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 (5a).
   (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.

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-trichlorethene and 1,1,2,2-tetrachloroethane 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

| Federal Register Reference | Compound | Federal Register Reference |
|---------------------------|----------|---------------------------|
| 49055 43 (1978)           | Anilazine|                           |
| 47793 43 (1978)           | p-Anisidine hydrochloride |                     |
| 14130 43 (1978)           | Anthranilic acid |                      |
| 40061 43 (1978)           | 1H-Benzotriazole |                      |
| 46382 43 (1978)           | 2-Chloro-p-phenylenediamine sulphate |           |
| 64444 42 (1977)           | Chlorpropanide |                      |
| 49674 43 (1978)           | 3-Chloro-p-toluidine |                     |
| 47793 43 (1978)           | Clonitralid1 |                      |
| 11760 43 (1978)           | Diarylanilide Yellow |                    |
| 43132 42 (1977)           | Dichlorvos |                       |
| 15140 42 (1977)           | Dimethoate |                        |
| 45645 43 (1978)           | Dioxathion |                        |
| 46382 43 (1978)           | Iodoform |                         |
| 43791 42 (1977)           | Lindane |                           |
| 12385 43 (1978)           | Malathion |                          |
| 11760 43 (1978)           | Methoxychlor |                     |
| 49574 43 (1978)           | Mexacarbate |                      |
| 49055 43 (1978)           | 4-Nitroanthranilic acid |                 |
| 49055 43 (1978)           | 1-Nitro naphthalene |                   |
| 26139 42 (1978)           | 3-Nitro propionic acid |                |
| 49055 43 (1978)           | 1-Phenyl-3-methyl-5-pyrazolone |            |
| 61316 42 (1977)           | Photodieldrin |                     |
| 50741 43 (1978)           | 2,3,5,6-Tetrachloro-4-nitroanisole | |
| 49674 43 (1978)           | Triphenyltin hydroxide |                  |
| 62212 42 (1977)           | Tolbutamide |                       |
| 49055 43 (1978)           | 2,3-Toluenediamine sulphate |         |

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

| Site affected | Federal Register Reference |
|--------------|---------------------------|
| Liver (m)    | 51451 43 (1978)           |
| Liver (f)    | 97289 43 (1978)           |
| Bladder (m)  | 43074 43 (1978)           |
| Bladder (f)  | 47289 43 (1978)           |
| Bladder (m)  | 49055 43 (1978)           |
| Liver (m)    | 14914 41 (1978)           |
| Liver (f)    | 23449 41 (1978)           |
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#### Site affected

| Compound | Rat | 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) | (m) | 2450 43 (1978) |
| 3-Amino-3-ethoxyacetanilide | (m) | (m) | 40062 43 (1978) |
| Captan | (f) | (f) | 59120 42 (1977) |
| Chlordane | | | 56805 42 (1977) |
| Chlorbenzilate | 43994 42 (1977) | 47793 43 (1978) |
| Dicofol | (m) | (m) | 44890 43 (1978) |
| Dieldrin | (m) | | 2450 43 (1978) |
| Heptachlor | | | 45359 42 (1977) |
| Hexachloroethane | | | 27238 43 (1978) |
| 5-Nitro-o-toluidine | | | 43074 43 (1978) |
| 1,1,2,2-Tetrachloroethane | | | 9360 43 (1978) |
| 1,1,2-Trichloroethane | | | 30365 43 (1978) |
| Trifuralin | (f) | (f) | 12385 43 (1978) |
4. Rat result positive; mouse negative, p.o. administration

| Compound                  | Rat | Mouse | Federal Register Reference |
|---------------------------|-----|-------|----------------------------|
| 4-Amino-2-nitrophenol     | (m) |       |                            |
| Aniline hydrochloride     |     |       |                            |
| Chlorothalonil            |     |       |                            |
| m-Cresidine               |     | 1     |                            |
| Dapsone                   | (m) |       |                            |
| 2,4-Dinitrotoluene        | 3   |       |                            |
| Pilocram                  | (f)3|       |                            |
| Pivalolactone             |     |       |                            |

