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An Assessment and Categorisation of the Animal Carcinogenicity Data on Selected Dyestuffs and an Extrapolation of those Data to an Evaluation of the Relative Carcinogenic Risk to Man

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SUMMARY

The animal carcinogenicity status of 97 chemicals associated with the dyestuffs industry has been reviewed.

The readily available literature describing animal carcinogenicity studies with these selected compounds was evaluated and the results were classified according to whether they were proven animal carcinogens or not. The degree of confidence that could be associated with that classification was assessed with regard to the current scientific standing of the experiments. In addition, an attempt has been made to extrapolate the results of these animal experiments to the potential human hazard which would be associated with undue exposure to these chemicals.

Only 29 of the 97 chemicals reviewed were considered to be adequately tested for carcinogenicity in animals and it is concluded that there remains a considerable need for an extension of toxicological knowledge of chemicals in use in the dyestuffs industry.

1. INTRODUCTION

The Ecological and Toxicological Association of the Dyestuffs Manufacturing Industry (ETAD) initiated an evaluation of the carcinogenicity to animals of selected dyestuffs with a view to interpreting this information in terms of carcinogenic risk to man. In addition, it was proposed that the survey should be used to provide a basis for the

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selection of representative chemicals of several structural classes for which there was sound biological information to conclude that they were either animal carcinogens or not. These chemicals could then be prepared pure and used in a validation study of short-term predictive carcinogenicity tests from which the most accurate tests could be selected and used to identify and give priority to compounds for future conventional animal studies.

The need for the current review and proposed programme of work to follow was seen to result from deficiencies in current toxicological knowledge and philosophy. The current bland assumption that chemicals shown to produce tumours in animals by any dosing regime were also necessarily human carcinogens and consequently required minimal, or even zero, human exposure before there was 'acceptable risk' needed to be challenged, not only because it was becoming increasingly impossible for chemical manufacturers to operate efficiently with such assumptions, but also because such assumptions are not scientifically justifiable.

2. DATA SELECTION AND REVIEW

As a first step, a list of chemicals for consideration of animal carcinogenicity was established and subdivided into categories of chemical structural class. Appropriate literature was obtained and examined (a total literature search was not undertaken) and the animal data assessed in each case for compliance with the principles outlined below. The chemical was then classified negative or positive with respect to animal carcinogenicity and the classification graded in terms of confidence in the results on a scale ranging from A to E. An attempt was made to give some indication of the possible human risk of cancer induction resulting from chronic exposure to the chemical in question. This extrapolation of the animal data to man must be viewed with a certain degree of scepticism since at this time there are no known criteria established by which such extrapolations can be made scientifically. For the purposes of this study, extrapolation has been made on a subjective basis with a view to generating further discussion and argument. In addition, it has been assumed that if a chemical has been established as an animal carcinogen, i.e. a substance inducing malignant tumours, it represents a potential human hazard, whereas those chemicals inducing only benign tumours (i.e. a tumourigen) represents no human hazard. The degree of hazard has in turn been assessed on an intuitive basis.

3. PRINCIPLES FOR ASSESSING ANIMAL CARCINOGENICITY

3.1. Chemicals tested

The chemical purity or composition of the material should be declared. Ideally only pure materials should be used when assessing a chemical for carcinogenicity but it is accepted that most frequently, commercially available materials have been tested and in the absence of data to the contrary it is assumed that any carcinogenic activity observed is due to the activity of the major chemical component of the material tested and not to an impurity present in the mixture although this may well be a gross and even erroneous oversimplification of the facts.

3.2. Numbers of animals tested and survival rates

Demonstrating the animal carcinogenicity of a potent carcinogenic material can be achieved with relatively few test animals, and if they survive the treatment with the carcinogen until they develop detectable malignant tumours then their subsequent survival is irrelevant as far as the identification of the effect is concerned. For a non-animal carcinogen, a negative effect is almost impossible to define since it can always be argued that the dose, duration of study, number of animals, number of species, number of strains, etc., were insufficient to detect a positive effect. However, it is assumed in this review that if about 25 rodents of each sex per dose level are treated and survive approximately two-thirds of their expected life-time, then the resulting information probably reflects the true experimental carcinogenicity situation. Experiments with non-rodent species have had to be assessed as and when they are used without any preconceived ideas of adequacy of non-rodent studies. There are several cases where, for example, fewer than ten dogs have been kept for several years without tumour induction by the test chemical and it is concluded in the literature that these studies indicate non-carcinogenicity. It is the current author's opinion that these data alone do not provide a satisfactory basis for concluding that there is no carcinogenic risk to man. On the other hand, however, a small number of dogs developing, say, bladder tumours in response to an oral dose of compound strongly suggests, even on its own, that a potentially serious risk of cancer to man could exist if gross exposure should occur.

3.3. Study controls

It is considered essential that all carcinogenicity assays should be controlled by including in the study a number of untreated animals at least equal to that in each dose level. If this is not done, a true assessment of the significance of an apparent increase in normally occurring tumours for that strain is not possible. Even with historical values available for studies in any given laboratory, experience has shown that considerable variation in the frequency of common tumours can occur between control groups in different rooms and over a period of several years the tumour pattern within the untreated population can change considerably. Positive controls using chemicals of a similar chemical group to that being studied are also useful in controlling animal studies, although for the purposes of this assessment it is accepted that these need not be applied in every case.

3.4. Dose

Inevitably, in those studies where no carcinogenic effect is observed, it could be argued that an insufficient dose of the test compound was given to the test animals. In order to circumvent this criticism a sufficiently high dose is sought in which a biological effect has been observed, e.g. reduction in bodyweight gain. If it can be established that such a biological effect took place in the study without the concomitant appearance of malignant tumours, it is assumed that the test material was non-carcinogenic to that species under the circumstances of the study.

An adequate study should contain at least three dose levels of test compound. Ideally a carcinogenic effect should exhibit a dose-related response but failure to demonstrate this dose relationship may not clear a material of carcinogenic activity since it may indicate a plateauing of the response or a changing target organ. If, however, the material is merely toxic and non-carcinogenic, a toxicity-dose response would strengthen the negative, non-carcinogenicity conclusion.

3.5. Route of administration

Several routes or methods of administration of chemicals have been studied by research workers over the years ranging from mixing with diet, through subcutaneous injection, to urinary bladder implantation. In addition, the discovery of promoting agents such as croton oil has

provided scientists with useful models for studies of tumour initiation and progression. From the point of view of assessing the degree of carcinogenicity of a chemical to animals and in turn interpreting that risk to man, only those studies involving routes of application other than urinary bladder implantation, or repeated subcutaneous injection resulting in injection site sarcomas, and those not involving promoting agents or co-carcinogens have been considered as appropriate to this report.

3.6. Duration of animal experiments

The animals under investigation should be available for observation for at least two-thirds of their expected lifetimes, i.e. 16 months for mice and two years for rats, and a good proportion of the animals initially in the study should have remained alive for this period. A study in which most of the animals died due to toxicity of the test compound or for other reasons in less than two-thirds of the expected life-time is unlikely to yield tumours at autopsy and consequently cannot be accepted as being meaningful unless a significant increase of tumours is observed. indicating a positive carcinogenic potential.

3.7. Pathological considerations

In strict etymological terms, an experimental animal chemical carcinogen is a material which will induce carcinomas, i.e. malignant neoplasms, in a significant proportion of animals when they are appropriately exposed to that chemical. However, by careless usage amongst toxicologists, the word 'carcinogen' has become the term used to describe a chemical inducing or enhancing the frequency of either benign or malignant neoplasms. For the purposes of this report, which is directed towards assessing human risk, it is the author's opinion that a distinction must be made between the relevance of induced malignant and benign tumours, the former being considered of much greater significance when assessing risk. Also, no evidence exists to suggest that the mechanism of induction of carcinomas and sarcomas differs, or that there is a significant difference in the consequences of the subsequent tumour invasion and metastases. For convenience, therefore, the term 'chemical carcinogen' will be taken to include chemicals inducing either carcinomas or sarcomas and the term 'tumourigen' will be used for chemicals inducing benign tumours only.

The exact parameters of the ideal chronic toxicity study continue to be debated on both sides of the Atlantic but it is the author's opinion that in a meaningful carcinogenicity study the target organs should be identified. An increase in the frequency of normally occurring tumours, particularly if those tumours are histologically benign, is not considered sufficient grounds for classifying a compound as an animal carcinogen. It is self-evident therefore that considerable gross pathology and histopathology need to be carried out and reported in detail before any valid conclusion can be drawn. The author accepts, however, that it has been the practice to report only the gross pathology together with histopathology of suspected target organs when publishing the results of chronic animal studies, and in such cases the reports have to be assessed at face value taking into account the written opinion of the investigators.

3.8. Number of species

The significance of a positive carcinogenic effect of a chemical in terms of its possible risk to man can be considerably strengthened if the chemical can be shown to be carcinogenic to more than one species of animal. However, because of the longevity and consequent expense incurred in keeping non-rodent species for chronic toxicity studies, the number of animals used in non-rodent studies tends to be smaller than that needed statistically to confirm a negative carcinogenic potential. When made, these studies tend to confound rather than to clarify the situation in some cases.

3.9. Evidence of human carcinogenicity

Any evaluation of the risk to man of chemical carcinogens must include a consideration of results derived from human epidemiology studies where these are available. In this report, however, no attempt has been made to re-evaluate the results of such studies; the conclusions of the relevant papers describing human effects have been taken at face value.

4. CLASSIFICATION OF ANIMAL CARCINOGENICITY

Six categories of animal carcinogens and non-carcinogens have been defined and applied in this report and these have been derived from a

consideration of the foregoing arguments concerning the adequacy of chronic animal carcinogenicity experiments. Whilst it is accepted that the system outlined below cannot be universally applied to the literature cited it has been applied in spirit and has, in general terms, been intended to reflect a grading in confidence from A (good) to E (poor).

Class A: The chemical has been tested in at least two species of animals resulting in generation of non-conflicting data. The experiments have had sufficient animals under test with a sufficient number surviving for approximately two-thirds of their expected life-span. The material has been chronically applied and a range of doses has been used up to and including a level where some biological effect of the compound was seen. Any route of application and dosing regime has been accepted with the exception of repeated injection (subcutaneous or intra-muscular) or urinary bladder implantation which have not been regarded as meaningful in the context of chemically induced neoplasia. In the case of a positive response a target organ has been identified and the induced tumours have been diagnosed as malignant for a chemical to be classified as a Class A carcinogen.

Class B: The chemical has been tested in a suitable bioassay as described above in Class A except that meaningful data have been generated for one species only.

Class C: The chemical has been tested in a bioassay system but with not quite sufficient numbers of test animals (i.e. less than about 25 per group) and/or too many premature deaths have occurred for results to be conclusive. In the case of a positive result or trend, an increase in the total number of animals with malignant tumours has been observed but without an obvious target organ being identified.

