THE EFFECT OF DIFFERENT TUMOR GROUPINGS ON FINDINGS OF ANTICARCINOGENIC RESPONSES IN LONG-TERM RODENT BIOASSAYS

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Abstract

In this study, we evaluate the influence of several alternative tumor classification schemes for the more than 3000 tumor types in the Cancer Bioassay Data System (CBDS) database of carcinogenesis test results on conclusions about anticarcinogenic effects of specific chemicals and the rates of classification as anticarcinogenic due to random variation in tumor rates. We compare the numbers of chemicals classified as anticarcinogenic in 1) our "standard" classification system, 2) a modification of that system to correct some deficiencies in the CBDS data base pointed out by Dr J. Haseman, 3) an alternative classification system developed by Dr. K.S. Crump and colleagues, 4) the number of animals displaying at least one tumor, or 5) the total number of tumors appearing in all animals in control and dosed groups. Although there is a difference in the number of chemicals classified as anticarcinogens by these alternative classification schemes, all of them show a statistically significant increase in the number of anicarcinogenic responses above the random rate predicted by a Monte-Carlo simulation of the rodent bioassay. The number of anticarcinogenic responses is similar in our standard and modified classification and classification scheme developed by Crump. If the total tumors or tumor-bearing animals scheme approaches are used, the number of anticarcinogenic responses decreases. This we believe is mainly because these schemes integrate the response of the entire animal and reflect both increases and decreases in tumor rates induced by chemical exposure. Clearly, the choice of classification system influences bioassay interpretation and must be considered when evaluating the likely human effects of exposure.

Introduction

Long-term treatment of rodents with high doses of chemicals clearly has led to decreases in tumor rates at specific sites (e.g., Weinberg and Storer, 1985; Davies and Monro, 1994; Haseman and Johnson, 1996; Dunnick *et al*., 1996; Elwell *et al*., 1996). In our previous studies (Linkov, *et al*., 1998a, Linkov, *et al*., 1998b, Linkov, *et al*., 2000, Gray et al., 2000) we have shown that the decreased tumor rates (anticarcinogenicity) commonly observed in the National Toxicology Program (NTP) rodent bioassays cannot be completely explained either by false-positive anticarcinogenic findings due to random effects (variations in tumor rates and the multiple comparisons undertaken in evaluating a bioassay) or by compound-induced decreases in body weight or decreases in survival of treated animals. We concluded that they must have biological significance.

One argument against the significance of anticarcinogenicity is that the effects may be an artifact of the manner in which tumor types and sites were combined for statistical analysis. The assignment of tumors to different classes for evaluation of rodent bioassays has been an issue of long standing but little study. Our group has used a consistent grouping of tumors into 102 classes for more than ten years beginning with Bailar *et al.*, 1988. This particular grouping into classes has been criticized by Haseman (1998) because (*inter alia*) (i) a "pathologist bias" existed in which chromophobe adenoma and pituitary adenoma were sometimes classified differently in dosed and control animals and (ii) a distinction between liver adenoma and carcinoma could lead to spurious anticarcinogenic responses as adenomas progress to carcinomas (Gray *et al*. 2000). An early response to some of Haseman's criticisms is in an erratum (Linkov et al. 1999) to Linkov *et al.* (1998a, 1998b). Our "modified" classification of 100 classes combines all liver tumors in one class and all pituitary tumors in another to evaluate the influence on judgment of anticarcinogenic responses of Dr. Haseman's suggestions. We have also obtained an alternative classification scheme constructed by Dr. Kenny Crump and colleagues in consultation with scientists from the National Toxicology Program (K.S. Crump, personal communication). This scheme seems to be based upon the NTP approach used in the TDMS data base, with a few tumor classes left over (see Wilson, 2000). Since a common response in bioassays is an increase in tumor rates at some sites and a decrease at others, we also consider two classification approaches capable of integrating both increases and decreases in tumor rates. Firstly we count all animals with *any* tumor. We call this scheme "tumor bearing animals". Since we focus on anticarcinogenicity the fact that the animals used in standard cancer bioassays have relatively high background tumor rates and often more than one type of tumor makes this approach somewhat less sensitive in detecting anticarcinogenic effects. We therefore evaluate a final classification where all tumors in an animal group are counted, even when there is more than one tumor in an animal.

This paper evaluates these alternative systems for classifying the organs and tissues examined in rodent bioassays for differences in the number of chemicals judged to be anticarcinogenic and the influence of random effects on interpretation of bioassay results.

Methods

We use the data base that we have used previously in the publications of this group (*e.g.*, Byrd *et al.*1990; Gray *et al.*1995, Linkov *et al.* 1998a,1998b, 1999). This is the CBDS database of chemicals tested by the National Toxicology Program prior to 1983. From this we identified 312 chemicals tested by NCI/NTP prior to 1983 that satisfied the following criteria:

-- at least one control group

-- long-term experiments (>70 weeks)

-- food, water and gavage routes

■ tested on both mice and rats

In response to concerns of Haseman (2000) we have also run the analysis with a few more criteria. When we exclude chemicals in the database with no NTP report issued and those for with a discrepancy between the database and NTP report (we have traditionally used the CBDS data) we are left with 256 compounds. We have been reluctant to ignore data when the reason for the lack of an NTP report was not clear. The results of the analysis are essentially identical to those reported here and are available at Wilson (2000). The only notable change is the removal of tert-butyl alcohol from the group of chemicals classified as anticarcinogenic by schemes 1, 2, and 3 (Table 2).

Tumor Classification:

In this database there are over 3000 combinations of tumor type and tumor sites. In addition, the classification and nomenclature of tumors was not consistent across the years of experiments covered by the CBDS. This means that tumors must be combined into categories for analysis. The goal of classification is maintaining the biologic integrity of each class while avoiding problems like inconsistent pathologic diagnosis. We evaluated the following five classification schemes (complete descriptions in Wilson, 2000).