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

APPENDIX 2

Summarized data from IARC Monograph Series

1. Rat and mouse negative

| Compound                  | Route (rat) | Route (mouse) | Reference |
|---------------------------|-------------|---------------|-----------|
| Aniline                   | p.o.        | s.c.          | 274 (1974) |
| y-Butyrolactone           | p.o.        | p.o.          | 231 11 (1976) |
|                           | s.c.        | s.c.          |           |
| Cis-9, 10-Epoxy stearic acid| s.c.       | s.c.          | 153 11 (1976) |
|                           | top         |               |           |
| 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.        | s.c.          | 279 8 (1975) |
| Yellow OB                  | p.o.        | s.c.          | 287 8 (1975) |
2. Rat and mouse positive

| Compound                  | Route | Site affected                     | Mouse Route | Site affected                     | Reference |
|---------------------------|-------|-----------------------------------|-------------|-----------------------------------|-----------|
| Amitrole                  | s.c.  | Thyroid, liver                    | p.o.        | Thyroid, liver                    | 31 7 (1974) |
|                          | p.o.  | Liver, bladder                    | i.p., s.c.  | Liver, lung                        | 61 8 (1975) |
| o-Aminoazotoluene         | p.o.  | Mammary gland, intestine          | p.o.        | In 1 of 4 strains tested: liver   | 39 5 (1974) |
| 4-Aminobiphenyl           | s.c.  | Mammary gland, intestine          | i.h.        | Lung                              | 17 2 (1973); 14 2 (1977) |
| Aramite                   | p.o.  | Liver                             | i.p.        | Forestomach                        | 91 3 (1975) |
| Asbestos                  | i.p.l | Lung                              | s.c.        | Liver                             | 80 1 (1972) |
| Benzidine                 | i.h.  | Liver                             | s.c.        | Liver                             | 100 2 (1973) |
| Benzo(a)pyrene            | p.o.  | Mammary gland, intestine          | p.o.        | Mammary gland, intestine          | 125 9 (1975) |
|                          | i.t.  | Mammary gland, intestine          | i.p.        | Mammary gland, intestine          | 100 2 (1973) |
|                          | p.o.  | Local tumours                     | i.p.        | Lung                              | 231 4 (1974) |
| Bis(chloromethyl)ether    | s.c.  | Lung, nasal cavities              | s.c.        | Lung                              | 167 9 (1975) |
| 4-Hydroxy-2-naphthalenyl  | i.h.  | Liver                             | i.v.        | Lung                              | 225 11 (1976) |
| Bis(2-chloroethyl)-2-carb | s.c.  | Tumours at site of admin.         | s.c.        | Intestinal-cell tumours of testis | 74 2 (1973) |
| Cadmium salts             | s.c.  | Mammary gland, intestine          | s.c.        | Liver                             | 53 1 (1972) |
| Chlorambucil              | i.p.  | Lymphomas                         | i.p.        | Ovary, lung                        | 151 15 (1977) |
| Chromium salts            | i.b.  | Lung                              | i.h.        | Lung                              | 100 2 (1973) |
| Calcium chromate          | p.o.  | Bladder                           | s.c.        | Bladder                           | 101 81 (1975) |
| Citrus Red No. 2          | p.o.  | Liver, kidney                     | i.v.        | Mammary gland, intestine          | 135 9 (1975) |
| Chlorosulfonamide         | s.c.  | Lung, liver, reproductive organs  | i.p.        | Mammary gland, intestine          | 223 7 (1974) |
| Diazomethane              | i.h.  | Lung                              | i.h.        | Mammary gland, intestine          | 178 3 (1973) |
| Dibenz(a,h)anthracene     | s.c.  | Lung                              | i.p.        | Mammary gland, intestine          | 260 3 (1973) |
| 7H-Dibenzo(C19) carbazole | s.c.  | 1 expt: sarcomas, no details      | s.c.        | Mammary gland, intestine          | 139 15 (1977) |
| 1,2-Dibromo-3-chloropropene| p.o. | Forestomach, mammary gland        | p.o.        | Mammary gland, intestine          | 55 6 (1974) |
| Diethylstilboestrol       | s.c.  | mammary gland, pituitary          | s.c.        | Mammary gland, intestine          | 77 6 (1974) |
| Dihydrosafrole            | p.o.  | Oesophagus                         | p.o.        | Liver (m), lung                    | 231 10 (1976) |
| 1,2-Dimethylhydrazide     | s.c.  | Intestine, lung                   | p.o.        | Liver, lung, muscle               | 146 4 (1974) |
| Ethynyleostadiol          | p.o.  | Liver                             | p.o.        | Pituitary, mammary gland          | 151 7 (1974) |
| Ethylene dibromide        | s.c.  | Liver                             | p.o.        | Forestomach, mammary gland        | 195 15 (1977) |
| Ethylmethane sulphonate   | i.p.  | Lung                              | p.o.        | Forestomach, mammary gland        | 245 7 (1974) |
