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FACTORS IN THE EVALUATION OF 200 NATIONAL CANCER INSTITUTE CARCINOGEN BIOASSAYS

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In determining the carcinogenicity of a chemical tested in a National Cancer Institute (NCI) bioassay, the following criteria are considered: (1) the adequacy of the bioassay data, (2) the presence of significantly increased incidences of tumors, (3) the adequacy of the number of animals at risk of developing tumors, (4) the adequacy of the dose of chemical administered, (5) the etiology and pathogenesis of the lesions, and (6) other factors that may influence an evaluation, such as a shortened latency period for tumor formation in dosed animals or the stability of the chemical. A decision tree for evaluating these factors is presented. A summary of the results of 200 NCI carcinogen bioassays is also reported. These procedures are presented in the hope that they may serve as discussion points for future developments in the field.

INTRODUCTION

It has been estimated that many human cancers are caused by chemical and environmental factors (Boyland, 1969; Higginson, 1972; Doll, 1977, 1978). A number of methods have been used to determine the potential health risk of chemicals to humans. These methods include epidemiologic studies, animal experiments (carcinogen bioassays), and *in vitro* studies. The most direct approach is to determine the effects of chemicals on humans. However, the testing of chemicals in humans is ethically unacceptable. After an accidental or unintentional exposure of humans to chemicals there may be a latency period of 20–30 yr (Doll, 1971, 1978) before the appearance of any carcinogenic effect, which precludes an immediate epidemiologic evaluation. Although *in vitro* tests show promise for the future, the carcinogen bioassay is presently the standard method for determining potential carcinogenic risks to humans. For more than 8 yr the National Cancer Institute (NCI) has been directing such tests.

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During this period, NCI has tested more than 200 chemicals in carcinogen bioassays with two species of rodents. The vast majority of the results of these studies are published in the NCI carcinogenesis technical report series. There have been more than 190 reports on 200 chemicals. Because of the importance of these reports in assessing the potential health hazards to humans, we will discuss the general criteria used in evaluating the carcinogenicity of a chemical tested in an NCI carcinogen bioassay. This paper represents the views of the authors and does not necessarily reflect the views of NCI.

MATERIALS AND METHODS

The NCI Carcinogen Bioassay

In a typical NCI chronic bioassay for carcinogenicity (Sontag et al., 1976; Page, 1977), the test chemical is administered continuously for 18–24 mo to groups of 50 male and female (C57BL/6N X C3H/HeN) F1(B6C3F1) hybrid mice and for 20–24 mo to groups of 50 male and female Fischer 344 rats. On past occasions, Osborne-Mendel and Sprague-Dawley rats have also been used. The dosing period may be followed by a 3–6 mo observation period. Generally, for each species, strain, and sex used there are a control group and two treated groups, one given the maximum tolerated dose (MTD), termed the high-dose group, and the other given half the MTD, termed the low-dose group. The MTD is taken as "the highest dose that causes no more than a 10% weight decrement, as compared to the appropriate control groups, and does not produce mortality, clinical signs of toxicity, or pathologic lesions (other than those that may be related to a neoplastic response) that would be predicted to shorten the animal's natural life span" (Sontag et al., 1976), as determined from the subchronic study. This dose is used to increase the sensitivity of the test by giving the animals as large a dose as possible, consistent with longevity. During the study, the animals that die are necropsied. At the end of the observation period, all surviving animals are sacrificed and necropsied. Diagnoses of lesions in any of the 25–30 tissues (Sontag et al., 1976) taken from each animal are made by pathologists by microscopic examination.

General Evaluation of the Bioassay

For the purpose of evaluation, an NCI carcinogen bioassay can be divided into four separate experiments. Each involves the high-dose, low-dose, and control groups of a species, strain, and sex. Thus there is an experiment on the male mice, the female mice, the male rats, and the female rats. Correspondingly, the carcinogenicity of a chemical is assessed for each experiment with a species, strain, and sex.

For each experiment, one of four possible conclusions can be drawn

for a species, strain, and sex: (1) the compound is carcinogenic, (2) the compound is a suspected carcinogen, (3) the compound has not been shown to be carcinogenic, or (4) the data are inadequate for further analysis and do not permit a determination of the carcinogenicity of the test chemical (inadequate test).

Guidelines for evaluating an NCI carcinogen bioassay on a species, strain, and sex are presented in Fig. 1.

Evaluating a Bioassay

One of the first steps in evaluating a bioassay is to determine whether the data are adequate for analysis and reporting. Irregularities in the

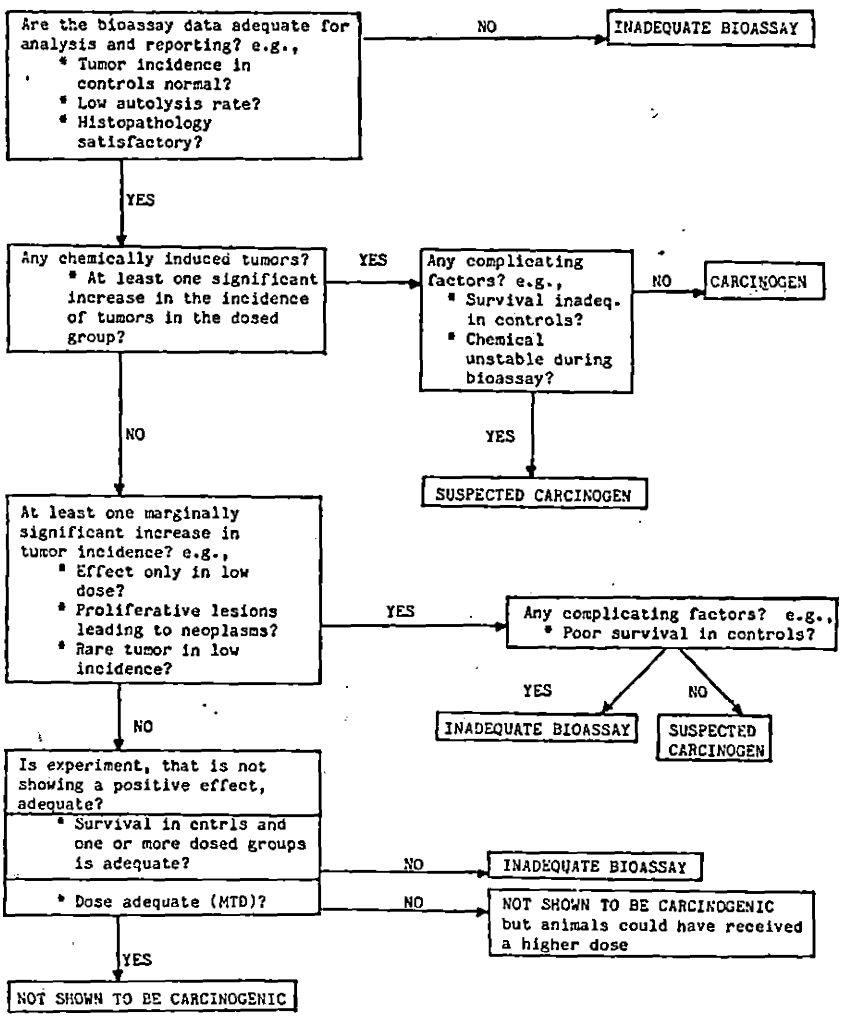

FIGURE 1. Guidelines for evaluating an NCI carcinogen bioassay.

experimental design or in the performance of the bioassay that bias the tumor incidences in the controls and/or the dosed groups can make further evaluation meaningless. Two major causes of invalid bioassay data are procedural and operational problems. The first problem occurs when the tumor incidence in the control group is unusually high due to flaws in the execution of the bioassay. For example, in the case of methiodal sodium, an unusually high incidence of leukemia was found in the control group as well as the dosed groups. These high incidences were, on further investigation, linked to the ip route of administration and/or the injection vehicle, not the chemical. Consequently, the bioassay was considered inadequate. The second problem occurs when the dosed animals have a high degree of autolysis, preventing histopathologic examination of the tissues. Specifically, in the bioassay of imidazole mustard a large number of animals were autolyzed, so that from each group of 25 animals only 5 to 10 animals could be evaluated. The data from this study were considered inappropriate for further analysis and were not reported in the NCI technical report series.