1) Our *standard* classification (due originally to Bailar *et al.,* 1988) of 102 groups described in several earlier papers (*e.g*., Byrd *et al.* 1990; Gray *et al.* 1995, Linkov *et al.* 1998a, 1998b, 1999) and listed here in Appendix I. Among these 102 categories (classes), 66 were classified as malignant primary neoplasms and 36 as benign primary neoplasms.

(2) The *modified* classification is similar to the standard one but all pituitary tumors (previous classes 10 and 36) combined into one class and all liver tumors (adenomas, carcinomas and other neoplastic lesions) previously in our classes 7 and 64 combined into one class. This combination was already mentioned in the "erratum" (Linkov *et al*., 1999) referred to above. This is now our preferred classification scheme.

(3) The *Crump* classification scheme was devised by Dr. K.S. Crump and colleagues in collaboration with Dr Joseph Haseman of the National Toxicology Program (K.S. Crump, personal communication). This system reduces the CBDS tumor codes to a total of 91 classes. This classification scheme is similar to that used by NTP in the TDMS database but adds a few classes for tumor sites and types not otherwise included**.**

(4) The *Tumor Bearing Animals* classification is a simple one class scheme that uses the individual animal, rather than the tumor, as the unit of analysis. We simply count the number of animals with at least one tumor in control and dosed groups.

(5) The *Total Tumors* classification combines all tumors into a single group. For a given control or dose group in a bioassay, all tumors in all animals are combined regardless of site and multiple tumors in a single animal all contribute to the total.

In practice, complications arise in deriving the total number of tumors in a given number of animals because not all animals in a dose group are examined for tumors at all sites so that the denominator (as in number of tumors/number of animals) differs within a study. We start with tumors in our standard classification (102 sites). For every group of animals, the number of tumors for each site in the standard classification was counted. The number of tumors in each experimental group was then normalized to an n of 50. If for example, the classification scheme had only 2 tumor types; a group of 50 animals had 10 tumors of type 1, but only 23 animals had been examined; and 13 tumors of type 2, for which 49 had been examined, then the number of "total tumors" is calculated as follows $(10/23) * 50 + (13/49) * 50 \approx 35$ total tumors in a standardized group of 50 animals. The normalized values of "total tumors" were the input data for response evaluation.

Response Evaluation:

A chemical is classified as anticarcinogenic if there is a significant decrease of tumors in any class of sites and tumor types in a group of rodents upon dosing. We recognize the factors other than statistical significance play a role in interpretation of bioassay tumor responses (Haseman and Elwell, 1996) but with a large database and varying classification schemes, we used solely statistical measures for evaluating tumor dose-response. Statistical significance was decided using Fishers exact test and the Cochran-Armitage trend test according to the criteria in Table 1.

The value of p_0 is varied throughout the analysis. This approach mirrors that used in many of our earlier papers.

Table 1

	Fisher Exact Test (group pairs)	**Cochran-Armitage Dose Trend Test**
Anti-carcinogen	$p < p_0$ for any one pair or $p < 2p_0$ for two pairs	$p < p_0$

Random Effects

As has been pointed out by Haseman and Johnson (1996) and Linkov *et al.* (1998a) an increase or decrease in tumor rate is expected for some chemicals as a purely random fluctuation in background tumor rates although, of course, we cannot tell which individual chemical is thereby spuriously labeled carcinogenic or anticarcinogenic. That random fraction was first estimated by a simple Monte Carlo calculation as described in Linkov *et al.* (1998a) with an assumption that the tumor rates in any class is independent of the rate in any other. In this paper we extend the model to include correlation in tumor rates. The responses in a specific tumor type were generated randomly, but not assuming independence as in our previous study, but rather by taking into consideration empirical data on all possible correlations among the tumor types. Detailed description of this simulation procedure is beyond the scope of this manuscript and is available at Wilson (2000).

Results and Discussions

Figures 1 through 4 compare the fraction (expressed as a percentage) of chemicals that would be judged anticarcinogenic in the four bioassay test groups (male and female mice and rats) using the five different classification schemes and four different values of p_0, 0.005, 0.01, 0.025 and 0.05. The fraction of anticarcinogens is almost the same for each of the first three schemes. But the fraction drops appreciably when the single class schemes 4 and 5 are used.

Many of the chemicals which are found to be anticarcinogenic under each scheme are different. This is shown in the Pie Graph of Figure 5. 29 chemicals are found to be anticarcinogens in male mice (MM) with $P < 0.005$ using the old classification scheme (1), 27 using the modified scheme (2) and 26 using the Crump scheme (3). But of these only 13 chemicals are common to each scheme. These chemicals are listed in Table 2.

Table 2. Chemicals classified as anticarcinogens by schemes 1, 2 and 3.

Chemical
2,7-DICHLORODIBENZO-P-DIOXIN
2-BIPHENYLAMINE HCL
8-HYDROXYQUINOLINE
AZOBENZENE
CHLORODIBROMOMETHANE
GUAR GUM
HEXYLRESORCINOL
N-BUTYL CHLORIDE
N-PHENYL-2-NAPHTHYLAMINE
O-ANISIDINE HYDROCHLORIDE
P-ANISIDINE HYDROCHLORIDE
ROTENONE
TERT-BUTYL ALCOHOL

The contribution of false positive (random) effects to findings of anticarcinogenicity is shown in Figure 6 for the original simulation model which assumes that the tumor rate at each site is independent (Linkov et al., 1998a), an assumption also made by others (Haseman and Johnson, 1996) (dash line); and for a model that approximately incorporates correlations in tumor rate (shaded portion of the bar). Clearly the model accounting for correlations predicts fewer positive responses due to random effects than the simple model. The figure also shows that at low values of p_0 (*e.g.*, 0.005) there are few if any positive responses due to random effects but at less stringent levels of statistical significance (*e.g.*, $p_0 = 0.05$) the number of random responses estimated using the simple model exceeds the number of measured real plus random responses. Nonetheless, at $p_0 = 0.05$ fully half of the findings of anticarcinogenicity are likely to be due to random variation in background tumor rates in classifications (1), (2) and (3). For the single class schemes (4) and (5) the random effects are correctly given by the simple Monte Carlo calculation and of course by the simple argument that at any value of p_0, the fraction of all responses are due to random effects is p_0.