Class D: The chemical has been tested in several animal assays, each of which individually is not adequate for conclusions to be drawn, but it is believed that these assays taken together represent sufficient evidence for an opinion to be drawn. In the case of a positive trend being identified this would include evidence drawn from experiments showing an increase in the frequency of, and/or a reduction in the induction time of, the appearance of tumours otherwise 'spontaneously' appearing in the control group, whether or not the 'induced' tumours were malignant.

Class E1: The chemical has been tested in a bioassay using a method

considered inappropriate for the evaluation of chemical carcinogenicity, e.g. by urinary bladder implantation, or with too few test animals having been assayed, or the conclusion of the study has been based on otherwise scientifically dubious information. In the event of a positive effect the results are tenuous but do not preclude the possibility of some carcinogenic activity.

Class E2: There are not sufficient data to permit any rational judgement to be made with respect to carcinogenicity.

5. ASSESSMENT OF HUMAN RISK

One of the objectives of the current report was to assign a degree of risk to the material in question by extrapolating the animal evidence of carcinogenicity to the human situation. Whilst it is appreciated that the degree of risk associated with exposure to a carcinogen is going to vary between the various applications and uses and the different exposures of populations to that chemical, and that individuals vary in their response to the exposure, it is also recognised that the manner in which some chemicals elicit a carcinogenic response from animals, either by virtue of their route of administration or other special circumstances such as in the response to restricted or modified diet, may be of little consequence to man. Also, when attempting to establish the human risk associated with exposure to the chemical in question, it has often been assumed that a potent rodent carcinogen will also be a potent human carcinogen and this concept of relating animal dose response relationships is commonly used in setting no-effect levels with a suitable safety margin of several orders of magnitude. In the absence of firm scientific evidence to the contrary this guideline should rightly be followed but it is questioned here on two counts. These are:

(a) It is not established that in all cases a potent carcinogen to one species is similarly potent (if indeed it is a carcinogen at all) in a second.
(b) It is not established that the mode of application of the test substance resulting in the description 'potent carcinogen' is relevant to its likely potency in the same or in a second species by an alternative route of exposure.

In other words it is questioned, for example, if a chemical which is a potent carcinogen to the mouse by repeated intraperitoneal injection is as much a risk to man when absorbed by inhalation or by exposure of the skin.

The concept of carcinogenic potency (i.e. a consideration of the frequency of tumour induction in a dosed population expressed as tumours per animal or as numbers of animals with tumours, the size and frequency of the dose applied, the induction period, the malignancy of the tumours induced, etc.) has been used in this report when assessing animal carcinogenicity *per se*. However, little regard has been placed on extrapolating this to the human situation. It has been assumed that if a chemical has been established as a carcinogen, but not if only a tumourigen, that it represents a potential human carcinogenic hazard. The degree of hazard has then in turn been assessed on an intuitive basis.

That being the case, the following assessment of degree of risk is directed at separating animal carcinogenicity into that which is thought to be of significance for man and that which is thought not to be so relevant in the light of current knowledge. In other words, proven animal carcinogens are further classified as potential human carcinogens or non-carcinogens. When no reliable data were available for assessment no evaluation of carcinogenicity is made. No attempt has been made to discriminate between carcinogens which may be a risk to humans by virtue of their use or application and those which could be claimed not to represent a risk during use. Such a classification is beyond the scope of this report.

6. CHEMICALS SELECTED AND GROUP SEGREGATION

Chemicals involved in the dyestuffs industry were selected from the current volumes of *Compounds Tested for Carcinogenicity* (NIEHS, USA) and the IARC *Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man*. These chemicals have been divided into monoazo, bisazo and miscellaneous compounds.

Table 1 lists the products reviewed, summarises animal test data and gives an assessment of the human carcinogenic risk which may be associated with excessive or protracted exposure to the chemical.

7. CONCLUSIONS AND RECOMMENDATIONS

Of the 97 chemicals reviewed and assessed for animal carcinogenic properties, only 29 were sufficiently well tested to warrant a Class B or better categorisation of test confidence. These included seven carcinogens and seven non-carcinogens in the monoazo group of chemicals, three carcinogens and five non-carcinogens in the bisazo group and two carcinogens and five non-carcinogens in the miscellaneous group.

Two animal carcinogens, Direct Blue 53 (CI 23860) and Direct Blue 14 (CI 23850), were thought not to represent a risk of carcinogenicity to humans under normal circumstances since these chemicals were shown to be carcinogens in rats only by intraperitoneal injection and were not carcinogens by other routes of dosing to rats or mice. Direct Blue 6 (CI 22610), however, appears to be extremely potent as a hepatocarcinogen to rats, producing a high incidence of tumours in only 13 weeks.

The paucity of sound animal carcinogenicity data in the dyestuffs field is of concern on two counts. These are:

(1) Legislative measures controlling the distribution and use of many dyestuffs are based on poor or erroneous information.
(2) There are insufficient animal data in the field to assess the overall human cancer risk associated with the dyestuffs industry.

It is recommended (a) that the 29 compounds identified above be obtained as pure compounds and used to establish a screen with which to predict the animal carcinogenicities of the remaining compounds used in the industry, (b) to extend the current search for compounds which have been adequately tested for animal carcinogenicity in order to broaden the baseline for (a) above, and (c) to undertake conventional animal carcinogenicity studies within the guidelines advocated for category B experiments with representative dyestuffs in order to provide a foundation for the future re-assessment of carcinogenic risk to humans of various dyestuffs.

ACKNOWLEDGEMENTS

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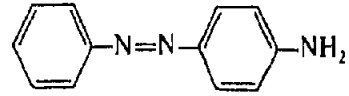
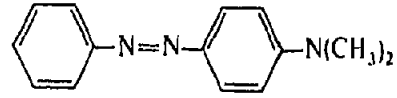
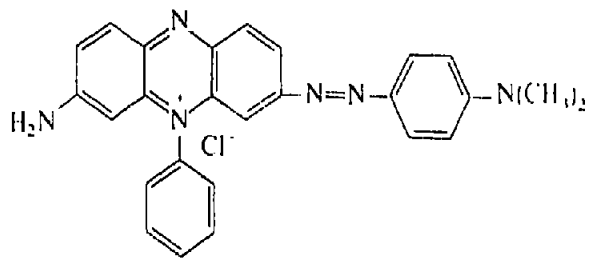
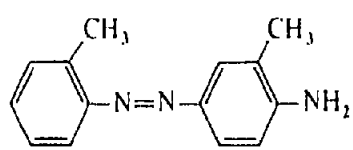
Table 1
Summary and Analysis of Animal Carcinogenicity Data Reviewed

Product number	*Product name*	*Structure and available data*
Monoazo Compounds		
1	CI 11000 Solvent Yellow 1	
		16 male rats on restricted diet dosed *per os*. 7 developed liver tumours, 2 of which were malignant. None in controls.[75] 32 male rats fed 800 mg/kg. No tumours after 60 weeks.[107] 6 rats skin painted and developed tumours.[33] 29 mice on restricted diet were insensitive.[75] See also ref. 20. Class E1. Probably carcinogenic. Assessment of risk complicated due to peculiar effect of restricted diet. However, production of skin tumours in rats following topical application is of concern in assessment of risk to man.
2	CI 11020 Solvent Yellow 2	
		85 male rats fed 0·06% diet. Induced 57 liver tumours (16 hepatomas, 20 adenocarcinomas and some mixed tumours).[31] 85 male rats fed 0·06% diet. Induced 57 tumours of liver of which 14 metastasised.[88] 6/6 skin tumours induced in rats by topical application.[33] Other studies include establishment of non-carcinogenicity to mice and possible bladder tumourigenicity in dogs. Numerous references quoted in IARC monographs. The carcinogenicity of dimethylaminoazobenzene (DAB) is at first sight diet-dependent in rats. The fact that it is non-carcinogenic to the mouse suggests species specificity, but a somewhat poor study in dogs also suggests trans-species activity.

(continued)

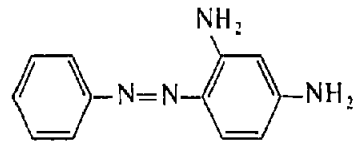
Table 1—*contd.*

Product number	*Product name*	*Structure and available data*
		Consequently, the skin exposure study in rats in which skin tumours were produced may reflect the human situation. See also refs 30 and 113. Positive (carcinogen) class B. Possible carcinogenic risk to man.
3	CI 11045 Basic Dye	 15 rats dosed by subcutaneous injection 5 mg every 2 weeks (pure compound used in the study). No tumours developed after 900 days. Also 20 rats fed 20 mg daily for 670 days. No tumours reported but no experimental details provided.[103] Class E1. No evidence of carcinogenic risk to man.
4	CI 11160 Solvent Yellow 3	 Several hundred mice dosed by subcutaneous injections of crystals. Haemangio-endotheliomas and injection site sarcomas induced. Some hepatomas and lung adenomas also induced. Injection site important in determining site of tumour and target organ.[1]

Skin application in mice is reported in several studies to produce liver tumours and topical application to pregnant mice has been shown to produce tumours in the F1 generation.[46]
50 Syrian hamsters dosed *per os* (diet containing 1 000 mg/kg) for 49 weeks. High frequency of malignant liver tumours induced.[122]
10 dogs fed 5 or 20 mg/kg bw/day. Malignant tumours induced in lower dose in 62 months.[98] See also ref. 77

Positive (carcinogen) class A. Significant risk of cancer to man.

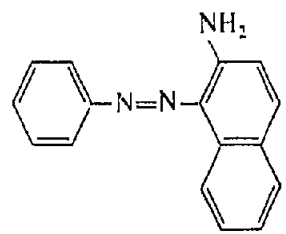
5 CI 11270:1 Solvent Orange 3



No reliable data reviewed. See refs 7, 70, 73.

Class E2. No evidence of carcinogenic risk to man.

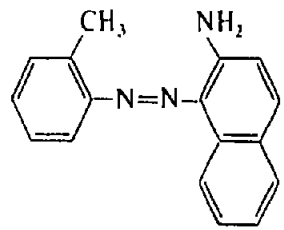
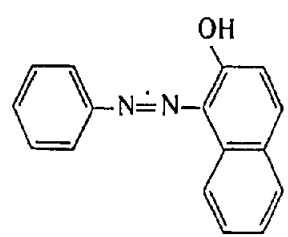
6 CI 11380 Solvent Yellow 5



Several mice dosed by various routes. Too small a study but no tumours reported.[12]
22 rats (male and female) fed dye in diet. Study report not detailed but no tumours induced.[118]
Hamster cheek pouch study showed no carcinogenic properties.[21]
Group of 24 rats (male and female) fed 500 and 1 000 ppm increased to 2 500 ppm. No tumours induced. Dogs dosed similarly did not develop tumours. Also, rat subcutaneous injection study was negative.[63] See also refs 13, 117 and 120.