If the bioassay data are adequate for analysis, the next step is to determine whether there are any chemically induced carcinogenic effects—that is, whether there are significantly increased incidences of tumors in the dosed groups as compared to the controls. This complex process involves evaluations by pathologists, statisticians, and toxicologists and is discussed later.

If there is a significant effect, additional complicating factors may alter the final conclusion about a chemical. For example, if there is a survival problem with the controls, the tumor incidences in the controls may be artificially low, since they were not at risk of developing tumors for as long a period as the dosed animals. In these cases, it may be appropriate to compare the tumor incidences in the dosed groups with historical data on laboratory controls with similar longevity, if other variables are similar. This may change the nature of the evidence so that it supports, not a carcinogenic effect, but only a suspected carcinogenic effect. Another complicating factor is the stability or reactivity of the test chemical. For example, during the bioassay of dicofol (NCI-TR-90, 1978), the chemical changed from a solid to a liquid during storage. If such a change suggests some type of decomposition, it would affect the conclusion drawn from the bioassay data. In the case of dicofol, although the test substance produced hepatocellular carcinomas in 77% of the male mice, the substance was considered a suspect carcinogen, rather than a carcinogen, because its exact identity was not known. These examples show that even though there is a significant positive effect, complicating factors may affect the final conclusion on an experiment.

Even when there are no significant positive effects, there may be evidence suggestive of a carcinogenic effect. For example, there may be no

statistically significant tumors, but a progression of proliferative lesions leading to a neoplasm may be seen in the dosed animals. In another case, a rare tumor may be observed in several dosed animals. In a third case, there may be a positive effect in only the low-dose group while the survival in all groups is similar. All these cases may lead to the conclusion that the test chemical is a suspected carcinogen, depending on the particular circumstances.

If there are no positive or suggestive effects, then one must examine the survival of the animals. A primary issue is the number of animals at risk of developing a tumor relative to the number initially on test. The basic concern is that a sufficient number of animals remain alive long enough to be at risk of forming late-developing tumors. To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at 1 yr (52 wk). For example, in the bioassay of methylchloroform (NCI-TR-3, 1977) no positive results were found. However, the survival in most groups was poor. Of the Osborne-Mendel rats used, 32 of 50 (62%) low-dose males, 36 of 50 (72%) high-dose males, 24 of 50 (48%) low-dose females, and 21 of 50 (42%) high-dose females died within 1 yr after the start of the study. Of the mice, 21 of 50 (42%) low-dose males, 25 of 50 (50%) high-dose males, 9 of 50 (18%) low-dose females, and 20 of 40 (40%) high-dose females died within 1 year after the start of the study. Because of this poor survival and the absence of positive results, the study was considered inadequate for a determination of the carcinogenicity of the chemical. On the other hand, if a study is positive, the survival criteria are not applicable. For instances, in the dibromochloropropane (DBCP) study (NCI-TR-28, 1978) the survival of the dosed mice was less than 50% at 1 yr, but the animals died from stomach tumors induced by DBCP. The bioassay is adequate and the compound is carcinogenic in spite of the low survival rate of the animals.

Another major concern with studies that show no significant positive results is the adequacy of the administered dose. In NCI bioassays where the objective is to determine whether a chemical is carcinogenic at the MTD, the concern is whether the animals actually receive the MTD. In these studies, a dose is considered adequate if there is a detectable weight loss of up to 10% in a dosed group relative to the controls. For example, the doses of chlorpropamide administered to Fischer 344 rats were considered adequate since there was a 10% weight depression in the dosed rats compared to the controls (NCI-TR-45, 1978). The administered dose is also considered an MTD if the dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical, so that larger doses of the chemical may be inappropriate or life-threatening. An example is the bioassay of photodieldrin (NCI-TR-17, 1977) in B6C3F1 mice and Osborne-Mendel rats. There was no depression of mean body

weights in the dosed animals compared to the controls, and there was no effect of the chemical on mortality of the dosed animals. However, there were chemically induced clinical signs—convulsions and hyperexcitability—in the dosed rats and male mice. Thus the dose administered to these animals was considered adequate. In addition, doses are considered adequate if the dosed animals show a slightly increased mortality compared to the controls. For example, in the bioassay of emetine (NCI-TR-43, 1978), the male mice did not exhibit any significant tumor incidences, clinical signs, or weight depression attributed to the chemical. However, there was a decrease in survival in the animals fed 1.6 mg/kg (higher doses led to greater mortality) relative to the controls. The median survival of this dosed group was 72 wk, compared to 80 wk for the controls. This difference in survival time was considered to indicate that a sufficient dose had been administered. Finally, doses of chemicals given as 5% of the diet are generally considered adequate (Sontag et al., 1976) whether or not there are any chemically related effects, since larger doses may interfere with the nutrition and survival of the dosed animals. The bioassay of diarylanilide yellow (NCI-TR-30, 1978) is a prime example. There were no chemically related lesions, weight depression, mortality, or other adverse effects, but the doses were considered adequate since the chemical was administered as 5 and 2.5% of the diet.

Just as there is concern about administering an insufficient dose, there is also concern that too large a dose may be given. Thus the toxicity of the chemical may cause the dosed animals to die before they can develop tumors. For example, when emetine (NCI-TR-43, 1978) was administered to male mice at 6.4 and 3.2 mg/kg, almost all the animals died before the end of the first year. Therefore a dose of 1.6 mg/kg was administered to a third group of mice.

The operational and procedural parts of a bioassay are generally evaluated by the toxicologists. Their evaluations are added to those of the pathologists and statisticians in making the final evaluation of an experiment.

Interpretation by the Pathologists

A principal role of the pathologist is to decide whether there are any chemically induced lesions. Before the tumor data are interpreted, the histopathologic diagnoses are checked for proper protocols, data recording, and consistency. All pathology reports are reviewed by a team of pathologists, and discrepancies are resolved before acceptance for any further evaluation (Ward et al., 1979). If the data are considered unevaluatable (i.e., incomplete) or uninterpretable, the experiment is termed inadequate to determine the carcinogenicity of the compound. The pathologists review the microscopic slides, make histopathologic diagnoses, and document the findings. They inspect the tumor and nontumor incidence tables and write up the interpretation of the findings.

The pathologist's conclusions are based on (1) a review of the

incidence of the lesions, (2) knowledge of the normal variation in the incidence of the lesions, and (3) an opinion on whether the lesions are induced by the chemical. The latter is determined by answering several questions:

1. Are the lesions morphologically different from naturally occurring lesions?
2. Are the lesions rare in control animals?
3. What are the pathogenesis and histogenesis of the lesions (e.g., are toxic lesions, hyperplasias, dysplasias, adenomas, and carcinomas of a tissue related)?

The histogenesis of a neoplastic lesion is its progression from its nonneoplastic origin, often hyperplasia, to a metastatic cancer that kills the animal. For example, the morphology and histogenesis of rat liver tumors were reviewed by Squire and Levitt (1975). Beginning with foci of cellular alteration (hyperplasia), the lesion progresses to neoplastic nodule, to hepatocellular carcinoma, and eventually to metastatic carcinoma. In certain cases, the morphology of a chemically induced lesion can be differentiated from that of a naturally occurring lesion, e.g., "induced" squamous cell carcinoma of the lung as compared to the usual "spontaneous" alveolar-bronchiolar tumor. From these types of considerations, the pathologist draws a conclusion about the significance of the tumors seen in the experiment. For example, in the bioassay of captan in B6C3F1 mice (NCI-TR-15, 1978), there was no statistically significant increase in duodenal tumors; the incidences were 1 in 43 of the low-dose and 3 in 46 of the high-dose male mice, and 0 in 49 of the low-dose and 3 in 48 of the high-dose female mice. However, the pathologists felt that this rare tumor was related to administration of the chemical. The chemical was called a suspected carcinogen. Another study is in progress to confirm this finding.