| Ethynodiol dicetate       | p.o.  | Mammary gland, benign (m)         | p.o.        | Mammary gland, castrated (m)      | 173 6 (1974) |
| 2[2-Formylhydrazino]-4-(5-| p.o.  | Mammary gland, gastrointestinal    | p.o.        | Stomach, lung                      | 151 7 (1974) |
| Nitro-2-furyl]thiazole    | s.c.  | tract                             | i.p.        | Liver                             | 231 10 (1976) |
| Isosafrole                | p.o.  | Liver                             | i.p.        | Liver                             | 167 9 (1975) |
| Compounds                        | Rat Route | Affected organ                  | Mouse Route | Affected organ                              | Reference |
|---------------------------------|-----------|---------------------------------|-------------|---------------------------------------------|-----------|
| Mestranol                       | p.o.      | Mammary gland (f)               | p.o.        | Mammary gland, pituitary                      | 87 6 (1974) |
| Methyl methanesulphonate        | i.p.      | Nervous system                  | i.p.        | Lung; thymic lymphomas                       | 253 7 (1974) |
| N-methyl-nitro-nitrosoguanidine | i.p.      | Stomach, forestomach, liver     | p.o.        | Stomach                                      | 183 4 (1974) |
| Methylthioureaic                | s.c.      | Thyroid, kidney (f)             | p.o.        | Thyroid                                      | 53 7 (1974) |
| Metronidazole                   | p.o.      | Mammary gland                   | p.o.        | Lung                                         | 113 13 (1977) |
| Nickel salts                    | i.h.      | Lung                            | i.m.        | Local tumours                                | 75 11 (1976) |
| Nickel sulphide, nickel oxide   | i.m.      | Local tumours                   | i.m.        | Local tumours                                | 75 11 (1976) |
| 5-Nitroacenaphthene             | 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.        | Lung, thymus                                 | 193 9 (1975) |
| Nitrogen mustard n-oxide hydrochloride | i.v. | Lymphoreticular tumours         | s.c.        | Lung, thymus, Harderian gland                | 209 9 (1975) |
| N-nitrosodimethylamine          | i.h.      | Liver                           | i.p.        | Liver, forestomach, oesophagus, lung         | 107 1 (1972) |
| N-nitrosodimethylamine          | i.p.      | Liver                           | s.c.        | Liver, lung                                  | 95 1 (1972) |
| Nitrosothiourea                  | i.p.      | Liver, kidney                   | i.p.        | Multiple tumours, including intracranial, neurogenic | 135 1 (1972) |
| Nitrosomethylurea               | i.v.      | Brain, peripheral nervous system | s.c.        | Lung; thymic lymphomas                       | 125 1 (1972) |
| Norethisterone                  | p.o.      | Liver (m) (benign)              | s.c.        | Liver (m, benign)                            | 179 6 (1974) |
| Norethynodriel                  | p.o.      | Liver, pituitary                | s.c.        | 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.        | 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-Propioloactone                | p.o.      | Forestomach                     | p.o.        | Liver (m), lymphomas                         | 259 4 (1974) |
| Propylthiouracil                | p.o.      | Thyroid                         | p.o.        | Thyroid, pituitary                           | 67 7 (1974) |
| Safran                           | p.o.      | Liver                           | p.o.        | Liver                                        | 231 10 (1976) |
| Sterigmatocystin                | top.      | Liver                           | top.        | Lung                                         | 245 10 (1976) |
| Streptozotocin                  | i.v.      | Kidney, liver                   | i.p.        | Lung, kidney                                 | 337 17 (1978) |
| Thiouracil                      | p.o.      | Thyroid                         | p.o.        | Liver                                        | 85 7 (1974) |
| Ureacil mustard                 | i.p.      | Peritoneum, pancreas, ovary, mammary gland | i.p. | Liver, ovary | 235 9 (1975) |
| Urethane                        | i.p.      | Liver, uterus etc.              | i.h.        | 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      | i.v.*       | 247 4 (1974) |
| sulphonate                    | p.o.        | 83 5 (1974) |
| DDT                           | p.o.        | 125 5 (1974) |
| Dieldrin                      | s.c., p.o.  | 159 4 (1974) |
| Isonicotinic acid hydrazide   | i.p., p.o.  |           |
| 2-Naphthylamine               | p.o.        | 97 4 (1974) |
| Trichlorethylene*             | p.o.        | 263 11 (1976) |

* Trichloroethylene also included in NCI list. IARC opinion based on early report of NCI data.