Conclusions

We find that the scheme used to classify tumors in long-term rodent bioassays may have a significant influence on judgements about the anticarcinogenicity of a specific chemical under test.

Although the proportion of chemicals judged as anticarcinogens is similar for the different site-specific classification systems, the specific chemicals found to be anticarcinogenic varies depending upon the classification scheme. As already noted in Linkov et al. (1999) there seem to be only small differences in the proportion of anticarcinogens between our standard classification scheme, and the modified scheme with liver tumors grouped together and pituitary adenomas grouped together.

The proportion of chemicals which show anticarcinogenicity purely by random effects, as judged by our simulation model, is a significant fraction of the chemicals found to be anticarcinogenic, especially at less stringent levels of statistical signficance. However, in no case do random effects account for all of the cases of anticarcinogenicity.

Use of the integrative classifications tumor-bearing animals or total tumors significantly reduces the number of chemicals judged to be anticarcinogenic. Interestingly, much of the reduction may be due to fewer random responses. The reduction is less if *total tumors* are used than if *tumor-bearing animals* are used.

We are able to detect significant levels of anticarcinogenicity although the rodent bioassay is not particularly sensitive to these effects. Anticarcinogenicity of a substance requires a reduction in tumors already present in the control group. It can only be detected if there is an appreciable rate in the control animals (typically in the range of 10 - 20% in our data). There are only a limited number of tumor types for which this occurs and these tend to be the same for the different schemes.

We have identified the fact that an anticarcinogenic response is more likely to be found if the number of animals with the tumor in the control group is higher than the number averaged over all studies (historical controls) as demonstrated in Figure 7. This could indicate that many findings of anticarcinogencity are due to fluctuations in the control rate with in the dosed groups demonstrating rates similar to historical controls. On the other hand, comparison with the control group may be the only appropriate way to evaluate responses because of other experimental effects.

Integrative classifications address both of these shortcomings. At the same time, there are clear sensitivity problems with measures like tumor-bearing animals or total tumors. Integrative classifications obviously exclude the common substances which are carcinogenic at one site and anticarcinogenic at another. The tradeoffs between different methods of classifying rodent bioassay tumors for risk assessment should be explicitly addressed in the context of the decision at hand.

We believe that the results of this and earlier papers are important for the use of rodent bioassay data in public policy decisions. Judgement of anticarcinogenic and carcinogenic potential based on rodent bioassays plays an important role in focusing attention on specific substances. If these judgments are incomplete (*i.e.*, only focus on increases in tumor rates) or faulty, due to high rates of false positive responses induced through multiple statistical comparisons and relatively loose levels of statistical significance, attention and resources may be misplaced.