A major issue in determining the carcinogenicity of a compound is the nature of the significant tumor types (Goodman et al., 1979; Ward et al., 1979). If malignant tumors or a combination of malignant and benign tumors are produced, then the compound is considered carcinogenic to the animals. If the significant result is only the production of benign tumors, then the compound may pose a potential health hazard and is termed a suspected carcinogen or a carcinogen, depending on the nature of the benign tumor. For example, 2,4-dinitrotoluene (NCI-TR-54, 1978) was considered a suspected carcinogen since it induced only benign tumors (fibromas of the skin and subcutaneous tissue in male Fischer 344 rats and fibroadenomas of the mammary gland in females). Ideally, a distinction should be made between truly benign tumors, which never progress to malignancy, and tumors that are in a benign state according to histopathologic criteria at the time of diagnosis. Scientific judgments in this area are limited by inability to predict the biological behavior of a lesion

on the basis of morphological criteria, but it appears that there are few, if any, truly benign tumors in rodents. If this were true, all chemicals that induce benign tumors would be termed carcinogens.

Statistical Analysis

A statistical analysis of tumor incidences is performed to determine whether the proportion of dosed animals with a tumor is different from the proportion of tumor-bearing animals in the controls. Accordingly, the incidence of neoplastic lesions is expressed as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. For example, if 50 animals were necropsied but only 49 liver tissues were examined, the denominator for the proportion with liver tumors, such as hepatocellular carcinomas, is 49. However, when gross examination was required to detect lesions for histological examination (e.g., skin or mammary gland) or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominator is the number of animals necropsied.

In almost all NCI bioassays, there are no serial sacrifices (no animals are killed at predetermined intervals before the termination of the bioassay), so that the reported "time to tumor" is the time of death of the animal with the tumor, i.e., the time to the detection of the tumor. If the tumor is life-threatening, then the time of death may be a good approximation for the time of tumor appearance. This is the case for leukemias and lymphomas, gastrointestinal cancers that lead to peritoneal metastases, and upper respiratory tract tumors that are associated with asphyxiation or pneumonia. In addition, if the tumors are observable and the time of their appearance is recorded, as for neoplasms of the skin or mammary gland, then the time to tumor appearance can be obtained. On the other hand, tumors that are not immediately life-threatening are generally detected at terminal sacrifice or at the death of the animal if the chemical is toxic.

The tumor incidences and time of death of each animal are used in analyzing the significance of tumor incidences. The basic statistics associated with the analysis of these ratios are presented here; a full discussion of the statistical methodology for analyzing bioassay data has been presented elsewhere (Gart et al., 1979).

Tumor incidences can be analyzed by the one-tailed Fisher exact test (Cox, 1970), which is used to compare the tumor incidence of a control group to that of a group of dosed animals at a given dose level. When the control is compared to k dosed groups pairwise, a correction to ensure an overall significance level of 0.05 is made. The Bonferroni inequality (Miller, 1966) requires that the p value for any comparison be less than or equal to $0.05/k$ to be significant at an overall level of 0.05, where $k = 2$ in most cases.

Tumor ratios can also be analyzed by the Cochran-Armitage test for a

linear trend in proportions with continuity correction (Thomas et al., 1977). Under the assumption of a linear trend, this test determines whether the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. This method also provides a two-tailed test of departure from linear trend. When time-to-tumor data are available, life-table methods are also appropriate (Gart et al., 1979; Thomas et al., 1977).

A scheme for the initial evaluation of these statistical tests is given in Table 1. These evaluations are based on the assumption that there was adequate and approximately equal survival in each group. The scheme is based on observing how statistical results are finally resolved in the 200 NCI reports. It is presented as an empirical formulation and does not necessarily reflect present or future evaluations. It is stressed that the scheme may be useful as a preliminary evaluation of the statistical tests. Discussions by the pathologists, toxicologists, and statisticans are necessary for a final evaluation.

Although these initial evaluations are, in general, independent of the spontaneous tumor rate, there is a major exception. This is when the low-dose comparison to controls is significant, while the high-dose comparison is not significant. If the tumor type is rare, there may be statistical evidence for a chemically related effect. If the low-dose comparison is highly significant, there may be limited evidence for an effect. For example, in the bioassay of lindane (NCI-TR-14, 1978), the only significant result was hepatocellular carcinomas and neoplastic nodules in male mice, with 5 in 49 of the pooled controls, 19 in 49 of the low-dose animals, and 9 in 46 of the high-dose animals. The incidence in the low-dose animals was statistically significant ($p = 0.001$); however, the mean incidence of hepatocellular carcinomas and neoplastic nodules in historical control animals at this laboratory was 23%, with spontaneous incidences as high as 35–40%. Thus it was concluded that the results could not be clearly associated with the chemical, and the substance was called a suspected carcinogen.

The heavy reliance on statistical evidence to support a positive effect poses the problem of assessing the error rates associated with these statistics. A recent report on error rates in bioassay results (Fears et al., 1977) reaches a number of informative conclusions. A false positive result can arise because the tumor incidence in the dosed group is greater than that in the controls due to sampling variations in the spontaneous tumor incidence rate and not to the chemical. In effect, a false positive result occurs because the dosed group has a random tumor incidence that is statistically significant. A rare tumor has less chance of occurring than a common tumor and therefore has less chance of causing a false positive. Accordingly, the chance of a false positive result occurring is highly dependent on the spontaneous tumor incidence rate. In general, tissue sites with spontaneous tumor rate above 5% have considerably higher chances

TABLE 1. Initial Evaluations of the Statistical Tests

Cochran-Armitage(1)	Fisher exact(2)	Fisher exact(2)	Statistical Conclusion(3)				
			<1%	1-5%		> 5%	
linear trend	low-dose comp.	high-dose comp.	Si	Si	HSi	Si	HSi
+	+	+	P	P	P	P	P
+	+	-	P	-	L	-	L
+	-	+	P	P	P	P	P
-	+	+	P	P	P	P	P
+	-	-	-(4)-		-	-	-
-	+	-	P	-	L	-	L
-	-	+	P	P	P	P	P
-	-	-	-(4)-		-	-	-

P = May be positive statistical evidence for carcinogenicity

L = May be limited statistical evidence for carcinogenicity

- = May be insufficient statistical evidence for carcinogenicity

(1) In the linear trend, "-" indicates non-significant result or significant result with a significant departure statistic.

(2) For the Fisher exact test, "-" means test is not significant.

(3) <1% = tumor types with <1% spontaneous tumors; 1-5% = tumor types with 1-5% spontaneous tumors; other = tumor types >5% spontaneous tumors. Si= significant result: $.001 < P < .025$; HSi = highly significant result $P < .001$.

(4) May be significant if the tumor type is rare and the binomial probability is significant, see text.

of generating false positives. The spontaneous primary tumor rates for untreated animals used in the NCI testing program, which are given in Table 2, show that there are only one to five sites with an incidence at least this high. For determining the overall false positive rate, Gart et al. (1979) proposed the formula $1-(1-p)^t$, where t is the number of target sites with spontaneous rates above 5% and p is the nominal

TABLE 2. *Percent Spontaneous Primary Tumors in Untreated Species Used at NCI for Carcinogen Bioassays*