4. Rat results positive, mouse negative

| Compound                      | Rat Route | Mouse Route | Reference |
|-------------------------------|-----------|-------------|-----------|
| Daunomycin                    | i.v. p.o. | 145 10 (1976) |
| p-Dimethylamino-azobenzene    | top., p.o.| 125 8 (1975) |
| Thiourea                      | i.p., p.o.| 95 7 (1974) |
| Aflatoxin B1                  | i.p., p.o.| 51 10 (1976) |

5. Different results from various species

| Compound                      | Species Route | Species Route | Reference |
|-------------------------------|---------------|---------------|-----------|
| Arsenic compounds             | Rat p.o.      | Man top.      | 48 2 (1973) |
| Chlormadinone acetate         | Mouse p.o.    | Dog p.o.      | 149 6 (1974) |
| 3,3'-Dimethylbenzidine        | Hamster p.o.  | Rat s.c.      | 87 1 (1972) |
| Hydrazine                     | Hamster p.o.  | Rat i.p.      |           |
|                               |               | Mouse i.p.    | 127 4 (1974) |
| Thioacetamide                 | Hamster p.o.  | Rat p.o.      |           |
|                               |               | 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. Hgy., 2, 433. |
| Acetone                       | M top.    | Roe et al. (1970) Br. J. Cancer, 24, 788. |
|                               | R top.²   | Glucksman & Cherry (1968) Br. J. Cancer, 22, 545. |
| Adipic acid dioctyl ester     | M top., s.c. | Hodge et al. (1966) Tox. Appl. Pharmacol., 9, 583. |
|                               | R p.o.    |           |
| 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.  | Boyland & Sims (1967) Int. J. Cancer, 2, 500. |
| Arachis oil                                  | M   | s.c.  | Carter et al. (1969) Fd. Cosmet. Tox., 7, 53. |
|                                              | R   | s.c.  | Dickens & Jones (1964) Br. Emp. Cancer Campaign, 42, 141. |
| Azobenzene                                   | M   | s.c. 2| Shear & Stewart (1941) In Hartwell & Shubick (1951). |
|                                              | R   | s.c.  | Spitz et al. (1950) Cancer, 3, 759.          |
| Benzene-1-azo-2-naphthol                     | M   | p.o.  | Clayson et al. (1955) 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.                 |
| Benzoyle peroxide                            | M   | p.o.  | Fitzhugh et al. (1950) J. Am. Pharm. Assoc., 40, 583. |
| 2-Biphenyloxy                                 | M   | p.o.  | Sharrat et al. (1964) Fd. Cosmet. Toxicol., 2, 527. |
| 3,6-Bis(dimethylamino)acridine               | M   | s.c. 2| Van Duuren et al. (1969) Br. J. Cancer, 23, 587. |
| (Acridine Orange)                            | R   | s.c. 2| Camphor                                      |
|                                              | M   | i.p., top. | Stoner et al. (1973) Cancer Res., 33, 3069. |
|                                              | R   | s.c.  | Graff et al. (1953) Arch. Geschwulstforsh., 5, 110. |
| Carboxymethylcellulose                       | M   | p.o.  | Ezezya (1982) Semana Med., 106, 663.         |
|                                              | R   | s.c.  | McElligott & Hurst (1968) Fd. Cosmet. Toxicol., 6, 449. |
| 2-Chloro-4,6-bis(ethylamino)-s-triazine       | M   | p.o.  | Teller et al. (1970) Cancer Res., 30, 179.    |
| (Simazin)                                    | R   | p.o.  | Innes et al. (1969) J. Natl Cancer Inst., 42, 1101. |
| Cholesterol                                  | M   | s.c.  | Bischoff (1957) J. Natl Cancer Inst., 19, 977. |
| CI Acid Blue 9, diammonium salt              | M   | s.c.  | Van Duuren et al. (1969) Br. J. Cancer, 23, 587. |
| (Brilliant Blue)                             | R   | p.o.  | Hansen et al. (1966) Fd. Cosmet. Toxicol., 4, 389. |