(continued)

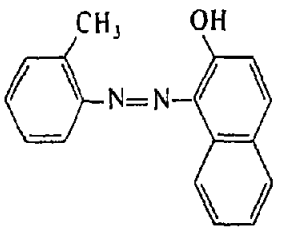
Table 1—*contd.*

Product number	*Product name*	*Structure and available data*
		Groups of 50 rats dosed *per os* 300, 15000 and 30000 mg/kg diet. No tumours induced.[2]
		Negative (non-carcinogen) class A. No evidence of carcinogenic risk to man.
7	CI 11390 Solvent Yellow 6	
		25 male and 25 female rats fed 0·03% diet. Survived 65 weeks without tumour induction.[2] 12 male and 12 female rats dosed orally without effect, but subcutaneous injections produced injection site sarcomas.[63] See also refs 3, 4 and 102.
		Negative (non-carcinogen) class C. No evidence of carcinogenic risk to man.
8	CI 12055 Solvent Yellow 14	
		Bladder implants in mice caused tumours.[14,18] 82 mice dosed orally did not develop tumours.[18]

Mice receiving subcutaneous injections developed hepatomas and some malignant liver tumours. Study not well reported and no controls.[78]
20 rats orally dosed for 2 years. 8 survived without tumour induction.[52] See also refs 10 and 17.

Negative (non-carcinogen) class C. Risk to man probably nil, only evidence of carcinogenicity is by subcutaneous injection.

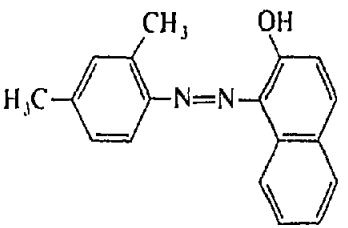
9 CI 12100 Solvent Orange 2



40 rats per group dosed 0·03, 1·5 and 3·0% of diet for 65 weeks without tumour induction. Too short to be conclusive.[3]
15 male and 15 female mice fed 1000 mg/kg for 1 year. 1 carcinoma, 9 benign neoplasms of intestine induced. Also similar tumours induced by subcutaneous injection.[8]

Positive (carcinogen) class C. Possible carcinogenic risk to man.

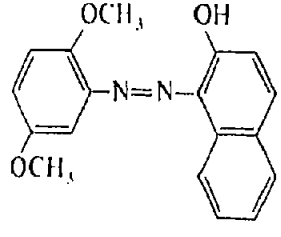
10 CI 12140 Solvent Orange 7



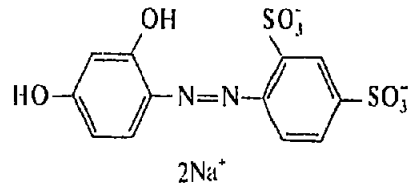
Fed to rats in diet at 0·03, 0·75 and 1·5% levels for 65 weeks. No tumours induced but high mortality and early deaths, particularly at high doses. Data difficult to interpret.[3] See also ref. 102.

(continued)

Table 1—*contd.*

Product number	*Product name*	*Structure and available data*
		30 mice dosed orally and by subcutaneous injection. 17/60 with lymphomas and 4 with benign intestinal tumours. Only 5/60 controls with lymphomas.[8] See also ref. 17. Negative (non-carcinogen tumourigen to mice) class C. No evidence of carcinogenic risk to man.
11	CI 12156 Solvent Red 80	 Groups of 50 male and 50 female mice fed diet containing 0·01, 0·03, 0·1, 0·3, 1·0 and 3·0% for 80 weeks. Toxic at high doses but no tumours induced.[113] Groups of 50 male and 50 female mice dosed by 50 subcutaneous injections for 80 weeks. Increase in total malignant tumour incidence in females only.[112] Mice and rats dosed in diet 0·05% and 0·25%. Some evidence of bladder tumour induction.[22] Not a good study but disturbing in light of tumours induced by bladder implants.[17] Positive (carcinogen) class C. Probably no significant risk of cancer to exposed humans.

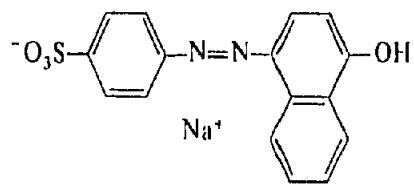
12 CI 14275 Acid Dye



110 rats of 5 strains fed 24 mg/day for life. Experimental details and pathology not reported. No tumours induced.[26]

Negative (non-carcinogen) class D. No evidence of carcinogenic risk to man.

13 CI 14600 Acid Orange 20



20 mice dosed orally without tumour induction.[16]
48 rats of both sexes fed diet containing 0·5 and 1·0%. No tumours induced, poorly reported study.[9]
18 rats received subcutaneous injections and 6 developed injection site sarcomas.[102]

Class E1. No evidence of carcinogenic risk to man.

14 CI 14700 Food Red 1

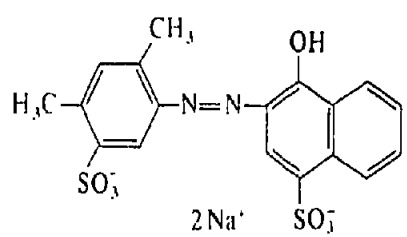
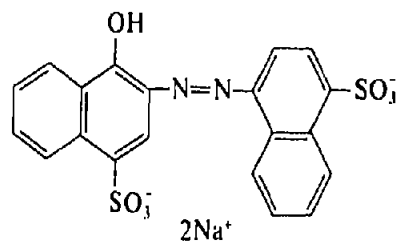
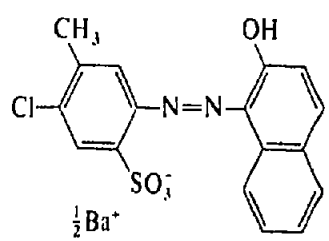


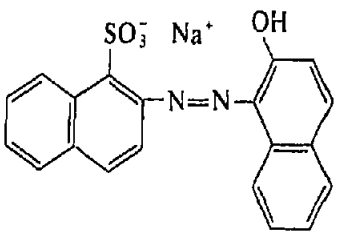
Table 1—*contd.*

Product number	*Product name*	*Structure and available data*
		Mice dosed orally and by subcutaneous injection without tumour induction. 24 male and female rats dosed by diet 0·5, 1·0, 2·0 and 5·0% without tumour induction. 5 beagle dogs dosed *per os* without tumour induction.[24] See also ref. 131. Negative (non-carcinogen) class A. No evidence of carcinogenic risk to man.
15	CI 14720 Acid Red 14	 30 male and female mice received subcutaneous injections. 7/30 observed with lymphomas but this is the same as in controls.[8] 30 male and female mice fed 100, 500, 2 500 and 12 500 mg/kg for 80 weeks. No treatment-related tumours induced.[83] Also, rats dosed *per os* and by subcutaneous injection without effect.[55] Negative (non-carcinogen) class B. No evidence of carcinogenic risk to man.
16	CI 15585:1 Pigment Red 53:1	

Groups of 50 male and female rats dosed *per os* at 1·0, 0·25, 0·05 and 0·01 % diet for 2 years. Splenomegaly at top dose but no tumours reported.[23] Lack of reported effect from dye when used in lipsticks supports non-carcinogenic classification.

Negative (non-carcinogen) class B. No evidence of carcinogenic risk to man.

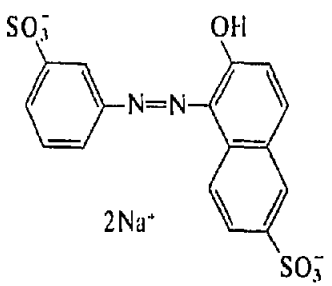
17 CI 15630 Pigment Red 49



25 male and 25 female rats per group dosed in diet 0·01, 0·05, 0·25 and 1·0 % for 2 years. No tumours induced.[25]

Negative (non-carcinogen) class B. No evidence of carcinogenic risk to man.

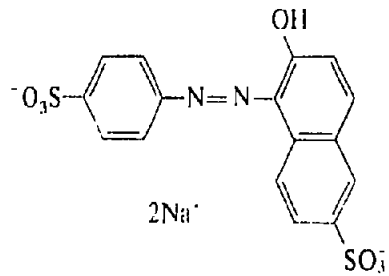
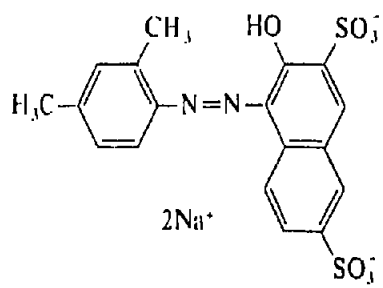
18 CI 15980 Food Orange 2



No useful data reviewed. See ref. 53.

Class E2. No evidence of carcinogenic risk to man.

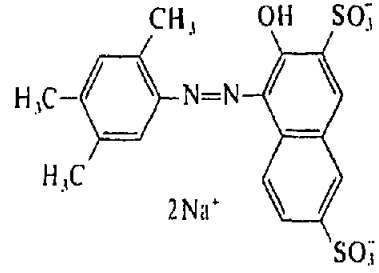
Table 1—*contd.*

Product number	*Product name*	*Structure and available data*
19	CI 15985 Food Yellow 3	
		30 mice dosed orally gave apparent increase in incidence of lymphomas.[8] 30 male and 30 female mice fed 2000, 4000 and 16000 mg/kg diet without tumour induction.[47] 3 good rat studies reported in IARC monographs with negative results. See also ref. 131. Negative (non-carcinogen) class D. No evidence of carcinogenic risk to man.
20	CI 16150 Acid Red 26	
		10 rats fed 4% in diet.[131] 15 male and 15 female mice dosed orally. Increased incidence of lymphomas reported.[8]

20 rats per group dosed 0·2, 1·0 and 5·0% diet. Livers reported to be pre-adenomatous but not malignant.[66]
50 male and 50 female mice per group fed 2000, 10000 and 50000 mg/kg diet. A dose response of adenomas and carcinomas in livers was observed.[67] See also refs 15, 16, 38.

Positive (carcinogen) class B. Dye shown to be carcinogenic in mouse by oral dosing causing liver tumours and possibly non-malignant intestinal tumours, therefore must be considered as potential carcinogenic risk to man.

21 CI 16155 Acid Dye



30 rats dosed 0·3, 1·0 and 3·0% diet. 90 control rats. Metastatic tumours produced in liver in dose-related manner.[44]
50 male and 50 female mice dosed in diet. Liver tumours reported but no good control data. Also rats with similar response.[64]

Positive (carcinogen) class B. Possible carcinogenic risk to man.

22 CI 16185 Acid Red 27

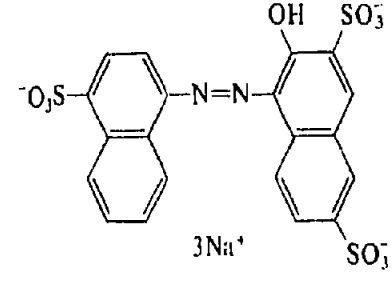
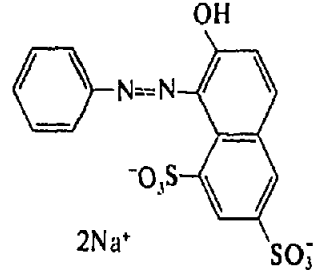
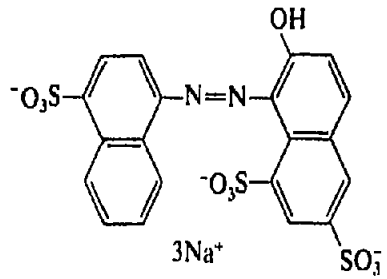


Table 1—*contd.*

Product number	*Product name*	*Structure and available data*
		20 mice dosed orally without effect.[16] 10 rats dosed orally with suggestion of 1 lymphosarcoma. 18 rats dosed by subcutaneous injection without effect.[104] Several other studies with rodents reporting carcinogenicity, but information conflicting and interpretation impossible.[131,135] Class E1. No evidence of carcinogenic risk to man.
23	CI 16230 Acid Orange 10	 20 mice dosed orally for life without effect.[16] Also 113 male and 78 female mice dosed orally for life resulting in 12 and 15 animals respectively with tumours, but this incidence was about the same as that in the controls.[132] Class E1. Mouse studies not adequately reported for full evaluation but suggests non-carcinogenic risk for man.