SPECIES:	MOUSE		RAT		RAT		RAT		RAT	
STRAIN:	B6C3F1		FISCHER 344		OSB-MNDL		SPR.-DAW.		CHAR. RIV. CD	
SEX:	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
NUMBER NECROPSIED (1)	3543	3617	2960	2924	270	270	440	205	184	184
ORGAN/TISSUE										
BRAIN	<.1%	.1%	.8%	.6%	---	---	.7%	.5%	2.7%	1.6%
SKIN	3.1	1.7	7.8	3.2	8.9	5.9	3.2	3.4	7.1	3.3
MAMMARY GLAND	---	1.3	1.5	20.9	3.7	28.5	1.4	39.0	.5	45.1
CIRCULATORY SYSTEM (2)	2.9	2.4	.7	.4	4.1	2.6	---	---	2.2	---
LUNG/BRONCHI/TRACHEA	13.7	5.2	3.0	1.9	1.5	.7	---	---	1.6	1.6
LIVER	24.6	4.7	2.2	1.9	1.1	1.9	.2	.5	.5	2.2
PANCREAS	<.1	<.1	.2	---	---	---	---	---	---	---
STOMACH	.4	.4	.3	.2	---	.4	---	---	---	.5
INTESTINES (3)	.5	.2	.6	.3	.4	.4	.2	---	---	.5
KIDNEY	.3	<.1	.5	.2	3.3	2.6	---	1.0	1.6	---
URINARY BLADDER	<.1	<.1	.1	.3	.4	---	.2	---	.5	---
PREPUTIAL GLAND (4)	---	---	2.4	1.8	1.6	1.2	---	---	---	---
TESTES (5)	.4	NA	82.3	NA	.7	NA	2.0	NA	3.9	NA
OVARY	NA	.9	NA	.4	NA	1.5	NA	---	NA	.5
UTERUS	NA	1.6	NA	17.0	NA	3.7	NA	4.4	NA	3.8
PITUITARY	.3	3.6	14.7	34.9	7.4	20.0	5.9	40.0	33.2	57.6
ADRENAL	1.4	.6	12.4	5.2	10.4	10.0	.7	2.9	7.6	4.3
THYROID	1.0	1.7	8.2	6.8	9.6	11.1	.9	2.0	3.8	---
PANCREATIC ISLETS	.4	.2	3.9	.8	3.0	1.9	.5	.5	2.7	---
BODY CAVITIES	.4	.3	2.6	.4	1.9	.4	.5	1.9	2.2	---
LEUKEMIA/LYMPHOMA	10.3	20.6	19.9	13.4	3.3	1.8	4.8	0.5	3.3	3.3

(1) STUDIES TERMINATED AT 21-25 MONTHS FOR MICE AND 23-25 MONTHS FOR RATS.
(2) HEMANGIOMA AND HEMANGIOSARCOMA.
(3) DUODENUM, JEJUNM, ILEUM, CEDUM AND COLON.
(4) CLITORAL GLAND IN FEMALES.
(5) SEMINAL VISICLE AND TESTIS.

significance level. If there are 50 animals in the control and dosed groups and the Fisher exact test yields a p of 0.028 for 5 dosed animals with a tumor compared to zero in the controls, the false positive rate for female F344 rats is less than 0.134 (Gart et al., 1979).

A possible false positive is characterized by several features. The bioassay of the four experiments has a statistically significant result in only one species, strain, and sex. More specifically, the p value of the result is in the range 0.005–0.05 and the tumor type has a spontaneous rate above 5%. On the other hand, a statistically significant result in a species, strain, and sex may be considered an effect of the chemical if the tumor type is rare, the incidence in the dosed group is much higher than the spontaneous incidence, or the significance of the tumor is confirmed in the opposite sex or a different species.

As stated earlier, the scheme in Table 1 may be useful for initial evaluations. Discussions by the pathologists, toxicologists, and statisticians will determine the final conclusion. Under certain circumstances, the pathologist has indicated that an incidence of a rare tumor is significant, but this result cannot be verified by the statistical methods discussed due to the small sample size. To quantify the assertion made by the pathologist, one can calculate the binomial probability that the observed number or a greater number of tumors will occur (Fears et al., 1977). If one assumes that the tumor incidence is binomially distributed, the probability of obtaining R tumor in N animals is given by:

$$P = \sum_{i=R}^{N} \binom{N}{i} p^i (1-p)^{n-i}$$

where p is the laboratory historical tumor incidence. When this probability was less than 0.001, it was used to indicate that a substance may be a suspected carcinogen in the particular species, strain, and sex.

In other circumstances, the pathologist may indicate that certain types of tumors for a particular species, strain, and sex may have spontaneous incidences that are so high and variable that the use of these tumors as end points is difficult. In these cases, statistically significant results may be nullified. For an extensive discussion of the variability of common naturally occurring lesions, see Tarone et al. (1981). Two examples in F344 rats are interstitial cell tumors of the testes in males, which have an incidence range of 70–100%, and pituitary chromophobe adenomas in females, which have an incidence range of 30–50%.

In certain other circumstances, discussions between the scientists may indicate that statistically significant results are not meaningful since the incidences in the dosed groups are not above the normal range of incidences in controls in this laboratory. Results that are statistically significant would then be interpreted as not important. This was the case

in the bioassay of malathion (NCI-TR-24, 1978) in male mice. There was a significant dose-related trend in the incidence of hepatocellular carcinomas, with 5 in 49, 7 in 48, and 11 in 50 of the control, low-dose, and high-dose animals, respectively. However, several control groups from the same laboratory had incidences of 35–40%, which are comparable to the incidences in the dosed male mice.

The principles described in the sections above were used to evaluate some 200 chemicals. Table 3 shows chemicals that were positive in both sexes of both species; Table 4, chemicals that were positive in at least one sex of both species; and Table 5, chemicals that were positive in one species. In Table 6 the chemicals with suspected carcinogenic effects are listed. Finally, chemicals not shown to be carcinogenic are listed in Table 7 and chemicals with inadequate bioassays are given in Table 8.

DISCUSSION

The purposes of this paper are threefold: (1) to explain some of the factors involved in determining the carcinogenicity of a test chemical; (2) to present summary results for 200 chemicals recently evaluated by the National Toxicology Program at NCI; (3) to explain the principles underlying the bioassay procedures. The first two objectives have been addressed, and the principles of testing will now be discussed.

The appropriateness of carcinogen bioassays is based on several characteristics of carcinogenicity. (1) Almost all human chemical carcinogens (except possibly As) are animal carcinogens. (2) It is ethically unacceptable to perform carcinogenicity tests on the human population. (3) A number of human carcinogens were first detected as animal carcinogens, i.e., vinyl chloride, Be, Cd, and diethylstilbestrol (DES). (4) Due to the small groups of animals, usually 50–100, used in carcinogen bioassays (designed to detect 5–10% tumor incidences in the dosed groups as compared to none in the controls), the bioassays are relatively insensitive. From these facts the following premises for carcinogen bioassays have been developed. (1) Long-term effects of toxicity studies in animals are applicable to humans. (2) Due to the relative insensitivity of bioassays, exposure of experimental animals to high doses of toxic agents is a necessary and valid method of assessing potential carcinogenic hazards in humans.

In the present analysis, the evaluation of the carcinogenicity of a chemical is based on the following premises. (1) A carcinogen is any agent that induces malignant or malignant and benign tumors in a valid carcinogen bioassay. (2) Any agent that induces only benign tumors in a valid carcinogen bioassay may be a carcinogen or a suspected carcinogen, depending on the etiology and pathogenesis of the lesions. (3) The NCI carcinogen bioassays (three groups of 50 animals per sex and species) are relatively insensitive, since they are designed to detect levels of tumor

TABLE 3. NCI Carcinogen Bioassays with Positive Evidence for Carcinogenicity in Both Sexes of Both Species Tested