Acknowledgments

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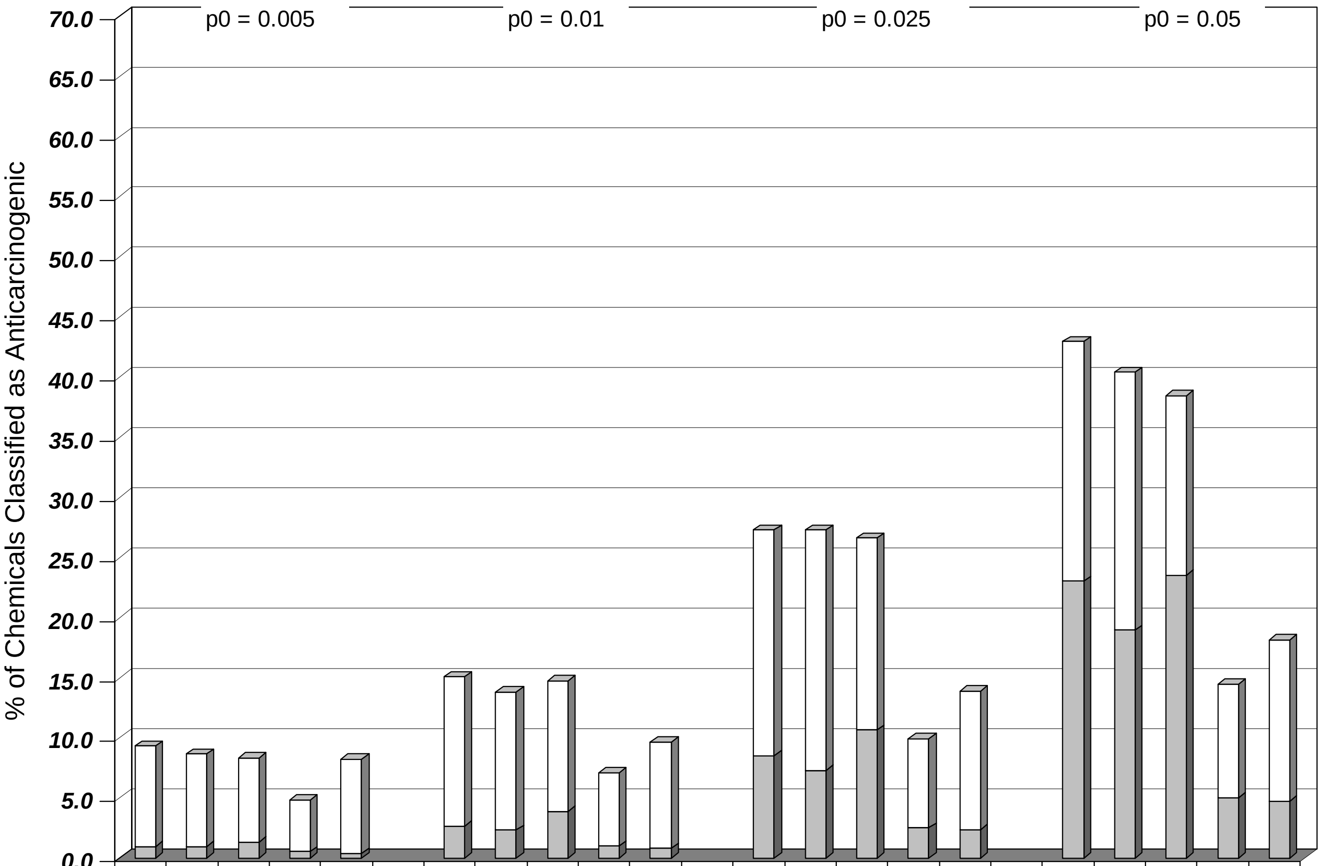
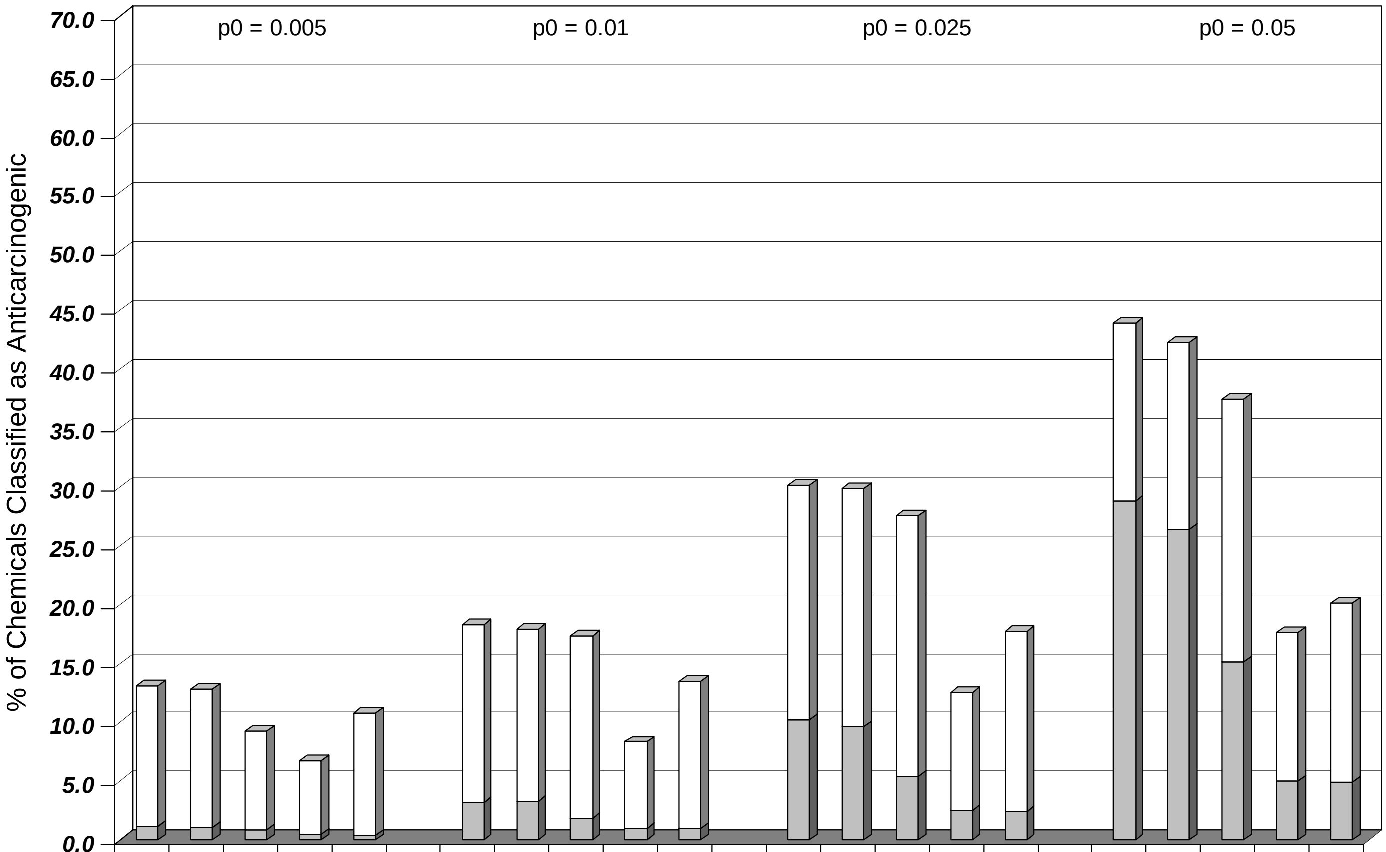
Figure 1. Percentage of chemicals in the database classified as anticarcinogenic in male mice at different levels of p_0 for each classification system: [1] standard (old) classification; [2] modified (preferred) standard; [3] Crump classification; [4] tumor-bearing animals; and [5] total tumors. The shaded portion of each bar reflects the estimated random response with the New Monte Carlo for that sex, species, classification and p_0.