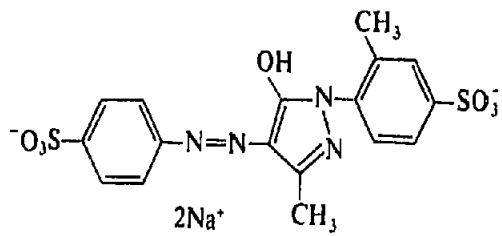
24 CI 16255 Acid Red 18



Chronic dietary study in mice with doses up to 1·25% diet showed no effect.[97]

Negative (non-carcinogen) class B. No evidence of carcinogenic risk to man.

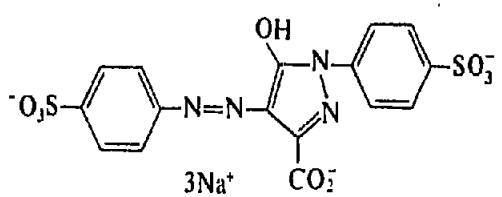
25 CI 19020 Acid Yellow 18



No relevant data reviewed.

Class E2. No evidence of carcinogenic risk to man.

26 CI 19140 Acid Yellow 23

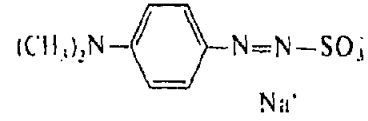
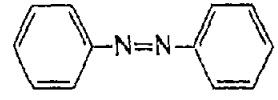


24 rats (male and female) per group fed diet containing 0·5, 1·0, 2·0 and 5·0% for 2 years. Good survival without tumour induction.[27] See also ref. 131.

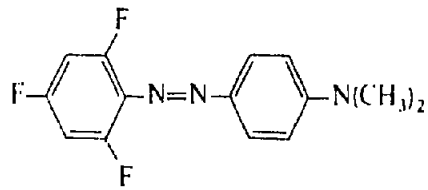
Negative (non-carcinogen) class B. No evidence of carcinogenic risk to man.

(continued)

Table 1—*contd.*

Product number	*Product name*	*Structure and available data*
27	Dimethylaminobenzene diazo sodium sulphonate	 Dietary study in rats at 1 000 mg/kg for 12 months. Hepatomas similar to those induced by Product No. 2 observed.[51] Groups of 20 rats fed 1·35 or 4·0 mM/kg diet for 15 months. No induced tumours but study too short to be conclusive.[95] Positive (carcinogen) class C. Animal data contradictory; however, negative study too short to be conclusive. Therefore must assume a hepatocarcinogen to rats and therefore could be of risk to humans if ingested. Fenaminosulf (a formulation containing 30–35% Product 27) was tested recently by the NCI and found to be non-carcinogenic to rats and mice by the oral route.[76] The classification shown here should therefore be more appropriately 'Negative (non-carcinogenic) Group A'.
28	Azobenzene	 66 Sherman strain rats (all female) dosed with 30 mg technical grade azobenzene by repeated SC injection for life. Benzidine used as positive control. No tumours induced.[114] Innes *et al.*[68] dosed 18 mice per sex with subcutaneous injections and duplicate numbers[65] by oral dosing. An apparent increase in hepatomas by oral dosing was observed but data inconclusive. Class E1. No evidence of carcinogenic risk to man.

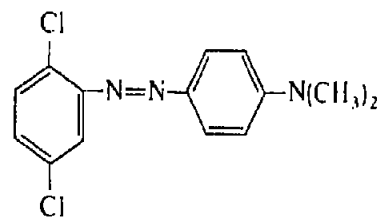
29 2,4,6-Trifluoro-4′-(dimethylamino)-azobenzene



16 rats fed 0·066% reducing to 0·049% diet for 3 months. Kept 2 months longer. 13/15 survivors with liver tumours.[84]

Positive (carcinogen) class B. Possible carcinogenic risk to man.

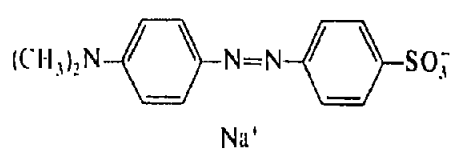
30 2,5-Dichloro-4′-(dimethylamino)-azobenzene



No reliable data reviewed. See ref. 96.

Class E2. No evidence of carcinogenic risk to man.

31 4-(Dimethylamino)azobenzene-4′-sulphonic acid

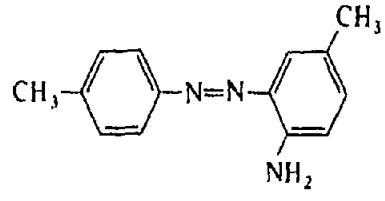
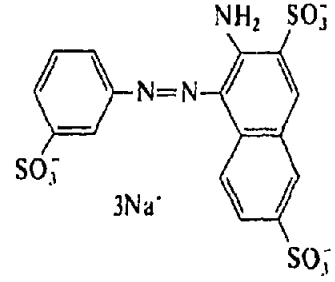
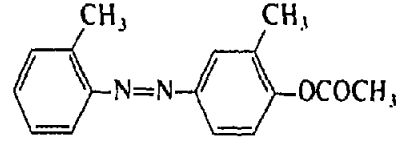


No reliable data reviewed. See ref. 74.

Class E2. No evidence of carcinogenic risk to man.

(*continued*)

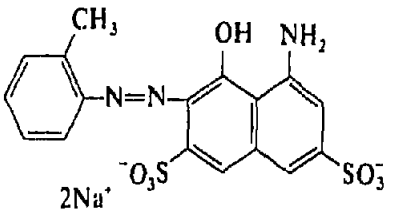
Table 1—*contd.*

Product number	*Product name*	*Structure and available data*
32	4-Aminoazotoluene	
		No relevant data reviewed. See ref. 72.
		Class E1. No evidence of carcinogenic risk to man.
33	3-Amino-4-(3-sulphonylazo)-2,7-naphthalene disulphonate	
		10 rats fed diet containing 0·1% and 0·02%. No tumours induced in 410 days.[53]
		Class E1. No evidence of carcinogenic risk to man.
34	4'-Acetoxy-2,3'-dimethylazobenzene	

31 rats dosed *per os* in diet. No tumours reported.[99]

Class E1. No evidence of carcinogenic risk to man.

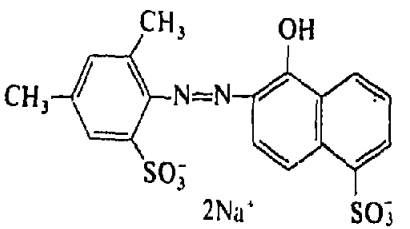
35 Semi-Trypan Blue



No useful data reviewed. See ref. 32.

Class E2. No evidence of carcinogenic risk to man.

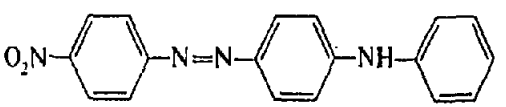
36 2-(6-Sulpho-2,4-xylylazo)-1-naphthol-5-sulphonic acid



10 rats fed dye 410 days in diet without tumour induction. Study too short and too few rats to be conclusive.[53]

Class E1. No evidence of carcinogenic risk to man.

37 4-(4'-Nitrobenzeneazo)-diphenylamine

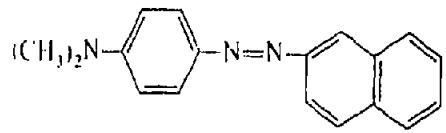
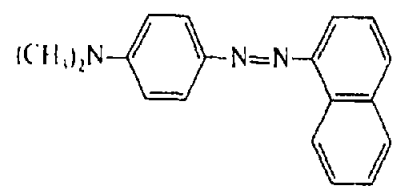


20 rats fed 0·1% in diet. Fibroadenomas of breast developed in 4 animals in 2 years.[52]

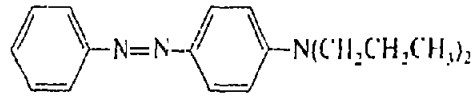
Class E1. Small potential risk of cancer to exposed humans.

(*continued*)

Table 1—*contd.*

Product number	*Product name*	*Structure and available data*
38	(4-Dimethylamino)benzeneazo-2-naphthalene	
		57 mice (male and female) topically dosed with 1% solution showed tumour induction.[89] 51 rats (male and female) dosed orally, developed liver tumours with metastases.[90] Positive (carcinogen) class A. Represents possible carcinogenic risk to man.
39	(4-Dimethylamino)benzeneazo-1-naphthalene	
		80 rats (males) fed 0·075% of diet. 36 developed liver tumours (26 hepatomas and 5 adenocarcinomas + 6 undifferentiated liver carcinomas).[31] 80 rats (males) fed 0·075% in diet. 36 developed tumours, some with metastases.[86–88,94] 80 rats (males) dosed *per os*. 3 developed squamous carcinoma of the forestomach, 8 developed mammary tumours, 1 described as a fibrosarcoma.[85] Positive (carcinogen) class B. Possible carcinogenic risk to man.

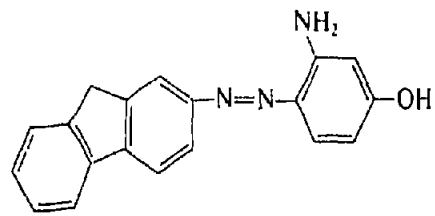
40 4-(Dipropylamino)azobenzene



10 rats dosed *per os* up to 207 days. No tumours induced.[116]

Class E1. No evidence of carcinogenic risk to man.

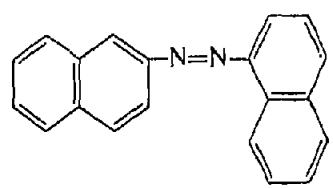
41 2'-Amino-4'-hydroxybenzeneazo-2-fluorene



62 rats dosed topically (36 x 0·1 mg). No tumours in stomach.[110]

Class E1. No evidence of carcinogenic risk to man.