NCI NO.	CHEMICAL NAME CAS NUMBER	REPORT STATUS	ANIMAL STRAIN	ROUTE	ORGAN SITES	RAT M	RAT F	MOUSE M	MOUSE F
C03043	3-Amino-9-Ethylcarbazole, Hydrochloride 132-32-1	REPORT 93 PUBLISHED	F344 B6C3F1	FEED					
					LIVER, HEPATOCELLULAR TUMORS	P	P	P	P
					SKIN/SUBCUTANEOUS TISSUE	P			
					ZYMBAL S GLAND	P	P		
					UTERUS NON-SARCOMA		P		
C03747	o-Anisidine Hydrochloride 134-29-2	REPORT 89 PUBLISHED	F344 B6C3F1	FEED					
					KIDNEY	P			
					BLADDER, URINARY	P	P	P	P
					THYROID FOLLICULAR	P			
C00191	Chlordecone (Kepone) 143-50-0	REPORT A PUBLISHED	OSB-MDL B6C3F1	FEED					
					LIVER, HEPATOCELLULAR TUMORS	P	P	P	P
C03292	4-Chloro-o-Phenylenediamine 95-83-0	REPORT 63 PUBLISHED	F344 B6C3F1	FEED					
					BLADDER, URINARY	P	P		
					FORESTOMACH	P	P		
					LIVER, HEPATOCELLULAR TUMORS			P	P
C02982	p-Cresidine 120-71-8	REPORT 142 PUBLISHED	F344 B6C3F1	FEED					
					BLADDER, URINARY	P	P	P	P
					NASAL	P	P		
					LIVER, HEPATOCELLULAR TUMORS	P			P
C03258	Cupferron 135-20-6	REPORT 100 PUBLISHED	F344 B6C3F1	FEED					
					HEMANGIOSARCOMA	P	P	P	P
					LIVER, HEPATOCELLULAR TUMORS	P	P		P
					FORESTOMACH	P	P		
					ZYMBAL S GLAND		P		P
					HARDERIAN GLAND				P
C01989	2,4-Diaminoanisole Sulfate 39156-41-7 (615-05-4)	REPORT 84 PUBLISHED	F344 B6C3F1	FEED					
					SKIN/SUBCUTANEOUS TISSUE	P			
					THYROID FOLLICULAR	P	P	P	P
					ZYMBAL S GLAND	P	P		
					THYROID C-CELL	P			
					PREPUTIAL GLAND	P			
C00500A	Dibromochloropropane 96-12-8	REPORT 28 PUBLISHED	OSB-MDL B6C3F1	GAV					
					FORESTOMACH	P	P	P	P
					MAMMARY GLAND		P		
C00522A	1,2-Dibromoethane 106-93-4	REPORT 86 PUBLISHED	OSB-MDL B6C3F1	GAV					
					FORESTOMACH	P	P	P	P
					HEMANGIOSARCOMA	P			
					LIVER, HEPATOCELLULAR TUMORS		P		
					LUNG			P	P
C00511	1,2-Dichloroethane 107-06-2	REPORT 55 PUBLISHED	OSB-MDL B6C3F1	GAV					
					FORESTOMACH	P			
					HEMANGIOSARCOMA	P			
					SQ FIBROMA	P			
					MAMMARY GLAND		P		P
					LUNG			P	P
					UTERUS SARCOMA				P

					SQ FIBROMA	P			
					MAMMARY GLAND		P		P
					LUNG			P	P
					UTERUS SARCOMA				P
C03689B	p-Dioxane 123-91-1	REPORT 80 PUBLISHED	OSB-MDL B6C3F1	WATER	NASAL	P	P		
					LIVER, HEPATOCELLULAR TUMORS		P	P	P
C01923	2-Methyl-1-nitroanthraquinone 129-15-7	REPORT 29 PUBLISHED	F344 B6C3F1	FEED	SQ FIBROMA	P	P		
					LIVER, HEPATOCELLULAR TUMORS	P			
					FORESTOMACH		S		
					BLADDER, URINARY		S		
					HEMANGIOSARCOMA			P	P
C02006	Michler's Ketone 90-94-8	REPORT 181 PUBLISHED	F344 B6C3F1	FEED	LIVER, HEPATOCELLULAR TUMORS	P	P		P
					HEMANGIOSARCOMA			P	
C01661	Phenoxybenzamine Hydrochloride 63-92-3	REPORT 72 PUBLISHED	SPR-DAW B6C3F1	IP/IJ	PERITONEAL SARCOMA	P	P	P	P
C01810B	Procarbazine 366-70-1	REPORT 19 PUBLISHED	SPR-DAW B6C3F1	IP/IJ	NASAL	P	P		
					LYMPHOMA	P	P	S	S
					MAMMARY GLAND		P		
					LUNG			P	P
					UTERUS NON-SARCOMA				P
C00453	Sulfallate 95-06-7	REPORT 115 PUBLISHED	OSB-MDL B6C3F1	FEED	FORESTOMACH	P			
					MAMMARY GLAND		P		P
					LUNG			P	
C01707	4,4'-Thiodianiline 139-65-1	REPORT 47 PUBLISHED	F344 B6C3F1	FEED	LIVER, HEPATOCELLULAR TUMORS	P		P	P
					COLON	P			
					THYROID FOLLICULAR	P	P	P	P
					ZYMBAL S GLAND	P	P		
					UTERUS NON-SARCOMA		P		
C01649	Thio-TEPA 52-24-4	REPORT 58 PUBLISHED	SPR-DAW B6C3F1	IP/IJ	SKIN/SUBCUTANEOUS TISSUE	P	P	P	
					HEMATOPOIETIC SYSTEM	P		P	P
					NASAL	S	S		
					UTERUS NON-SARCOMA		S		
C02335	o-Toluidine Hydrochloride 636-21-5	REPORT 153 PUBLISHED	F344 B6C3F1	FEED	SPLENIC SARCOMA	P	P		
					MESOTHELIOMA	P			
					SQ FIBROMA	P			
					BLADDER, URINARY		P		
					MAMMARY GLAND		P		
					HEMANGIOSARCOMA			P	
					LIVER, HEPATOCELLULAR TUMORS				P
C03270	Tris (2,3-Dibromopropyl) Phosphate 126-72-7	REPORT 76 PUBLISHED	F344 B6C3F1	FEED	KIDNEY	P	P	P	
					LUNG			P	P
					FORESTOMACH			P	P
					LIVER, HEPATOCELLULAR TUMORS				P

F344 = Fischer 344 rat
OSB-MDL = Osborne Mendel rat
SPR-DAW = Sprague Dawley rat

GAV = Gavage
IP/IJ = Intraperitoneal injection
P = Positive evidence for carcinogenicity

S = Suggestive evidence for carcinogenicity
N = Not shown to be carcinogenic
I = Inadequate test

TABLE 4. NCI Carcinogen Bioassays with Positive Evidence for Carcinogenicity in at Least One Sex of Both Species Tested

NCI NO.	CHEMICAL NAME CAS NUMBER	REPORT STATUS	ANIMAL STRAIN	ROUTE	ORGAN SITES	RAT M	 F	MOUSE M	 F
C01876	2-Aminoanthraquinone 117-79-3	REPORT 144 PUBLISHED	F344 B6C3F1	FEED			N		
					LIVER, HEPATOCELLULAR TUMORS	P		P	P
					LYMPHOMA				P
C01901	1-Amino-2-Methylanthraquinone 82-28-0	REPORT 111 PUBLISHED	F344 B6C3F1	FEED					
					KIDNEY	P		S	
					LIVER, HEPATOCELLULAR TUMORS	P	P		P
C02686	Chloroform 67-66-3	REPORT D PUBLISHED	OSB-MDL B6C3F1	GAV			N		
					KIDNEY	P			
					LIVER, HEPATOCELLULAR TUMORS			P	P
C03838	3-(Chloromethyl)Pyridine Hydrochloride 6959-48-4	REPORT 95 PUBLISHED	F344 B6C3F1	GAV			N		
					FORESTOMACH	P		P	P
C03305	4-Chloro-m-Phenylenediamine 5131-60-2	REPORT 85 PUBLISHED	F344 B6C3F1	FEED			N	N	
					ADRENAL MEDULLA	P			
					LIVER, HEPATOCELLULAR TUMORS				P
C02302	2,4-Diaminotoluene 95-80-7	REPORT 162 PUBLISHED	F344 B6C3F1	FEED				N	
					LIVER, HEPATOCELLULAR TUMORS	P	P		P
					SQ FIBROMA	P			
					MAMMARY GLAND		P		
					LYMPHOMA				S
C01854	Hydrazobenzene 122-66-7	REPORT 92 PUBLISHED	F344 B6C3F1	FEED				N	
					LIVER, HEPATOCELLULAR TUMORS	P	P		P
					ZYMBAL S GLAND	P			
					MAMMARY GLAND		P		
C01627	ICRF-159 21416-87-5	REPORT 78 PUBLISHED	SPR-DAW B6C3F1	IP/IJ		N		N	
					UTERUS NON-SARCOMA		P		
					LYMPHOMA				P
C01638	Isophosphamide 3778-73-2	REPORT 32 PUBLISHED	SPR-DAW B6C3F1	IP/IJ				N	
					LYMPHOMA	S			P
					UTERUS NON-SARCOMA		P		
					MAMMARY GLAND		S		
C01990	4,4'-Methylenebis(N,N-Dimethyl)Benzen-amine 101-61-1	REPORT 186 PUBLISHED	F344 B6C3F1	FEED					
					THYROID FOLLICULAR	P	P		
					LIVER, HEPATOCELLULAR TUMORS			S	P
C03021	1,5-Naphthalenediamine 2243-62-1	REPORT 143 PUBLISHED	F344 B6C3F1	FEED					
					CLITORAL GLAND	N			
					UTERUS SARCOMA		P		
					THYROID FOLLICULAR		P		
					LIVER, HEPATOCELLULAR TUMORS			P	P
					LUNG				P
					THYROID C-CELL				P