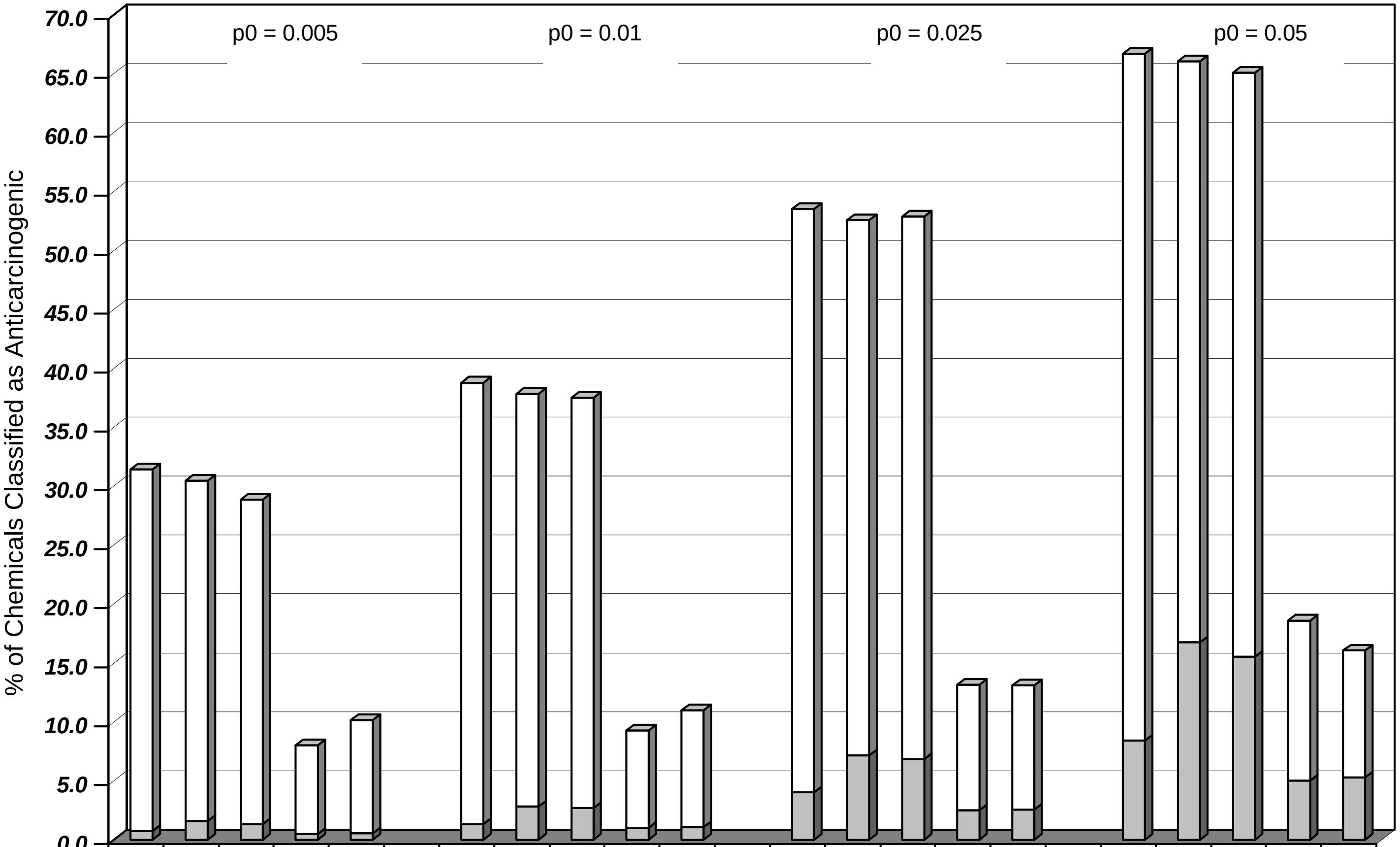
	[1]	[2]	[3]	[4]	[5]		[1]	[2]	[3]	[4]	[5]		[1]	[2]	[3]	[4]	[5]		[1]	[2]	[3]	[4]	[5]
Random Fraction of Responses	10.0	11.2	16.1	10.4	4.6		17.6	16.7	26.1	14.2	8.4		31.1	26.8	40.0	25.2	16.8		53.6	46.9	61.2	34.7	26.0
☐ Actual Values minus Randoms	8.4	7.7	7.0	4.3	7.8		12.4	11.5	10.9	6.1	8.8		18.8	20.0	16.0	7.4	11.6		20.0	21.5	14.9	9.4	13.4
▨ Random Responses	0.9	1.0	1.3	0.5	0.4		2.7	2.3	3.8	1.0	0.8		8.5	7.3	10.6	2.5	2.3		23.0	18.9	23.5	5.0	4.7

Figure 2. Percentage of chemicals in the database classified as anticarcinogenic in female mice at different levels of p_0 for each classification system: [1] standard (old) classification; [2] modified (preferred) standard; [3] Crump classification; [4] tumor-bearing animals; and [5] total tumors. The shaded portion of each bar reflects the estimated random response with the New Monte Carlo for that sex, species, classification and p_0.