42 1,2-Azonaphthalene

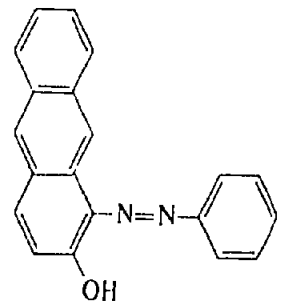
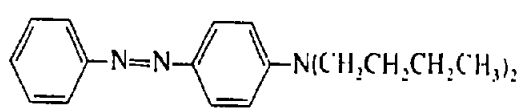


Recrystallised material (mp 144–145 °C) applied to mice by subcutaneous injection *per os* and topically. No tumours induced but pathology and study poorly described.[16]

Class E1. No evidence of carcinogenic risk to man.

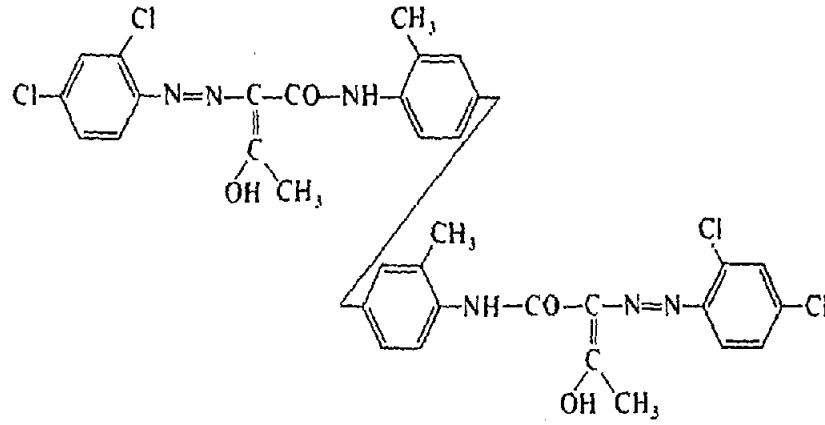
(continued)

Table 1—*contd.*

Product number	*Product name*	*Structure and available data*
43	Phenylazo-2-anthrol	 30 mice of both sexes dosed by subcutaneous injection. Injection-site sarcomas induced and evidence of 1 or 2 squamous carcinomas of stomach. Data somewhat contradictory.[8] Data available on bladder implantation in mice. All publications suggested tumourigenic activity.[10,15,38] Class E1. No evidence of carcinogenic risk to man.
44	4-(Di-n-butylamino)azobenzene	 10 rats dosed orally 4·8 mg daily for up to 500 days. No tumours induced. Dimethylbenzanthracene (DMBA) used as positive control.[116] Class E1. No evidence of carcinogenic risk to man.

Bisazo Compounds

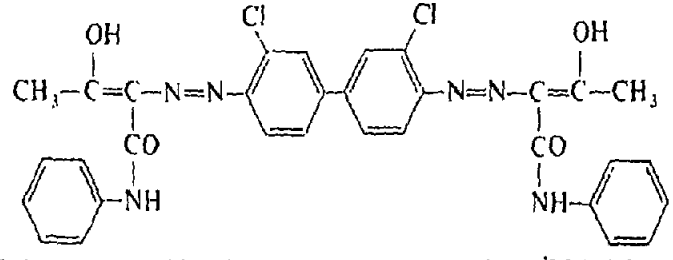
45 CI 20040 Pigment Yellow 16



Purified sample tested in mice and rats at concentrations of 0·1, 0·3 and 0·9% in the feed for 2 years. 100 animals used per test group. No tumours induced, but highest dose did not indicate any biological response and could consequently be considered too low.[81]

Negative (non-carcinogen) class A. No evidence of carcinogenic risk to man.

46 CI 21090 Pigment Yellow 12



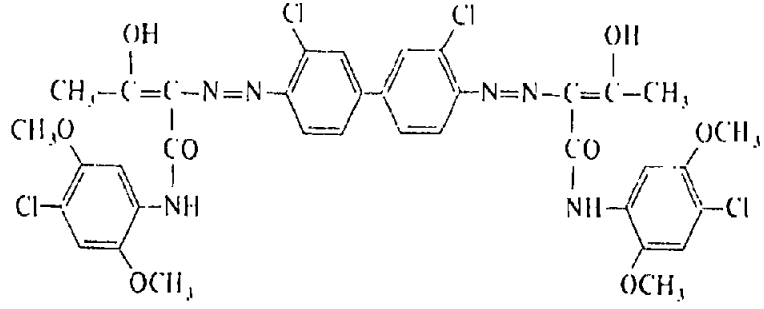
Purified sample tested in mice and rats at concentrations of 0·1, 0·3 and 0·9% in the feed for 2 years. 100 animals used per test group. No tumours induced, but highest dose did not indicate any biological response and could consequently be considered too low.[81]

Negative (non-carcinogen) class A. No evidence of carcinogenic risk to man.

(continued)

Table 1--*contd.*

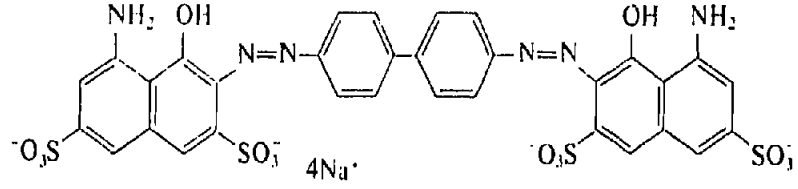
Product number	*Product name*	*Structure and available data*
47	CI 21108	Pigment Yellow 83



Purified sample tested in mice and rats at concentrations of 0·1, 0·3 and 0·9% in the feed for 2 years. 100 animals used per test group. No tumours induced, but highest dose did not indicate any biological response and could consequently be considered too low.[81]

Negative (non-carcinogen) class A. No evidence of carcinogenic risk to man.

48	CI 22610	Direct Blue 6

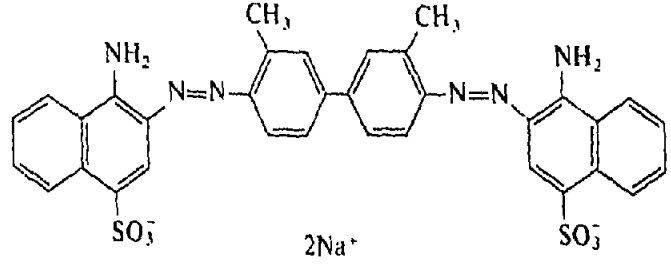


90% pure sample dosed to 20 rats by repeated subcutaneous injections (200 mg in all). 2 injection site sarcomas induced.[32]

NCI 13 week study in rats and mice produced hepatocellular carcinomas in rats only,[100] but see also ref. 101.

Positive (carcinogen) class B. Possible carcinogenic risk to man.

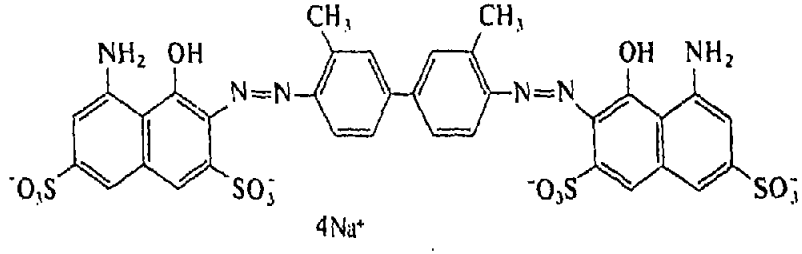
49 CI 23500 Direct Red 2



23 Wistar rats (male and female) dosed 1 ml 2% aqueous solution by intraperitoneal injections every 2 weeks for 7 months. Trypan Blue used as positive control. No toxic effect observed during short study period.[91]

Negative (non-carcinogen) class C. No evidence of carcinogenic risk to man.

50 CI 23850 Direct Blue 14

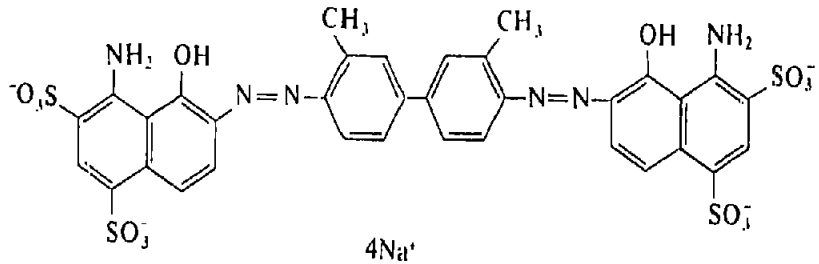
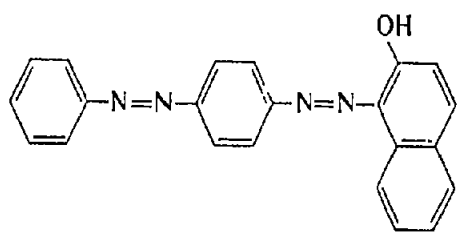


Subcutaneous injection into rats induces malignant tumours in 8 months.[91]
Mice not susceptible.[123]
Numerous other studies confirm carcinogenicity to rats by injection and suggest impurity is active agent.[12,13,35,36]

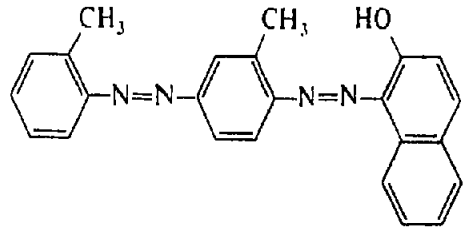
Positive (carcinogen) class B. Unlikely to be carcinogenic risk to man because of unusual effect in rats only.

(*continued*)

Table 1—*contd.*

Product number	*Product name*	*Structure and available data*
51	CI 23860 Direct Blue 53	 25 male and female Wistar rats dosed intraperitoneally with 1 ml % aqueous dye every 2 weeks for 8 months. 10 histiocyte liver tumours and 1 reticulum cell sarcoma induced.[91] Positive (carcinogen) class B. Risk to man probably negligible since this appears to be specific to rats by intraperitoneal injection.
52	CI 26100 Solvent Red 23	 83 male and 54 female mice dosed orally without tumour induction.[132] See also ref. 58. Class E1. No evidence of carcinogenic risk to man.

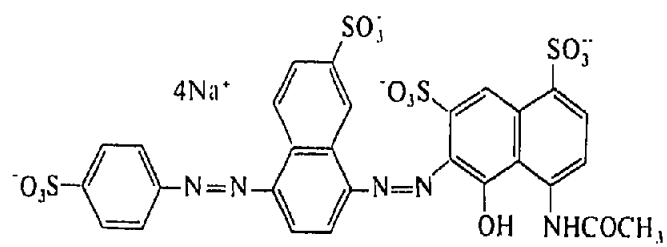
53 CI 26105 Solvent Red 24



No reliable data but reported to have, on the mouse, no effect by oral route,[132] and no effect by skin application.[29]
Rats and rabbits reported briefly in IARC monograph No. 8. See also refs 127, 129, 131.

Negative (non-carcinogen) class D. No evidence of carcinogenic risk to man.