C03021	1,5-Naphthalenediamine 2243-62-1	PUBLISHED	B6C3F1		UTERUS SARCOMA			P		
					THYROID FOLLICULAR				P	P
					LIVER, HEPATOCELLULAR TUMORS					P
					LUNG					P
					THYROID C-CELL					P
C03792	Nithiazide 139-94-6	REPORT 146 PUBLISHED	F344 B6C3F1	FEED		N				
					SKIN/SUBCUTANEOUS TISSUE		P			
					LIVER, HEPATOCELLULAR TUMORS				P	S
C02766	Nitrilotriacetic Acid (NTA) 139-13-9	REPORT 6 PUBLISHED	F344 B6C3F1	FEED		N				N
					BLADDER, URINARY		P			
					KIDNEY			P		
C01967	5-Nitroacenaphthene 602-87-9	REPORT 118 PUBLISHED	F344 B6C3F1	FEED					N	
					ZYMBAL S GLAND	P	P			
					LUNG	P	P			
					CLITORAL GLAND		P			
					MAMMARY GLAND		P			
					LIVER, HEPATOCELLULAR TUMORS					P
					OVARY					P
C01934	5-Nitro-o-Anisidine 99-59-2	REPORT 127 PUBLISHED	F344 B6C3F1	FEED						
					LIVER, HEPATOCELLULAR TUMORS				S	P
					SKIN/SUBCUTANEOUS TISSUE	P	P			
					ZYMBAL S GLAND	P	P			
					CLITORAL GLAND		P			
C00420B	Nitrofen 1836-75-5	REPORT 26 PUBLISHED	OSB-MDL B6C3F1	FEED		I				
					PANCREAS ISLET-CELL		P			
					LIVER, HEPATOCELLULAR TUMORS				P	P
					HEMANGIOSARCOMA					P
C02244	P-Nitrosodiphenylamine 156-10-5	REPORT 190 PUBLISHED	F344 B6C3F1	FEED			N			N
					LIVER, HEPATOCELLULAR TUMORS	P			P	
C01672	Phenazopyridine Hydrochloride 136-40-3	REPORT 99 PUBLISHED	F344 B6C3F1	FEED					N	
					COLON	P	P			
					LIVER, HEPATOCELLULAR TUMORS					P
C01558	Phenesterin 3546-10-9	REPORT 60 PUBLISHED	SPR-DAW B6C3F1	GAV		N				
					MAMMARY GLAND		P			
					LUNG				P	P
					LYMPHOMA				P	P
					HEART SARCOMA				P	P
C50157	Reserpine 50-55-5	REPORT IN REVIEW	F344 B6C3F1	FEED			N			
					ADRENAL MEDULLA	P				
					SEMINAL VESICLE				S	
					MAMMARY GLAND					P
C02904	2,4,6-Trichlorophenol 88-06-2	REPORT 155 PUBLISHED	F344 B6C3F1	FEED			N			
					HEMATOPOIETIC SYSTEM	P				
					LIVER, HEPATOCELLULAR TUMORS				P	P
C02299	2,4,5-Trimethylaniline 137-17-7	REPORT 160 PUBLISHED	F344 B6C3F1	FEED					N	
					LIVER, HEPATOCELLULAR TUMORS	P	P			P
					LUNG		P			
C03781	Trimethylphosphate 512-56-1	REPORT 81 PUBLISHED	F344 B6C3F1	FEED			N	N		
					SQ FIBROMA	P				
					UTERUS NON-SARCOMA					P

F344 = Fischer 344 rat
OSB-MDL = Osborne Mendel rat
SPR-DAW = Sprague Dawley rat

GAV = Gavage
IP/IJ = Intraperitoneal injection
P = Positive evidence for carcinogenicity

S = Suggestive evidence for carcinogenicity
N = Not shown to be carcinogenic
I = Inadequate test

TABLE 5. NCI Carcinogen Bioassays with Positive Evidence for Carcinogenicity in Only One Species

NCI NO.	CHEMICAL NAME CAS NUMBER	REPORT STATUS	ANIMAL STRAIN	ROUTE	ORGAN SITES	RAT M	 F	MOUSE M	 F
C01536	Acronycine 7008-42-6	REPORT 49 PUBLISHED	SPR-DAW B6C3F1	IP/IJ				I	I
					OSTEOSARCOMA	P			
					PERITONEAL SARCOMA	P	P		
					MAMMARY GLAND		P		
C00044	Aldrin 309-00-2	REPORT 21 PUBLISHED	OSB-MDL B6C3F1	FEED					N
					THYROID FOLLICULAR	S	S		
					ADRENAL CORTEX		S		
					LIVER, HEPATOCELLULAR TUMORS			P	
C01887	3-Amino-4-Ethoxyacetanilide 17026-81-2	REPORT 112 PUBLISHED	F344 B6C3F1	FEED		N	N		N
					THYROID FOLLICULAR			P	
C03963	4-Amino-2-Nitrophenol 119-34-6	REPORT 94 PUBLISHED	F344 B6C3F1	FEED				N	N
					BLADDER, URINARY	P	S		
C03065	2-Amino-5-Nitrothiazole 121-66-4	REPORT 53 PUBLISHED	F344 B6C3F1	FEED			N	N	N
					HEMATOPOIETIC SYSTEM	P			
C03736	Aniline Hydrochloride 142-04-1	REPORT 130 PUBLISHED	F344 B6C3F1	FEED				N	N
					HEMANGIOSARCOMA	P			
					MULTIPLE SITES, SARCOMA	P	P		
					SPLENIC SARCOMA	P			
C01569	5-Azacytidine 320-67-2	REPORT 42 PUBLISHED	SPR-DAW B6C3F1	IP/IJ		I	I	I	
					HEMATOPOIETIC SYSTEM				P
C02926	Azobenzene 103-33-3	REPORT 154 PUBLISHED	F344 B6C3F1	FEED				N	N
					ABDOMINAL CAVITY SARCOMA	P	P		
					MULTIPLE SITES, SARCOMA	P			
					OSTEOSARCOMA		S		
C00077	Captan 133-06-2	REPORT 15 PUBLISHED	OSB-MDL B6C3F1	FEED		N	N		
					DUODENUM			P	S
C00055	Chlorambon 133-90-4	REPORT 25 PUBLISHED	OSB-MDL B6C3F1	FEED		N	N		
					LIVER, HEPATOCELLULAR TUMORS			S	P
C00099	Chlordane 57-74-9	REPORT 8 PUBLISHED	OSB-MDL B6C3F1	FEED					
					FIBROUS HISTIOCYTOMA.	S			
					THYROID FOLLICULAR		S		
					LIVER, HEPATOCELLULAR TUMORS			P	P
C00408A	Chlorobenzilate 510-15-6	REPORT 75 PUBLISHED	OSB-MDL B6C3F1	FEED		N	N		
					LIVER, HEPATOCELLULAR TUMORS			P	P
C00102	Chlorothalonil 1897-45-6	REPORT 41 PUBLISHED	OSB-MDL B6C3F1	FEED				N	N
					KIDNEY	P	P		
C02051	5-Chloro-o-Toluidine 95-79-4	REPORT 187 PUBLISHED	F344 B6C3F1	FEED		N	N		
					HEMANGIOSARCOMA			P	P

C00102	Chlorothalonil 1897-45-6	REPORT 41 PUBL[illegible]D
C02051	5-Chloro-o-Toluidine 95-79-4	REP[illegible]37 PUBL[illegible]D