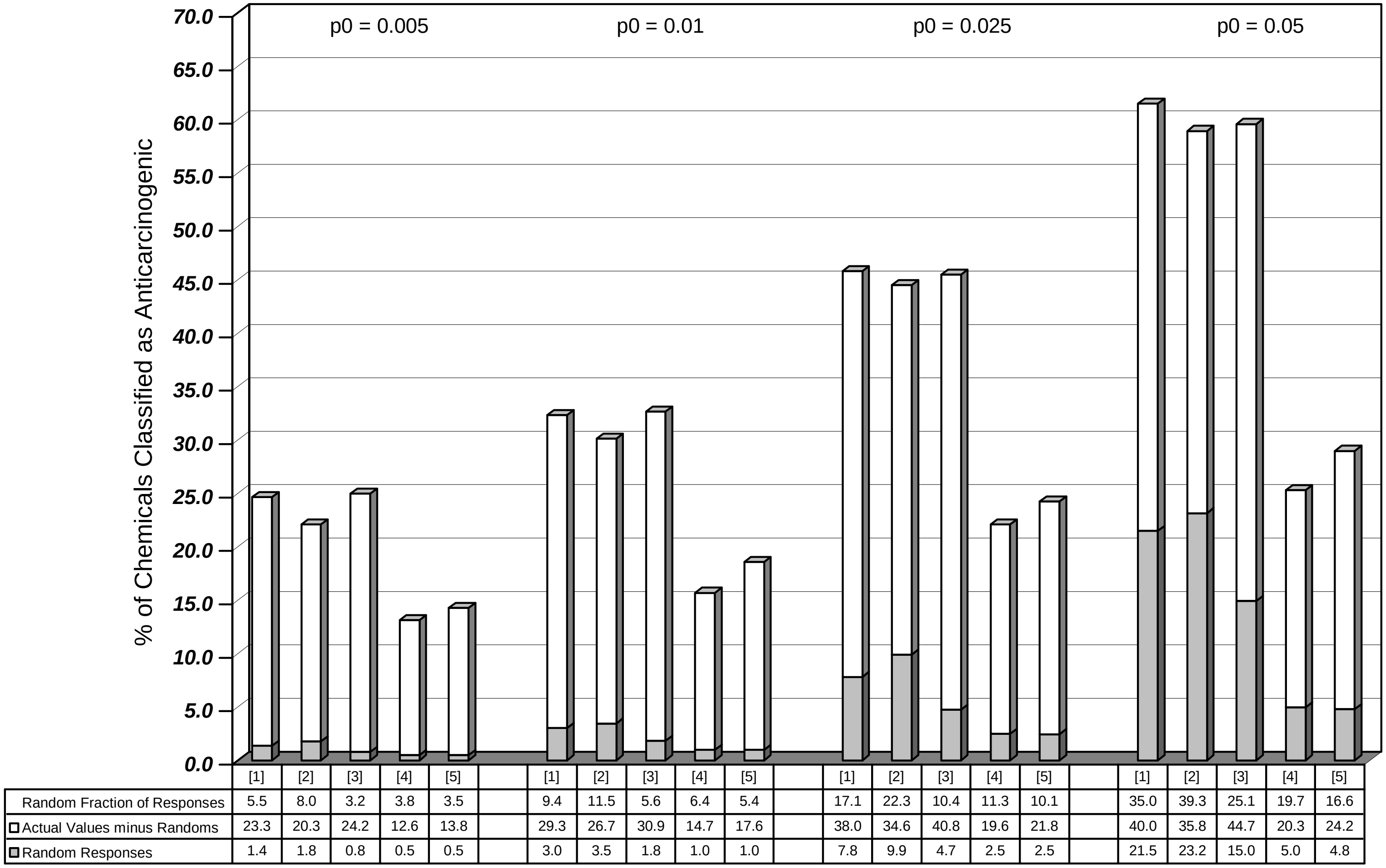
	[1]	[2]	[3]	[4]	[5]		[1]	[2]	[3]	[4]	[5]		[1]	[2]	[3]	[4]	[5]		[1]	[2]	[3]	[4]	[5]
Random Fraction of Responses	9.1	8.3	9.4	7.4	4.0		17.5	18.4	10.7	12.0	7.1		33.8	32.3	19.4	20.0	13.3		65.5	62.4	40.3	28.4	24.4
☐ Actual Values minus Randoms	11.9	11.8	8.4	6.2	10.4		15.1	14.7	15.5	7.3	12.6		19.9	20.2	22.2	10.0	15.4		15.1	15.9	22.4	12.6	15.2
▨ Random Responses	1.2	1.1	0.9	0.5	0.4		3.2	3.3	1.9	1.0	1.0		10.2	9.6	5.4	2.5	2.4		28.8	26.4	15.1	5.0	4.9

Figure 3. Percentage of chemicals in the database classified as anticarcinogenic in male rats at different levels of p_0 for each classification system: [1] standard (old) classification; [2] modified (preferred) standard; [3] Crump classification; [4] tumor-bearing animals; and [5] total tumors. The shaded portion of each bar reflects the estimated random response with the New Monte Carlo for that sex, species, classification and p_0.



	[1]	[2]	[3]	[4]	[5]		[1]	[2]	[3]	[4]	[5]		[1]	[2]	[3]	[4]	[5]		[1]	[2]	[3]	[4]	[5]
Random Fraction of Responses	2.4	5.2	4.6	6.2	5.3		3.4	7.4	7.1	10.8	9.8		7.5	13.6	12.9	19.0	19.4		12.6	25.3	23.9	26.9	33.0
☐ Actual Values minus Randoms	30.7	28.9	27.5	7.5	9.6		37.5	35.0	34.8	8.3	9.9		49.5	45.4	46.1	10.6	10.5		58.3	49.3	49.5	13.6	10.7
▨ Random Responses	0.7	1.6	1.3	0.5	0.5		1.3	2.8	2.7	1.0	1.1		4.0	7.2	6.8	2.5	2.5		8.4	16.7	15.5	5.0	5.3

Figure 4. Percentage of chemicals in the database classified as anticarcinogenic in female rats at different levels of p_0 for each classification system: [1] standard (old) classification; [2] modified (preferred) standard; [3] Crump classification; [4] tumor-bearing animals; and [5] total tumors. The shaded portion of each bar reflects the estimated random response with the New Monte Carlo for that sex, species, classification and p_0.



	[1]	[2]	[3]	[4]	[5]		[1]	[2]	[3]	[4]	[5]		[1]	[2]	[3]	[4]	[5]		[1]	[2]	[3]	[4]	[5]
Random Fraction of Responses	5.5	8.0	3.2	3.8	3.5		9.4	11.5	5.6	6.4	5.4		17.1	22.3	10.4	11.3	10.1		35.0	39.3	25.1	19.7	16.6
☐ Actual Values minus Randoms	23.3	20.3	24.2	12.6	13.8		29.3	26.7	30.9	14.7	17.6		38.0	34.6	40.8	19.6	21.8		40.0	35.8	44.7	20.3	24.2
▨ Random Responses	1.4	1.8	0.8	0.5	0.5		3.0	3.5	1.8	1.0	1.0		7.8	9.9	4.7	2.5	2.5		21.5	23.2	15.0	5.0	4.8

Figure 5. Percent of chemicals found to be anticarcinogens in one of the first three schemes (Male Mice @ p0 = 0.005)