54 CI 28440 Food Black 1

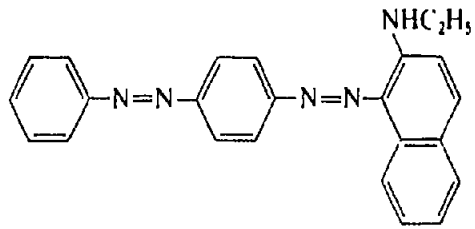
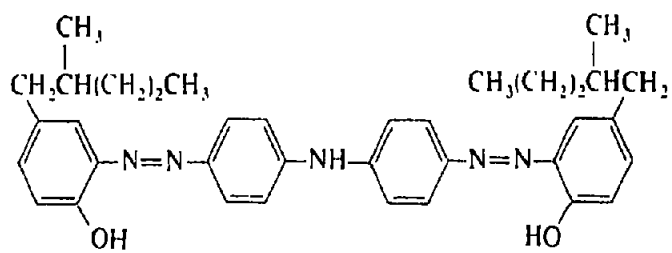


10 rats dosed *per os* in diet. No tumours at 410 days.[53]
48 rats per group dosed 100, 5 000 and 10 000 ppm in diet for 2 years. No evidence of carcinogenicity.[42]

Negative (non-carcinogen) class B. No evidence of carcinogenic risk to man.

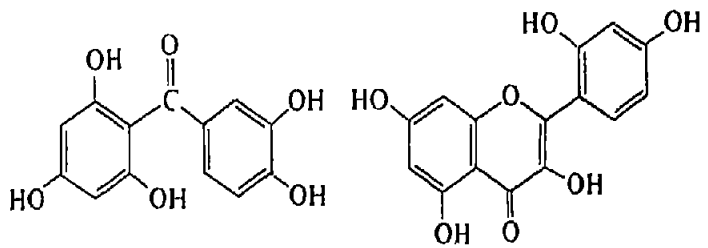
(continued)

Table 1—*contd.*

Product number	*Product name*	*Structure and available data*
55	*N*-Ethyl-1-((*p*-(phenylazo)phenyl)azo)-2-naphthylamine	
		20 rats dosed by 0·1% diet. 5 alive after 2 years. No tumours induced.[52]
		Negative (non-carcinogen) Class C. No evidence of carcinogenic risk to man.
56	Diphenylamino-4,4'-bis-(1-azo-2-hydroxy-5-isohexylbenzene)	
		20 rats fed 0·1% in diet. No tumours reported.[52]
		Class E1. No evidence of carcinogenic risk to man.

57 Food Brown 2

Monazo dye produced by coupling diazotised naphthionic acid with a mixture of the naturally occurring colorants maclurin (CI 75240) and morin (CI 75660).



maclurin

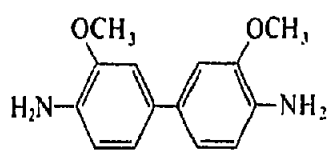
morin

30 male and 30 female rats per group fed 1 000, 3 000, 10 000 and 30 000 ppm for 2 years without tumour induction.[34]

Negative (non-carcinogen) class B. No evidence of carcinogenic risk to man.

Diazo Components

58 CI 37235 Azoic diazo component 48

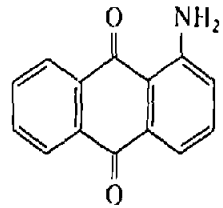
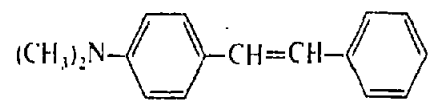
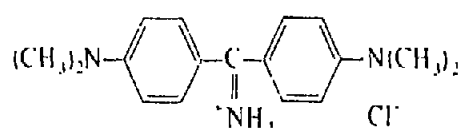


30 rats per group dosed by gavage (1, 3, 10, 30, 100 and 300 mg total). Increased incidence of malignant tumours but no target organ identified.[59] Several rats per sex dosed by gavage (10 mg/day). Numerous ill-defined tumours induced.[134]

Positive (carcinogen) class C. Possible carcinogenic risk to man.

(continued)

Table 1—*contd.*

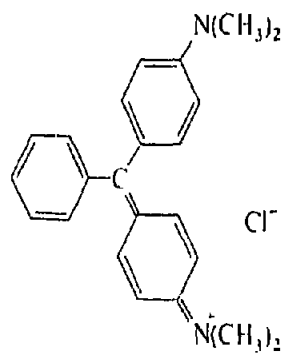
Product number	*Product name*	*Structure and available data*
59	CI 37275 Azoic diazo component 36	 40 rats dosed 10 mg *per os*. Duration only 14 months. No controls and no apparent tumour induction but 6 benign and 2 malignant tumours reported.[80] See also ref. 15. Class E1. No evidence of carcinogenic risk to man.
Stilbene		
60	4-Dimethylaminostilbene	 70 rats dosed 26 mg by intraperitoneal injections. Various tumours developed but mainly cholangiomas and lung tumours.[28] Positive (carcinogen) class B. Possible carcinogenic risk to man.
61	CI 41000 Basic Yellow 2	 49 rats per group dosed *per os* (0, 50, 100 and 200 ppm diet) for 2 years. Only one malignant liver tumour (hepatocellular carcinoma) was reported in the 200 ppm group. There was no dose-related increase in the total number of malignant tumour-bearing animals attributable to auramine.[79]

20 rats per group dosed *per os* (0, 50, 100 and 200 ppm diet) for 3 months followed by up to 2 years observation period. A marginal dose-related increase in the total numbers of malignant tumours was observed in both sexes but no target organ was identified.[79]

Several other studies of doubtful significance are described where mice, rats, rabbits and dogs were fed auramine *per os*. In no case is there any evidence described that suggests malignant tumours are induced except where in the same text a repeated subcutaneous injection study is claimed to induce fibrosarcomas and intestinal carcinomas.[69]

Negative (non-carcinogen) class C. A carcinogenic risk to man was identified in the process of manufacture of auramine and other materials in England[19] but not in Germany.[48]

62 CI 42000 Basic Green 4

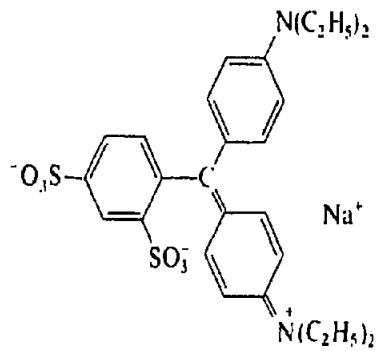
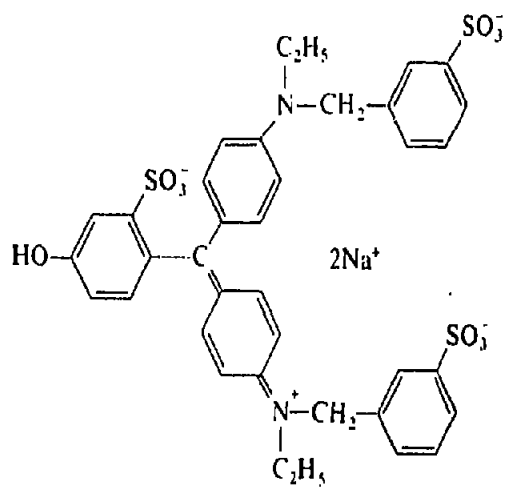


No relevant literature assessed. See ref. 133.

Class E2. No evidence of carcinogenic risk to man.

(continued)

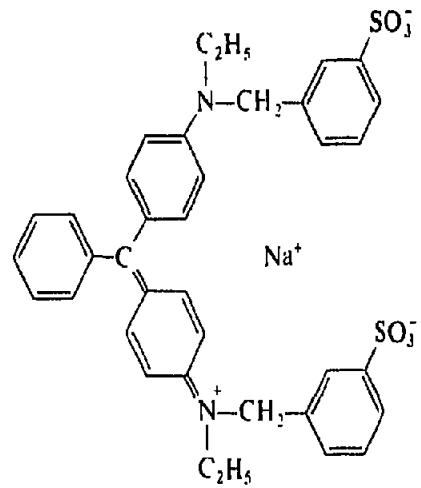
Table 1—*contd.*

Product number	*Product name*	*Structure and available data*
63	CI 42045 Acid Blue 1	 Groups of rats dosed by repeated intramuscular injection. High proportion of rhabdomyosarcomas induced at injection site.[39] See also refs 17, 37, 40, 87, 93. Class E1. No evidence of carcinogenic risk to man.
64	CI 42053 Food Green 3	

50 rats per group dosed *per os* (0·5, 1, 2% diet) for 2 years. No treatment-related tumours reported.[50]
100 mice per group dosed *per os* (1 or 2% diet) for 2 years. No induced tumours.[50]
See also refs 61, 104.

Negative (non-carcinogen) class A. No evidence of carcinogenic risk to man.

65 CI 42085 Acid Green 3

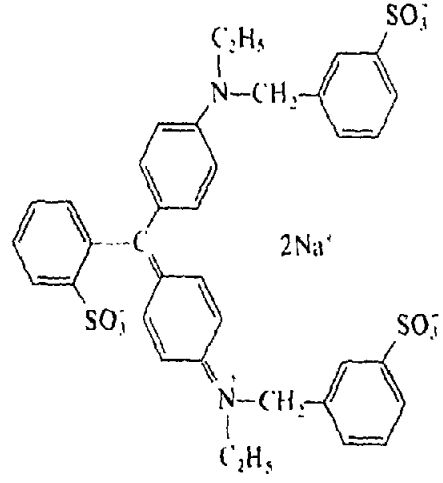


40 rats exposed by skin contact for 100 weeks. Treatment induced some benign mammary tumours.[92]
50 rats per group dosed *per os* (0·5, 1, 2, 5% diet) for 2 years. A dose-related increase in incidence of benign hepatomas was observed. Also, 100 mice dosed *per os* (1 and 2% of diet) but with no induced tumours.[50] See also refs 104, 132.

Negative (tumourigen) class D. Probably represents some tumourigenic risk to man by chronic skin contact.

(continued)

Table 1—*contd.*

Product number	*Product name*	*Structure and available data*
66	CI 42090 Acid Blue 9	

10 rats dosed *per os* (4% diet) for 2 years. No tumours induced.[131]

25 rats dosed by repeated subcutaneous injection (1·07 g). Induced injection site sarcomas. Also 40 rats similarly treated with total of 2·5 g and injection site sarcomas induced.[45]

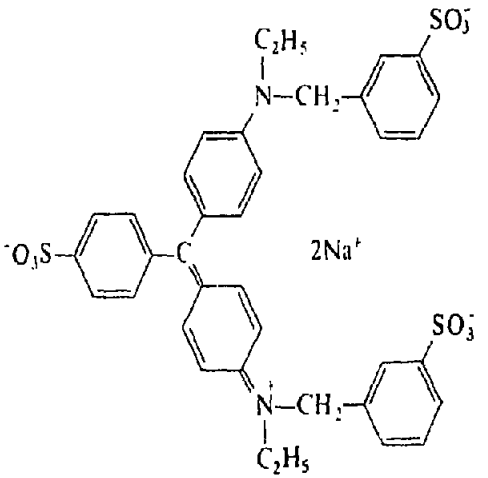
24 rats per group dosed *per os* (0·5, 1·0, 2·0 and 5·0% diet) for 2 years and 18 rats dosed by subcutaneous injection and kept 2 years. No tumours induced.[56]

30 rats per group dosed *per os* (0·03, 0·3 and 3·0% diet) for 75 weeks. No induced tumours were reported.[82] See also ref. 43.

