Schmahl *et al.* (1963) *Naturwissenschaften*, **50**, 717.
	R	p.o.	Oesophagus	Thomas & So (1969) *Arzneimittelforschung*, **19**, 1077.
N-nitrosobutylurea	M	p.o.	Thymus, leukaemia	Yokoro *et al.* (1970) *Gann*, **61**, 287.
	R	p.o.	Zymbal gland	Odashima (1970) *Gann.*, **61**, 245.

Compound	M/R	Route	Affected organ	Reference
N-nitrosomethylaniline	M	p.o.	Lung, lymphoreticular	Greenblatt *et al.* (1971) *J. Natl Cancer Inst.*, **46**, 1029.
	R	p.o.	Lymphoreticular, stomach	Goodall *et al.* (1970) *Tox. Appl. Pharmacol.*, **17**, 426.
N-4-((5-Nitro-2-furyl)-2-thiazolyl)formamide	M	p.o.	Bladder	Erturk *et al.* (1970) *Cancer Res.*, **30**, 1309.
	R	p.o.	Bladder	Erturk *et al.* (1969) *Proc. Am. Assoc. Cancer Res.*, **10**, 23.
3-Nitro-3-hexene	M	inh.	Lung	Deichmann *et al.* (1965) *Indus. Med. Surg.*, **34**, 800.
	R	inh.	Lung	
4-Nitroquinoline 1-oxide	M	s.c.	Lung	Mori *et al.* (1966) *Gann.*, **57**, 559.
	R	s.c.	Lung	
4-Nitrosopiperazine	M	p.o.	Lung	Greenblatt *et al.* (1971) *J. Natl Cancer Inst.*, **46**, 1029.
	R	p.o.	Lymphoreticular	Garcia *et al.* (1970) *Z. Krebsforsch*, **74**, 179.
19-Nor-17α-pregn-1,3,5(10)-trien-20-yne-3,17-diol	M	p.o.	Mammary, uterine	Committee on Safety of Medicines (1972) Carcinogenicity tests of oral contraceptives, London; HMSO.
	R	p.o.	Mammary, liver	

3. Rat results negative; mouse positive

Compound	M/R	Route	Reference
6-Aminochrysene	M	top.	Lambelin *et al.* (1975) *Eur. J. Cancer*, **11**, 327.
	R	p.o.[2]	Higgins (1964) *Proc. Natl Acad. Sci.*, **51**, 737.
1,1-Dimethylhydrazine	M	p.o.	Toth (1972) *Proc. Am. Assoc. Cancer Res.*, **13**, 34.
	R	p.o.	Argus & Hoch-Ligeti (1961) *J. Natl Cancer Inst.*, **27**, 695.

4. Rat results positive; mouse negative

Compound	M/R	Route	Reference
4-Aminostilbene	M	p.o.	Clayson *et al.* (1965) *Br. J. Cancer*, **19**, 297.
	R	p.o.[2]	Anderson *et al.* (1964) *Cancer Res.*, **24**, 128.
Oestrone	M	p.o.	Biancifiori *et al.* (1967) *Br. J. Cancer*, **21**, 452.
	R	s.c.	Cutts (1964) *Cancer Res.*, **24**, 1124.
Poly(1,2-dihydro-2,2,4-trimethyl-quinoline)	M	s.c., top.	Hodge *et al.* (1966) *Tox. Appl. Pharmacol.*, **9**, 583.
	R	p.o.	
Polyethyleneglycol monostearate	M	p.o.	Hueper & Payne (1963) *Arch. Env. Hlth*, **6**, 484.
	R	p.o.	
4-Styrylacetanilide	M	p.o.	Clayson *et al.* (1965) *Br. J. Cancer*, **19**, 297.
	R	p.o.	Baldwin *et al.* (1968) *Br. J. Cancer*, **22**, 133.

Footnote

[1] Data not quoted by IARC Monograph Vol. 4, p. 137.
[2] Animal group sizes relatively small.

Routes abbreviated as follows:
p.o.—gavage or addition to diet.
top.—topical application.
i.vag.—intravaginal instillation.