| CI Acid Green 5, disodium salt               | M   | p.o.  | Hansen et al. (1966) Fd. Cosmet. Toxicol., 4, 389. |
| (Light Green SP Yellowish)                   | R   | p.o.  | Hansen et al. (1966) Fd. Cosmet. Toxicol., 4, 389. |
| CI Acid Red 26, isodium salt                 | M   | p.o.  | Waterman & Lignac (1958) Acta Physiol Pharmacol. Neerl., 7, 35. |
| (Ponceaux MX)                                | R   | p.o.  | Ikeda et al. (1966) Fd. Cosmet. Toxicol., 4, 485. |
| CI Food Blue 1, disodium salt                | M   | s.c.  | Hansen et al. (1966) Fd. Appl. Pharmacol., 8, 29. |
| (FD & C Blue No. 2)                          | R   | p.o.  | Hansen et al. (1966) Fd. Cosmet. Toxicol., 4, 389. |
| CI Food Green 3, disodium salt               | M   | p.o.  | Hansen et al. (1966) Fd. Cosmet. Toxicol., 4, 389. |
| (Fast Green PCF)                             | R   | p.o.  | Hansen et al. (1966) Fd. Cosmet. Toxicol., 4, 389. |
| CI Food Red 1, disodium salt                 | M   | p.o.  | Davis et al. (1966) Fd. Appl. Pharmacol., 8, 306. |
| (Ponceaux SX)                                | R   | p.o.  | Davis et al. (1966) Fd. Appl. Pharmacol., 8, 306. |
| CI Solvent Yellow 5                          | M   | s.c. 2| CI Solvent Yellow 6 (I-2-methylbenzyl/azo-2-naphthalamine) |
| (phenylazo-2-naphthylamine)                  | R   | s.c., p.o. 2 | Hansen et al. (1963) Tox. Appl. Pharmacol., 5, 16. |
| CI Solvent Yellow 6 I (2-methylbenzyl/azo-2-naphthalamine) | M   | s.c. 2| CI Solvent Yellow 6 (I-2-methylbenzyl/azo-2-naphthalamine) |
| Cyclohexanesulfonic acid, monosodium salt    | M   | p.o.  | Rudali et al. (1969) C. R. Acad. Sci., 269, 1910. |
| Cyclohexene hydroperoxide                    | M   | s.c.  | Grasso et al. (1971) Fd. Cosmet. Toxicol., 9, 463. |
| D-glucose                                    | M   | s.c.  | Van Duuren et al. (1966) J. Natl Cancer Inst., 37, 825. |
| 2,6-Dichloro-4-nitroaniline                  | M   | p.o.  | Hucier (1965) Cancer Res., 25, 440.          |
| Dicyclohexylamine                            | M   | s.c.  | Pliss (1958) Vopr. Onkol., 4, 699.           |
| 3,3'-Dihydroxyazobenzidine                   | M   | s.c.  | Bonsen et al. (1956) Br. J. Cancer, 10, 533. |
| p-Diethylaminobenzazobenzene                 | M   | s.c.  | Pliss (1961) Vopr. Onkol., 7, 33.            |
| 17α,21-Dihydroxyprogesterone-3,11,20-trione  | M   | s.c. 2| Kirby (1947) Cancer Res., 7, 333.           |
| (Cortisone)                                  | R   | p.o.  | 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. |
| o,o-Dimethyl-1-hydroxy-2,2,2-         | M    | top.  | Gibel et al. (1971) Arch. Geschwulstforsch, 37, 303. |
| trichloroethylphosphonate             | R    | s.c.  | Van Duuren et al. (1967) J. Natl Cancer Inst., 39, 1213. |
| (Diperox, Trichlorophon)              |      |       |                                  |
| 2-(2-(2-(dodecyl)oxy)ethoxy)ethanol   | M    | top.  | Tusing et al. (1962) Tox. Appl. Pharmacol., 4, 402. |
| 3-(Dodecyl)-1,2-propanediol-2-(2-(   | M    | top.  |                                  |
| (hydrogen sulphate), sodium salt      | R    | s.c.  |                                  |
| 9,10-Epoxystearic acid                | M    | top.  | Barry et al. (1935) Proc. R. Soc. Lond. [Biol.], 117, 318. |
| Ergosterol                            | R    | s.c.  | Van Duuren et al. (1966) J. Natl Cancer Inst., 37, 825. |
| Ethanol                               | R    | i.p.  | Pizzolato & Beard (1945) Exp. Med. Surg., 3, 95. |
| (Ethylenebis(dithiocarbamato)) Manganse (Maneb) | M | p.o. | Kuratsune et al. (1971) Gann, 62, 395. |
| Zinc (Zineb)                          | R    | p.o.  | Yamamoto et al. (1967) Int. J. Cancer, 2, 337. |
| Hexamethylenetetramine               | M    | p.o.  | Innes et al. (1969) J. Natl Cancer Inst., 42, 1101. |