98 mice fed diets containing 0, 0·015, 0·15 or 1·5% dye for 80 weeks. No significant increase in tumour incidence but some indication of induced benign kidney tumours.[111]

Negative (non-carcinogen but possibly tumourigen) class A. No evidence of carcinogenic risk to man.

67 CI 42095 Acid Green 5

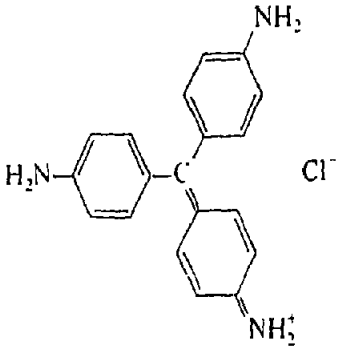


At least 25 rats per group exposed by feeding 0·03, 1·5 and 3·0% diet for 65 weeks. No tumours but short study.[3]

50 rats per group dosed *per os* (0·5, 1, 2 and 5% diet) for 2 years, 100 mice per group fed 1 and 2% diet for 2 years. No treatment-related tumours observed.[50] See also refs 52, 54, 57, 61, 102, 104, 115, 131.

Negative (non-carcinogen) class A. No evidence of carcinogenic risk to man.

68 CI 42500 Basic Red 9

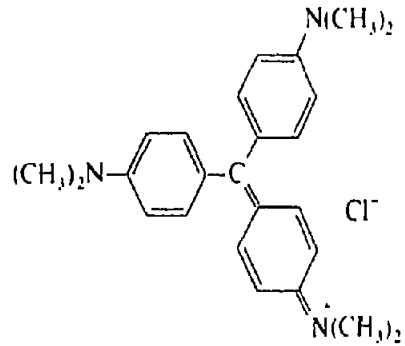
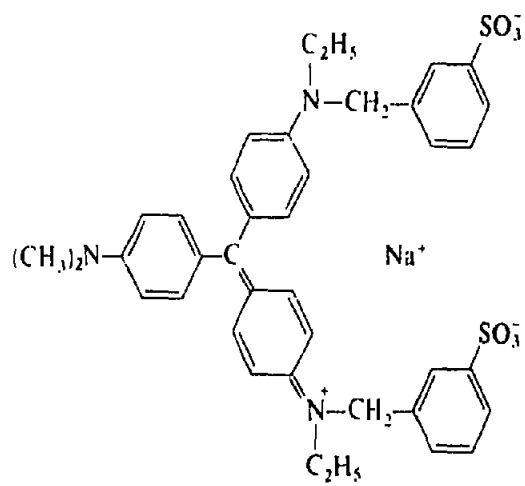


10 rats dosed *per os* (4% in diet). No tumours in 18–24 months.[131] See also ref. 136.

No evidence of carcinogenic risk to man.

(continued)

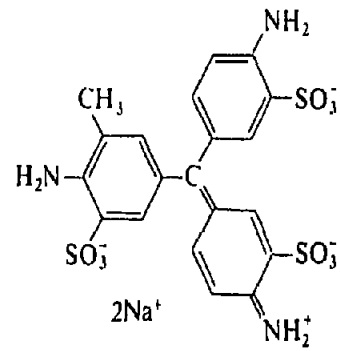
Table 1—*contd.*

Product number	*Product name*	*Structure and available data*
69	CI 42555 Basic Violet 3	 No useful information reviewed. See ref. 70. Class E1. No evidence of carcinogenic risk to man.
70	CI 42640 Acid Violet 49	

40 rats exposed by skin contact for 100 weeks. Benign mammary tumours induced.[92] 40 rats dosed *per os* (5% diet) for 1 year. Mammary carcinomas and ear duct carcinomas induced.[125] See also ref. 102.

Positive (tumourigen and carcinogen) class B. Possible carcinogenic risk to man.

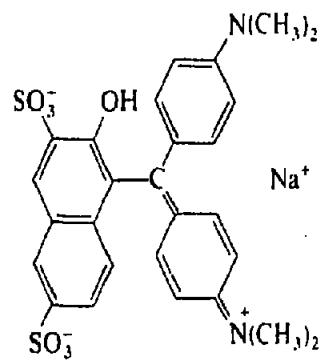
71 CI 42685 Acid Violet 19



10 rats dosed *per os* (4% in diet). Study duration 18–24 months.[131]

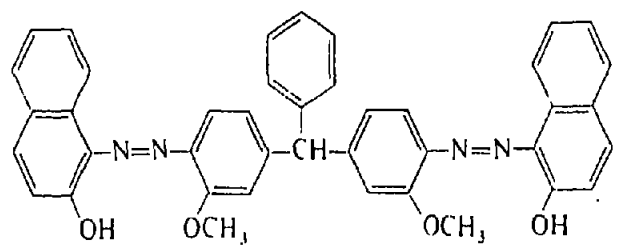
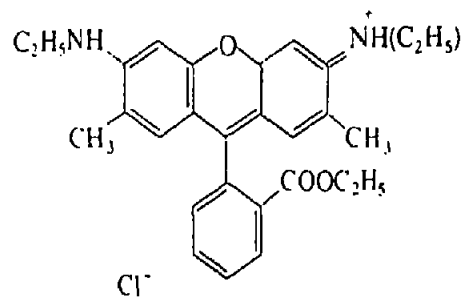
Negative (non-carcinogen) class C. No evidence of carcinogenic risk to man.

72 CI 44090 Acid Green 50



(continued)

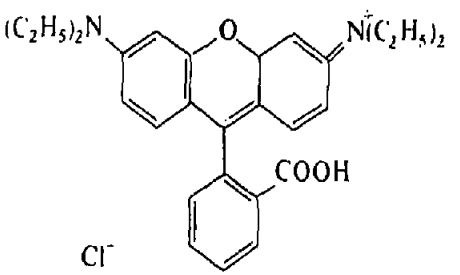
Table 1--*contd.*

Product number	*Product name*	*Structure and available data*
		20 rats dosed by repeated subcutaneous injection (900 mg). Duration 71 weeks. No induced tumours reported.[93]
		Class EI. No evidence of carcinogenic risk to man.
73	3,3'-Dimethoxytriphenylmethane-4,4'-bis(1-azo-2-naphthol)	
		20 rats dosed orally by 0·1% diet. Tumours induced in 4 animals but no details available.[52]
		Positive (carcinogen) class C. Possible carcinogenic risk to man.
Xanthenes		
74	CI 45160 Basic Red 1	

40 mice fed rice diet containing up to 0·02% dye. No tumours induced in 223 days. Also, 16 rats received repeated subcutaneous injection and developed fibrosarcomas.[128]

Class E1. No evidence of carcinogenic risk to man.

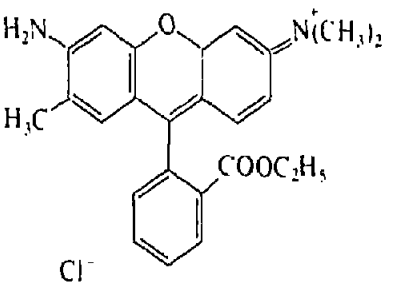
75 CI 45170 Basic Violet 10



21 rats fed rice diet containing 0·13% dye increased to 0·2% after 7 months. No animals with tumours up to 661 days. Also groups of rats dosed by subcutaneous injection. Injection site sarcomas induced. Large number of mice also dosed by subcutaneous injection. High mortality but no tumours induced.[128]
30 mice dosed *per os* (0·05% drinking water) for 1 year. Some evidence of gastrointestinal tract tumours but no controls reported.[8] See also ref. 131.

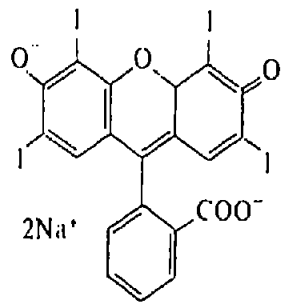
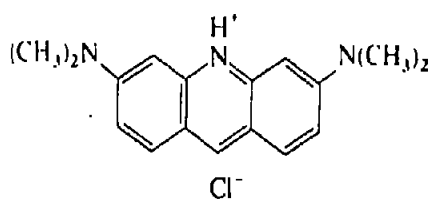
Negative (non-carcinogen, tumourigen) class D. No evidence of carcinogenic risk to man.

76 CI 45210 Basic Red 3



(continued)

Table 1—*contd.*

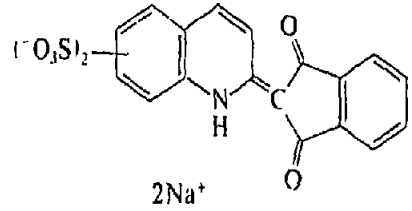
Product number	*Product name*	*Structure and available data*
		20 rats received subcutaneous injections (total about 65 mg) for 1 year. No tumours observed.[128]
		Class E1. No evidence of carcinogenic risk to man.
77	CI 45430 Acid Red 51	
		50 rats (male and female) fed for 86 weeks a diet containing 0·5, 1, 2 and 4% dye. Also duplicate population dosed by intubation and both groups kept 2 years. No tumours induced.[49]
		Negative (non-carcinogen) class B. No evidence of carcinogenic risk to man.
Acridine		
78	CI 46005 Basic Orange 14	

Shown to inhibit skin cancer induced by dimethylbenzanthracene (DMBA). Pure sample (mp 181 °C) dosed to mice (Swiss females) by: (a) topical application. No skin tumours but 3/20 with nondescript liver tumours; (b) subcutaneous injections which induced local tumours in 2/30 mice. Female Sprague-Dawley rats dosed by subcutaneous injections. 1/20 developed a local tumour.[130]

Positive (carcinogen and tumourigen) class D. Potential risk to man by virtue of liver cancers being induced by skin contact.

Quinoline

79 CI 47005 Acid Yellow 3

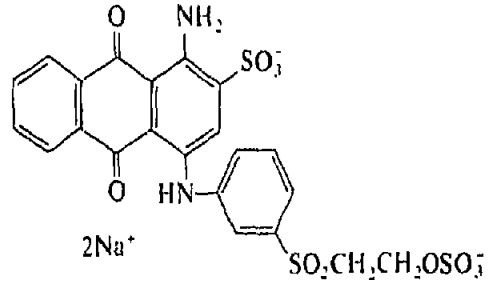


80 rats dosed *per os* (10 g/kg diet) for 2 years. Experiment terminated at 33 months. No treatment-related tumours observed. Also 40 rats dosed by subcutaneous injection. No tumours induced.[108]

Negative (non-carcinogen) class C. No evidence of carcinogenic risk to man.