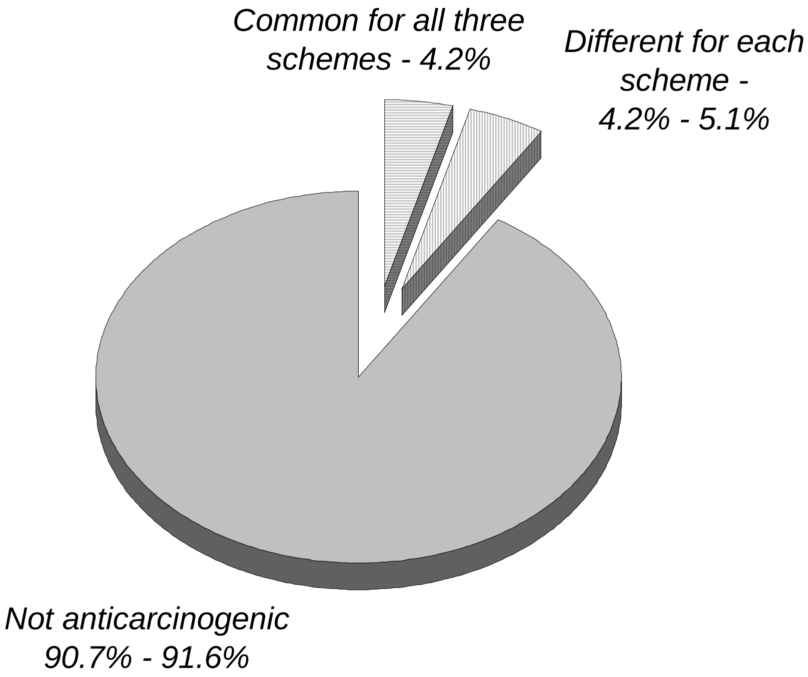


Figure 6. Percentage of chemicals in the database classified as anticarcinogens in male rats at different values of p_0 using the modified classification (2) and fraction of chemicals classified as anticarcinogenic in Monte Carlo simulations of the bioassay in the absence of chemical effects using the unadjusted model ("old") and the model accounting for significant correlations between tumor types ("new").

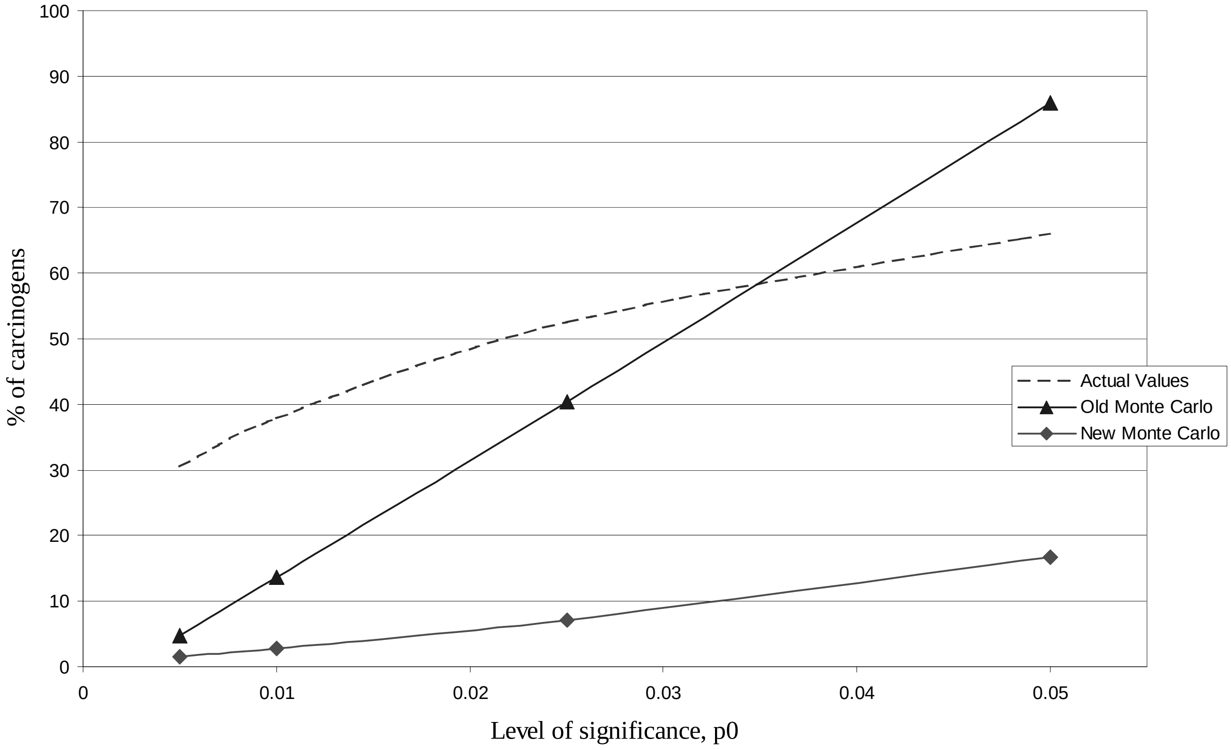
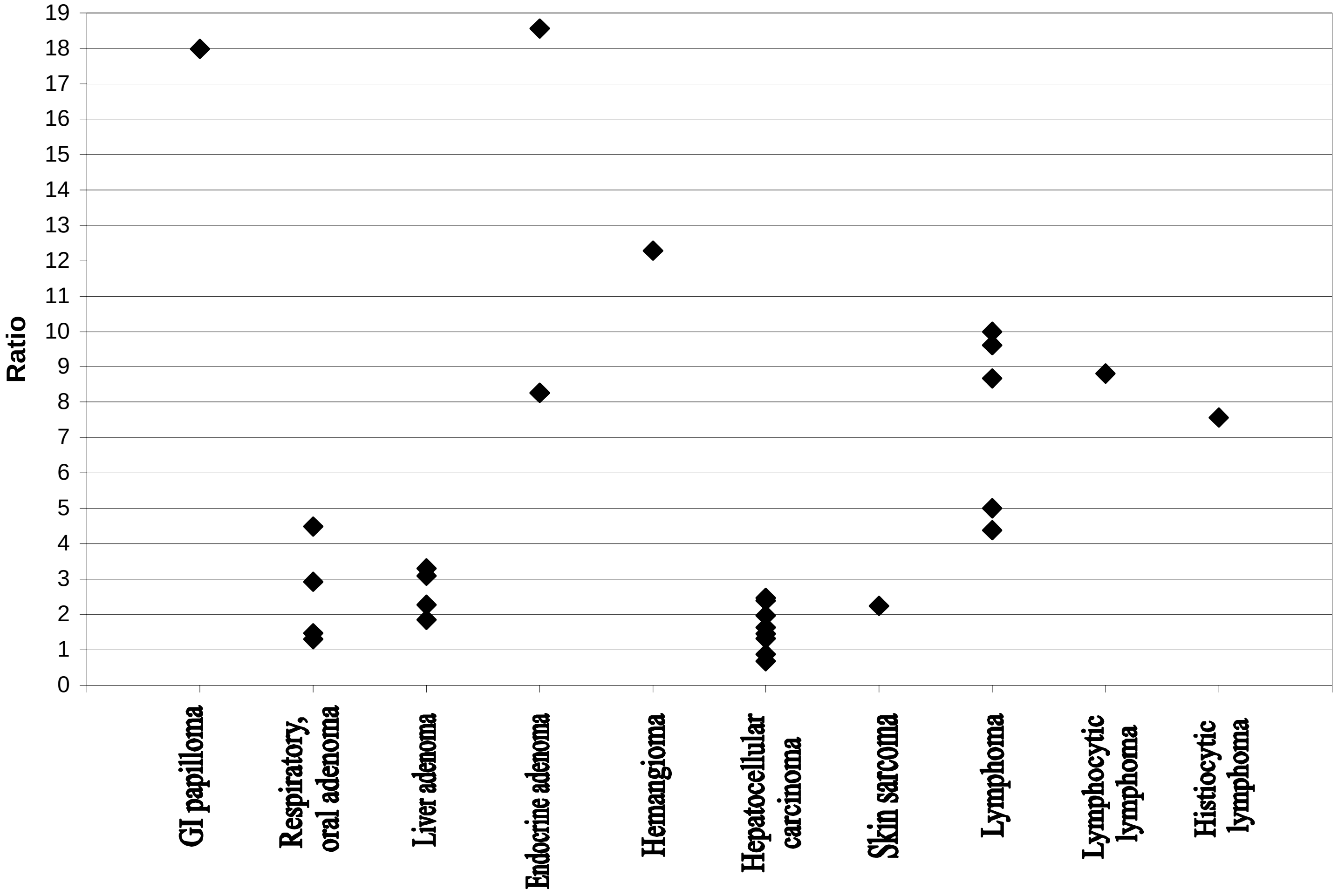