C02368	4-Chloro-o-Toluidine Hydrochloride 3165-93-3	REPORT 165 PUBLISHED
C03565	C.I. Vat Yellow 4 128-66-5	REPORT 134 PUBLISHED
C02993	m-Cresidine 102-50-1	REPORT 105 PUBLISHED
C01718	Dapsone 80-08-0	REPORT 20 PUBLISHED
C00555	p,p'-DDE 72-55-9	REPORT 131 PUBLISHED
C03827	Diaminozide 1596-84-5	REPORT 83 PUBLISHED
C00486	Dicofol 115-32-2	REPORT 90 PUBLISHED
C03816	N,N'-Diethylthiourea 105-55-5	REPORT 149 PUBLISHED
C02175	3,3'-Dimethoxybenzidine- 4,4'-Diisocyanate 91-93-0	REPORT 128 PUBLISHED
C01865	2,4-Dinitrotoluene 121-14-2	REPORT 54 PUBLISHED
C54557	Direct Black 38 1937-37-7	REPORT 108 PUBLISHED
C54579	Direct Blue 6 2602-46-2	REPORT 108 PUBLISHED
C54568	Direct Brown 95 16071-86-6	REPORT 108 PUBLISHED
C01570	Estradiol Mustard 22966-79-6	REPORT 59 PUBLISHED
C02857	Ethyl Tellurac 30145-38-1	REPORT 152 PUBLISHED
C00180	Heptachlor 76-44-8	REPORT 9 PUBLISHED

OSB-MDL B6C3F1	FEED	KIDNEY	P	P	N	N
F344 B6C3F1	FEED	HEMANGIOSARCOMA	N	N	P	P
		LIVER, HEPATOCELLULAR TUMORS			P	P
F344 B6C3F1	FEED	HEMANGIOSARCOMA	N	N	P	P
F344 B6C3F1	FEED	LYMPHOMA	N	N	P	N
F344 B6C3F1	GAV	BLADDER, URINARY	P	P	I	N
F344 B6C3F1	FEED	SPLENIC SARCOMA PERITONEAL SARCOMA	P P	N	N	N
OSB-MDL B6C3F1	FEED	LIVER, HEPATOCELLULAR TUMORS	N	N	P	P
F344 B6C3F1	FEED	UTERUS NON-SARCOMA UTERUS SARCOMA LIVER, HEPATOCELLULAR TUMORS	N	P P	S	N
OSB-MDL B6C3F1	FEED	LIVER, HEPATOCELLULAR TUMORS	N	N	P	N
F344 B6C3F1	FEED	THYROID FOLLICULAR	P	P	N	N
F344 B6C3F1	FEED	LYMPHOMA ZYMBAL S GLAND SKIN/SUBCUTANEOUS TISSUE UTERUS NON-SARCOMA	P P P	P P P	N	N
F344 B6C3F1	FEED	SKIN/SUBCUTANEOUS TISSUE MAMMARY GLAND	P	P	N	N
F344 B6C3F1	FEED	LIVER, HEPATOCELLULAR TUMORS	P	P	N	N
F344 B6C3F1	FEED	LIVER, HEPATOCELLULAR TUMORS	P	P	N	N
F344 B6C3F1	FEED	LIVER, HEPATOCELLULAR TUMORS	N	P	N	N
SPR-DAW B6C3F1	GAV	LUNG HEMANGIOSARCOMA FORESTOMACH LYMPHOMA	N	N	P P P P	S P P P
F344 B6C3F1	FEED	MESOTHELIOMA HARDERIAN GLAND	S	N	P	S
OSB-MDL B6C3F1	FEED	LIVER, HEPATOCELLULAR TUMORS	N	N	P	P

TABLE 5. NCL Carcinogen Bioassays with Positive Evidence for Carcinogenicity in Only One Species *(continued)*

NCI NO.	CHEMICAL NAME CAS NUMBER	REPORT STATUS	ANIMAL STRAIN	ROUTE	ORGAN SITES	RAT M	 F	MOUSE M	 F
C04604A	Hexachloroethane 67-72-1	REPORT 68 PUBLISHED	OSB-MDL B6C3F1	GAV		N	N		
					LIVER, HEPATOCELLULAR TUMORS			P	P
C01547	IPD 3458-22-8	REPORT 18 PUBLISHED	SPR-DAW B6C3F1	IP/IJ					
					PERITONEAL SARCOMA	S	S	P	P
C01478	Lasiocarpine 303-34-4	REPORT 39 PUBLISHED	F344	FEED					
					LIVER, HEPATOCELLULAR TUMORS	P	P		
					LIVER, ANGIOSARCOMA	P	P		
					LYMPHOMA		P		
C01978	3'-Nitro-p-Acetophenetide 1777-84-0	REPORT 133 PUBLISHED	F344 B6C3F1	FEED		N	N		N
					LIVER, HEPATOCELLULAR TUMORS			P	
C01912	6-Nitrobenzimidazole 94-52-0	REPORT 117 PUBLISHED		FEED		N	N		
					LIVER, HEPATOCELLULAR TUMORS			P	P
C00420A	Nitrofen 1836-75-5	REPORT 184 PUBLISHED	F344 B6C3F1	FEED		N	N		
					LIVER, HEPATOCELLULAR TUMORS			P	P
C02222	2-Nitro-p-Phenylenediamine 5307-14-2	REPORT 169 PUBLISHED	F344 B6C3F1	FEED		N	N	N	
					LIVER, HEPATOCELLULAR TUMORS				P
C03076	3-Nitropropionic Acid 504-88-1	REPORT 52 PUBLISHED	F344 B6C3F1	GAV			N	N	N
					LIVER, HEPATOCELLULAR TUMORS	P			
					PANCREAS ISLET-CELL	S			
C02880	N-Nitrosodiphenylamine 86-30-6	REPORT 164 PUBLISHED	F344 B6C3F1	FEED				N	N
					BLADDER, URINARY	P	P		
					SQ FIBROMA		S		
C01843	5-Nitro-o-Toluidine 99-55-8	REPORT 107 PUBLISHED	F344 B6C3F1	FEED		N	N		
					HEMANGIOSARCOMA			P	P
					LIVER, HEPATOCELLULAR TUMORS			P	P
C01445A	NTA Trisodium Salt.H2O 18662-53-8	REPORT 6 PUBLISHED	F344	FEED					
					KIDNEY	P	P		
					URETER	P			
					BLADDER, URINARY		P		
C02824	Piperonyl Sulfoxide 120-62-7	REPORT 124 PUBLISHED	F344 B6C3F1	FEED		N	N		N
					LIVER, HEPATOCELLULAR TUMORS			P	
C04126	Pivalolactone 1955-45-9	REPORT 140 PUBLISHED	F344 B6C3F1	GAV				N	N
					FORESTOMACH	P	P		
C03850	p-Quinone Dioxime 105-11-3	REPORT 179 PUBLISHED	F344 B6C3F1	FEED		N		N	N
					BLADDER, URINARY		P		