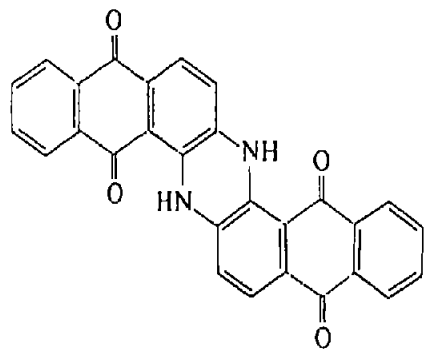
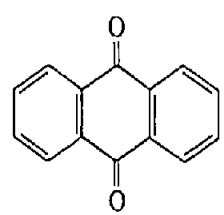
Anthraquinones

80 CI 61200 Reactive Blue 19



(continued)

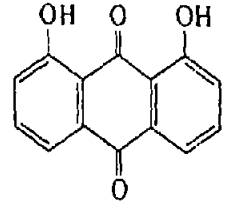
Table 1—*contd.*

Product number	*Product name*	*Structure and available data*
		50 rats dosed by subcutaneous injection (60 mg/week for 19 months). No tumours induced. Also 50 rats fed 30 mg in food for 25 months. 2 Sarcomas observed plus others not described. Also, 49 mice dosed subcutaneously (10 mg/week for 11 months) provided 1 lung tumour and 34 mice fed diet containing dye for 11 months provided 2 tumours. No controls. Very marginal data.[109] Class E1. No evidence of carcinogenic risk to man.
81	CI 69800 Vat Blue 4	 83 rats dosed by diet. No reported induced tumours.[108] Negative (non-carcinogen) class C. No evidence of carcinogenic risk to man.
82	Anthraquinone	

Groups of male and female rats dosed orally and subcutaneously. Thyroid tumours appeared but these also occurred in rhubarb-treated animals. There were no controls.[124]
72 mice dosed intragastrically *per os*. After 18 months no significant elevation of tumour incidence.[65]

Negative (non-carcinogen) class C. No evidence of carcinogenic risk to man.

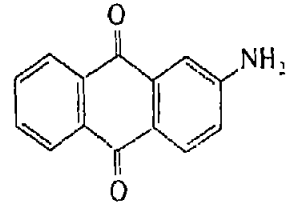
83 1,8-Dihydroxyanthraquinone



20 mice dosed topically. No tumours induced at 490 days.[119]

Class E1. No evidence of carcinogenic risk to man.

84 2-Aminoanthraquinone

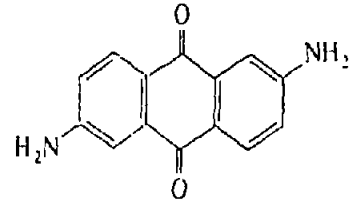
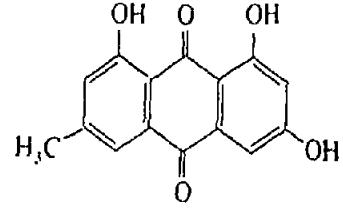
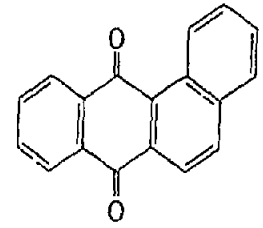


NCI Bioassay with rats and mice gave good evidence of induced cancers but analysis of test substance indicated considerable impurities present. Data therefore inadequate for assessment of this chemical structure.[5,105]
20 rats dosed intragastrically (total 1 000 g). Positive controls in study but duration only 9 months. No tumours induced.[41]

Class E1. No evidence of carcinogenic risk to man, but see ref. 84 for predictive test result with anthraquinones.

(continued)

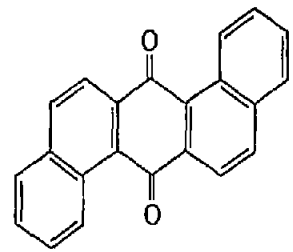
Table 1—*contd.*

Product number	*Product name*	*Structure and available data*
85	2,6-Diaminoanthraquinone	 20 rats dosed intragastrically (total 1 000 g). No tumours induced at 9 months. Positive controls gave high tumour incidence but study too short.[41] Class E1. No evidence of carcinogenic risk to man, but see ref. 84 for predictive test result with anthraquinones.
86	1,3,8-Trihydroxy-6-methylanthraquinone	 25 mice dosed topically (0·5% in acetone) for 85 weeks. No tumours induced.[121] Class E1. No evidence of carcinogenic risk to man.
87	Benz[*a*]anthracene-7,12-dione	

No relevant data assessed. See ref. 71.

Class E2. No evidence of carcinogenic risk to man.

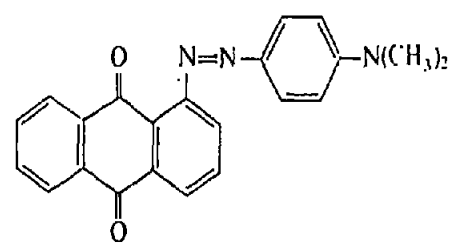
88 Dibenz[*a*,*h*]anthracene-7,14-dione



12 mice dosed topically (80 x 0·05 mg) for 40 weeks. Also, 10 mice dosed subcutaneously (0·1 mg). No tumours induced up to 40 weeks.[62]
10 mice topically dosed (0·3% in benzene). Papillomas induced at 570 days.[6]

Class E1. No evidence of carcinogenic risk to man.

89 1-(4-Dimethylamino)phenylazo-anthraquinone

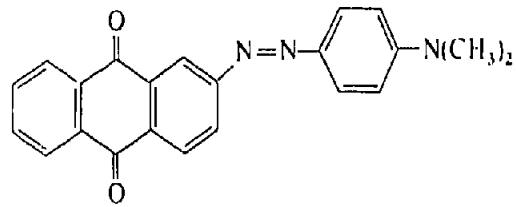
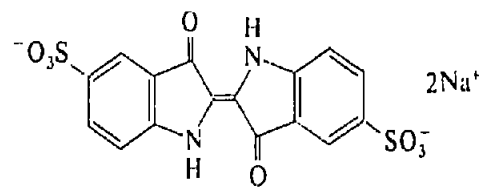


10 male Sprague-Dawley rats dosed on low protein and riboflavin-deficient diet. 6 months study only. No tumours induced.[11]

Class E1. No evidence of carcinogenic risk to man.

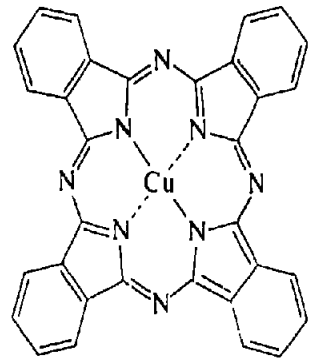
(continued)

Table 1—*contd.*

Product number	*Product name*	*Structure and available data*
90	2-(4-Dimethylamino)phenylazo-anthraquinone	
		6 months study in rats. No tumours reported.[11]
		Class E1. No evidence of carcinogenic risk to man.
Indigo **91**	CI 73015 Acid Blue 74	
		Groups of 24 male and female rats received diet containing 0·5, 1·0, 2·0 and 5·0% for 2 years. No apparent effect reported. Also, 18 rats dosed by subcutaneous injection for 2 years. 16 fibrosarcomas induced at injection site but not in controls. No other effect save toxicity. 50 mice received subcutaneous injections weekly for 2 years. No effect save toxicity reported.[56]
		Negative (non-carcinogen) class A. No evidence of carcinogenic risk to man.

Phthalocyanines

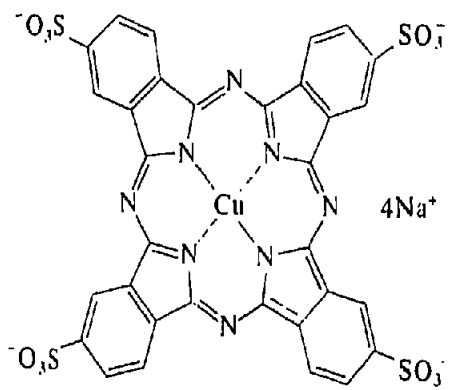
92 CI 74160 Pigment Blue 15



20 mice dosed subcutaneously (34 × 0·5 mg injections). No tumours in 8 months.[60]

Class E1. No evidence of carcinogenic risk to man.

93 CI 74220 Acid Blue 249

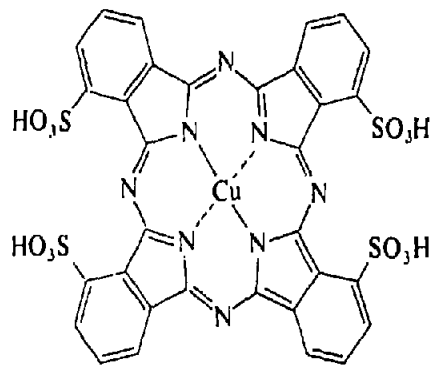
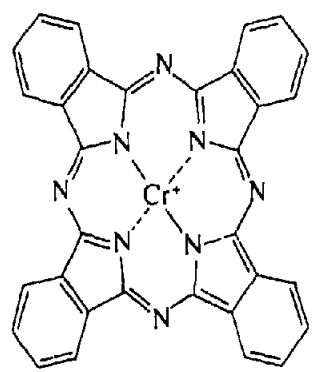


20 mice dosed subcutaneously (25 × 0·5 mg injections). No tumours in 8 months.[60]

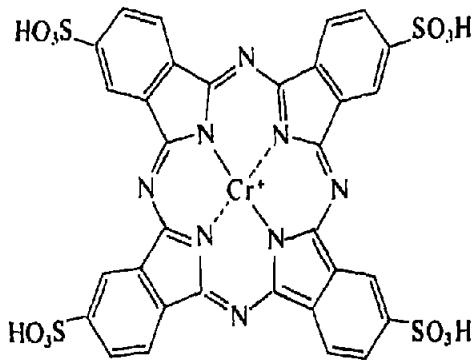
Class E1. No evidence of carcinogenic risk to man.

(continued)

Table 1—*contd.*

Product number	*Product name*	*Structure and available data*
94	Copper phthalocyanine tetra-3-sulphonate	 20 mice dosed subcutaneously (36 × 0·5 mg injections). No tumours in 8 months.[60] Class E1. No evidence of carcinogenic risk to man.
95	Chromium phthalocyanine	 20 mice dosed subcutaneously (11 × 0·5 mg injections). No tumours in 8 months.[60] Class E1. No evidence of carcinogenic risk to man.

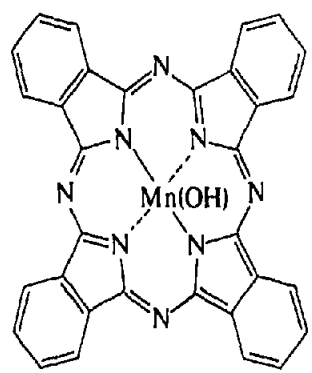
96 Chromium phthalocyanine tetra-4-sulphonate



20 mice dosed subcutaneously (23 x 0·5 mg injections). No tumours in 8 months.[60]

Class E1. No evidence of carcinogenic risk to man.

97 Hydroxymanganese phthalocyanine



20 mice dosed subcutaneously (8 x 0·5 mg injections). No tumours at 9 months.[60]

Class E1. No evidence of carcinogenic risk to man.

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