| (Urotropin)                           | R    | p.o.  | Innes et al. (1969) J. Natl Cancer Inst., 42, 1101. |
| 4-Hydroxy-3-nitrobenzenearsonic acid  | M    | p.o.  | Innes et al. (1969) J. Natl Cancer Inst., 42, 1101. |
| Indole                                | M    | s.c.  | Larson et al. (1960) Tox. Appl. Pharmacol., 2, 659. |
| Isopropyl-N-(3-chlorophenyl) carbamate | R    | p.o.  | Smith et al. (1955) J. Pharmacol. Exp. Therap., 109, 159. |
| Lactose                               | M    | s.c.  | Della Porta et al. (1968) Fd Cosmet. Toxicol., 6, 707. |
| Lauroyl peroxide                      | R    | s.c.  | Della Porta et al. (1970) Tumori, 56, 325. |
| Maltose                               | M    | s.c.  | Prier et al. (1963) Tox. Appl. Pharmacol., 5, 526. |
| 1-Naphthyl-N-methylcarbamate (Crag Sevin) | M | p.o.  | Felistovich (1964) Vopr. Onkol., 10, 70. |
| N-dodecylguanidine acetate            | R    | p.o.  | McDonald et al. (1962) J. Urol., 87, 381. |
| N,N-diphenylnitrosamine               | M    | s.c.  | Innes et al. (1969) J. Natl Cancer Inst., 42, 1101. |
| Ochratoxin A                          | R    | p.o.  | Innes et al. (1969) J. Natl Cancer Inst., 42, 1101. |
| Polyethylene glycols                  | M    | s.c.  | Boyland et al. (1968) Eur. J. Cancer, 4, 233. |
| Polyvinyl pyridine-n-oxide            | R    | i.v.  | Purchase & Van der Watt (1971) Fd Cosmet. Toxicol., 9, 681. |
| Procaine penicillin                   | M    | i.m.  | Innes et al. (1969) J. Natl Cancer Inst., 42, 1101. |
| Procaine penicillin                   | R    | i.m.  | Schmähl et al. (1969) Arzneimittelforschung, 19, 1313. |
| 1,2-Propanediol (propylene glycol)    | M    | top.  | Gilman & Ruckerbauer (1962) Cancer Res., 22, 152. |
| Sorbose                               | M    | s.c.  | Fujino et al. (1965) J. Natl Cancer Inst., 35, 907. |
| Sucrose                               | M    | s.c.  | Hine et al. (1958) Arch. Ind. Hith, 17, 129. |
| Sulfosuccinic acid, 1,4-bis-          | M    | p.o.  | Hueper (1965) Cancer Res., 25, 440. |
| (2-ethylhexyl)ester, sodium salt      | R    | p.o.  | Klein (1963) Cancer Res., 23, 1701. |
|                                    |      |       | Fitzhugh & Nelson (1948) J. Pharmacol. Exp. Therap., 93, 147. |
### 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.                                   |
| 2-Amino-fluorene                | M top. |     | Liver                                                | Goodall (1965) *Endocrinology*, 76, 1027.                                   |
|                                 | R p.o. |     | Mammary gland                                        | Lennox (1955) *Br. J. Cancer*, 9, 631.                                     |
| Bis(acetato)dihydroxytriphenylen| M p.o. |     | Kidney                                              | Van Esch & Kroes (1969) *Br. J. Cancer*, 23, 765.                           |
| Carbon tetrachloride            | M p.o. |     | Liver                                                | Oyaswi et al. (1970) *Cancer Res.*, 30, 1249.                               |
|                                 | R s.c. |     | Liver                                                | Unakar (1966) *Arch. Path.*, 82, 170.                                      |
| 2,7-Diacetylaminofluorene       | R p.o. |     | Liver                                                | Reuber & Glover (1970) *J. Natl Cancer Inst.*, 44, 419.                    |
| p-Dimethylanilinobenzene-1-azo-2-naphthalene | M top. |     | Skin                                                | Yamada et al. (1971) *Gann.*, 62, 471.                                     |
| 7,12-Dimethylbenz(a)anthracene  | M i.v. |     | Leukaemia, ovary                                     | Mulay & Saxen (1952) *J. Natl Cancer Inst.*, 13, 1259.                    |