Figure 7. Ratio (tumor rate in controls for experiments with anticarcinogenic responses) / (historical tumor rate in controls). Male Mice only, modified standard classification.



Appendix I. The "standard" tumor classification (102 classes).

No	Class
1	Skin, breast papilloma
2	Respiratory, oral papilloma
3	GI papilloma
4	Urinary, reprod. papilloma
5	Skin, breast adenoma
6	Respiratory, oral adenoma
7	Liver adenoma
8	GI adenoma
9	Urinary, reprod. adenoma
10	Pituitary adenoma
11	Endocrine adenoma
12	Skin, urinary adenoma
13	Reprod., endocrine adenoma
14	Tubular cell adenoma
15	Follicular, clear cell adenoma
16	Cortical adenoma
17	Skin, breast, liver cystadenoma
18	GI, urinary, reprod. cystadenoma
19	Endocrine cystadenoma
20	Acinar cell adenoma
21	Keratoacanthoma
22	Tubular adenoma
23	Interstitial cell tumor
24	Pheochromocytoma
25	Skin, breast fibroma
26	Blood, bone fibroma
27	Fibroma, other sites
28	Lipoma
29	Leiomyoma
30	Endometrial stromal polyp
31	Fibroadenoma
32	Hemangioma
33	Osteoma
34	Hamartoma
35	Ganglioneuroma
36	Chromophobe adenoma
37	Skin, breast carcinoma
38	Blood, bone carcinoma
39	Lung carcinoma
40	Oral, GI carcinoma
41	Urinary carcinoma
42	Reproductive carcinoma
43	Pituitary carcinoma
44	Endocrine carcinoma
45	Brain carcinoma
46	Skin, breast papillary carcinoma
47	Lung papillary carcinoma
48	GI, urinary papillary carcinoma
49	Uterus, ovary papillary
50	Thyroid papillary carcinoma
51	Skin squamous carcinoma
52	Lung squamous carcinoma
53	Oral, GI squamous carcinoma
54	Urinary, reprod. squamous
55	Skin, GI basal cell carcionma
56	Urinary transitional cell
57	Skin, breast adenocarcinoma
58	Lung adenocarcinoma
59	Oral, GI adenocarcinoma
60	Urinary, reprod. adenocarcinoma
61	Endocrine, brain adenocarcinoma
62	Islet cell carcinoma
63	Bile duct carcionma
64	Hepatocellular carcinoma
65	Alveolar, broncheolar carcinoma
66	Chromaphobe carcinoma
67	Tubular cell adenocarcinoma
68	Thyroid follicular cell carcinoma
69	Cortical carcinoma
70	Clear cell carcinoma
71	Adnexal, sebaceous carcinoma
72	Thymoma
73	Granulousa cell carcinoma
74	Interstitial cell carcinoma
75	Pheochromocytoma, malignant
76	Skin sarcoma
77	Other sites sarcoma
78	Blood, bone sarcoma
79	Liposarcoma
80	Leiomyosarcoma
81	Endometrial stromal sarcoma
82	Carcinosarcoma
83	Mesothelioma, osteosarcoma
84	Teratoma
85	Hemangiosarcoma
86	Granular cell tumor
87	Glioma
88	Oligodendroglioma
89	Astrocytoma

90	Olfactory neuroblastoma
91	Neurofibrosarcoma
92	Lymphoma
93	Lymphocytic lymphoma
94	Histiocytic lymphoma
95	Mixed lymphoma
96	Malignant reticulosis
97	Leukemia
98	Myelomonocytic leukemia
99	Lymphocytic leukemia
100	Plasmacytic leukemia
101	Granulocytic leukemia
102	Monocytic leukemia