|                                 | R p.o. |     | Liver                                                | Mulay & Longdon (1953) *J. Natl Cancer Inst.*, 14, 571.                    |
| 4'-Fluoro-4-aminodiphenyl      | M p.o. |     | Mammary gland                                        | Geyer et al. (1953) *Cancer Res.*, 13, 503.                                 |
|                                 | R s.c. |     | Kidney, liver                                        | Clayson et al. (1965) *Br. J. Cancer*, 19, 297.                            |
| Imuran                          | M i.m. |     | Thymus etc.                                          | Matthews & Walpole (1958) *Br. J. Cancer*, 12, 234.                        |
|                                 | R p.o. |     | Zymbal gland                                         | Casey (1968) *Blood*, 31, 396.                                             |
| 3-Methylcholanthrene            | M top., s.c. |   | Leukaemia, local                                     | Frankel et al. (1970) *Tox. Appl. Pharmacol.*, 17, 462.                  |
|                                 | R p.o., s.c. |   | Mammary gland, local                                 | Rubin (1971) *Progr. Exp. Tumor Res.*, 14, 138.                           |
| 7-Methylbenz(a)-anthracene      | M s.c. |     | Local                                                | Matsuyama et al. (1963) *Nature*, 197, 805.                                |
|                                 | R s.c. |     | Local                                                | Gruenstein et al. (1966) *J. Natl Cancer Inst.*, 36, 483.                 |
| N-Fluoren-2-y1 acetohydroxamic acid | M p.o. |     | Mammary gland, stomach, liver                        | Millet et al. (1984) *Cancer Res.*, 24, 2018.                             |
|                                 | R p.o. |     | Liver, bladder                                       | Weisburger et al. (1970) *J. Natl Cancer Inst.*, 45, 29.                  |
| N-Isopropyl-a-(2-methylhydrazino)-p-toluamide monochloride | M i.p. |     | Leukaemia, lung                                      | Kelly et al. (1969) *J. Natl Cancer Inst.*, 42, 337.                      |
| N-nitrosobutylethylamine        | M p.o. |     | Mammary gland                                        | Kelly et al. (1968) *J. Natl Cancer Inst.*, 40, 1027.                     |
|                                 | R p.o. |     | Stomach                                              | Schmahl et al. (1963) *Naturwissenschaften*, 50, 717.                     |
| N-nitrosobutyrlurea             | M p.o. |     | Thymus, leukaemia                                    | Thomas & So (1969) *Arzneimittelforschung*, 19, 1077.                     |
|                                 | R p.o. |     | Zymbal gland                                         | Odashima (1970) *Gann.*, 61, 245.                                          |
### I. F. H. PURCHASE

| 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. | Lymphoreticular | Greenblatt et al. (1971) J. Natl Cancer Inst., 46, 1029. |
| | | | Mammary, uterine, liver | Committee on Safety of Medicines (1972) Carcinogenicity tests of oral contraceptives, London; HMSO. |
| 19-Nor-17α-pregn-1,3,5(10)-trien-20-yne-3,17-diol | M | p.o. | Mammary | Garcia et al. (1970) Z. Krebsforch, 74, 179. |
| | R | p.o. | Lung | ||
| | | | Liver | Hueper & Payne (1963) Arch. Env. Hlth, 6, 484. |

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. | 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. | 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. |
| Polyethylene glycol monostearate | M | p.o. | Huerper & 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.