C03850	p-Quinone Dioxime 105-11-3	REPORT [illegible] PUBLISH	F344 B6C3F1	FEED	BLADDER, URINARY	N	P	N	N	
C03554	1,1,2,2-Tetrachloroethane 79-34-5	REPORT 27 PUBLISHED	OSB-MDL B6C3F1	GAV	LIVER, HEPATOCELLULAR TUMORS	N	N	P	P	
C04580A	Tetrachloroethylene 127-18-4	REPORT 13 PUBLISHED	OSB-MDL B6C3F1	GAV	LIVER, HEPATOCELLULAR TUMORS	I	I	P	P	
C00168	Tetrachlorvinphos 961-11-5	REPORT 33 PUBLISHED	OSB-MDL B6C3F1	FEED	THYROID C-CELL ADRENAL CORTEX LIVER, HEPATOCELLULAR TUMORS	N	5 5	P	S	
C01581	B-TGDR 789-61-7	REPORT 57 PUBLISHED	SPR-DAW B6C3F1	IP/IJ	ZYMBAL S GLAND	S	P	I	I	
C00259	Toxaphene 8001-35-2	REPORT 37 PUBLISHED	OSB-MDL B6C3F1	FEED	THYROID FOLLICULAR LIVER, HEPATOCELLULAR TUMORS	S	S	P	P	
C04579	1,1,2-Trichloroethane 79-00-5	REPORT 74 PUBLISHED	OSB-MDL B6C3F1	GAV	LIVER, HEPATOCELLULAR TUMORS ADRENAL	N	N	P S	P P	
C04546A	Trichloroethylene 79-01-6	REPORT 2 PUBLISHED	OSB-MDL B6C3F1	GAV	LIVER, HEPATOCELLULAR TUMORS	N	N	P	P	
C00442	Trifluralin 1582-09-8	REPORT 34 PUBLISHED	OSB-MDL B6C3F1	FEED	LIVER, HEPATOCELLULAR TUMORS LUNG FORESTOMACH	N	N	N	P S S	
C02186	Trimethylthiourea 2489-77-2	REPORT 129 PUBLISHED	F344 B6C3F1	FEED	THYROID FOLLICULAR	N	P	N	N	

F344 = Fischer 344 rat
OSB-MDL = Osborne Mendel rat
SPR-DAW = Sprague Dawley rat
GAV = Gavage
IP/IJ = Intraperitoneal injection
P = Positive evidence for carcinogenicity
S = Suggestive evidence for carcinogenicity
N = Not shown to be carcinogenic
I = Inadequate test

TABLE 6. NCI Carcinogen Bioassays with Evidence Suggestive of a Carcinogenic Effect

NCI NO.	CHEMICAL NAME CAS NUMBER	REPORT STATUS	ANIMAL STRAIN	ROUTE	ORGAN SITES	RAT M	 F	MOUSE M	 F
C03247	Acetohexamide 968-81-0	REPORT 50 PUBLISHED	F344 B6C3F1	FEED			N	N	N
					LEUKEMIA	S			
C04615	Allyl Chloride 107-05-1	REPORT 73 PUBLISHED	OSB-MDL B6C3F1	GAV		N	N		
					FORESTOMACH			S	S
C03758	p-Anisidine Hydrochloride 20265-97-8	REPORT 116 PUBLISHED	F344 B6C3F1	FEED			N	N	N
					PREPUTIAL GLAND	S			
C02664	Arochlor-1254 27323-18-8	REPORT 38 PUBLISHED	F344	FEED	LIVER, HEPATOCELLULAR TUMORS	S	S		
					GASTROINTESTINAL TRACT	S	S		
C00066	Azinphosmethyl 86-50-0	REPORT 69 PUBLISHED	OSB-MDL B6C3F1	FEED			N	N	N
					THYROID FOLLICULAR	S			
					PANCREAS ISLET-CELL	S			
C03521	1H-Benzotriazole 95-14-7	REPORT 88 PUBLISHED	F344 B6C3F1	FEED				N	
					BRAIN	S	S		
					LUNG				S
C03598	Butylated Hydroxytoluene (BHT) 128-37-0	REPORT 150 PUBLISHED	F344 B6C3F1	FEED		N	N		N
					LUNG			S	
C02039A	p-Chloroaniline 106-47-8	REPORT 189 PUBLISHED	F344 B6C3F1	FEED			N		
					SPLENIC SARCOMA	S			
					HEMANGIOSARCOMA			S	S
C03316	2-Chloro-p-Phenylenediamine Sulfate 61702-44-1	REPORT 113 PUBLISHED	F344 B6C3F1	FEED				N	N
					BLADDER, URINARY	S	S		
C00431	Clonitralid 1420-04-8	REPORT 91 PUBLISHED	OSB-MDL B6C3F1	FEED		N		I	N
					MAMMARY GLAND		S		
					FORESTOMACH		S		
C02028	Dibutyltin Diacetate 1067-33-0	REPORT 183 PUBLISHED	F344 B6C3F1	FEED		N		N	N
					UTERUS NON-SARCOMA		S		
C03667B	2,7-Dichlorodibenzo-p-Dioxin (DCDD) 33857-26-0	REPORT 123 PUBLISHED	OSB-MDL B6C3F1	FEED		N	N		N
					LYMPHOMA			S	
					LIVER, HEPATOCELLULAR TUMORS			S	
					HEMANGIOSARCOMA			S	
C04535	1,1-Dichloroethane 75-34-3	REPORT 66 PUBLISHED	OSB-MDL B6C3F1	GAV		N		N	
					MAMMARY GLAND		S		
					HEMANGIOSARCOMA		S		
					UTERUS NON-SARCOMA				S
C00113A	Dichlorvos 62-73-7	REPORT 10 PUBLISHED	OSB-MDL B6C3F1	FEED		N	N		N
					ESOPHAGUS			S	
C04524	N,N'-Dicyclohexylthiourea	REPORT 56	F344	FEED			N	N	N

C00113A	Dichlorvos 62-73-7	R 10 P HED
C04524	N,N'-Dicyclohexylthiourea	REPORT 56
	1212-29-9	PUBLISHED
C00124A	Dieldrin 60-57-1	REPORT 21 PUBLISHED
C03009	2,5-Dithiobiurea 142-46-1	REPORT 132 PUBLISHED
C02868	p,p-Ethyl DDD (Perthane) 72-56-0	REPORT 156 PUBLISHED
C08651	Fenthion 55-38-9	REPORT 103 PUBLISHED
C00226	Parathion 56-38-2	REPORT 70 PUBLISHED
C00588	Phosphamidon 13171-21-6	REPORT 16 PUBLISHED
C00237A	Picloram 1918-02-1	REPORT 23 PUBLISHED
C04137	Proflavine 952-23-8	REPORT 5 PUBLISHED
C02200	Styrene 100-42-5	REPORT 185 PUBLISHED
C00475	TDE 72-54-8	REPORT 131 PUBLISHED

F344 = Fischer 344 rat
OSB-MDL = Osborne Mendel rat
SPR-DAW = Sprague Dawley rat
GAV = Gavage
IP/IJ = Intraperitoneal injection
P = Positive evidence for carcinogenicity
S = Suggestive evidence for carcinogenicity
N = Not shown to be carcinogenic
I = Inadequate test

		UTERUS NON-SARCOMA				S
OSB-MDL B6C3F1	FEED	ESOPHAGUS	N	N	S	N
F344	FEED			N	N	N

B6C3F1		THYROID FOLLICULAR	S			
OSB-MDL B6C3F1	FEED	LIVER, HEPATOCELLULAR TUMORS	N	N	S	N
F344 B6C3F1	FEED	LIVER, HEPATOCELLULAR TUMORS	N	N	N	S
F344 B6C3F1	FEED	LIVER, HEPATOCELLULAR TUMORS	N	N	N	S
F344 B6C3F1	FEED	SKIN/SUBCUTANEOUS TISSUE	N	N	S	N
OSB-MDL B6C3F1	FEED	ADRENAL CORTEX	S	S	N	N
OSB-MDL B6C3F1	FEED	HEMANGIOSARCOMA THYROID C-CELL	S	S	N	N
OSB-MDL B6C3F1	FEED	LIVER, HEPATOCELLULAR TUMORS	S	S	N	N
F344 B6C3F1	FEED	GASTROINTESTINAL TRACT LIVER, HEPATOCELLULAR TUMORS	S	I	I	S
F344 B6C3F1	GAV	LUNG	N	N	S	N
OSB-MDL B6C3F1	FEED	THYROID FOLLICULAR	S	N	N	N

TABLE 7. NCI Carcinogen Bioassays with No Significant Evidence for Carcinogenicity

NCI NO.	CHEMICAL NAME CAS NUMBER	REPORT STATUS	ANIMAL STRAIN	ROUTE	ORGAN SITES	RAT M	RAT F	MOUSE M	MOUSE F
C08640	Aldicarb 116-06-3	REPORT 136 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C08684	Anilazine 101-05-3	REPORT 104 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C01730	o-Anthranilic Acid 118-92-3	REPORT 36 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C02697	Aspirin, Phenacetin, And Caffeine 8003-03-0	REPORT 67 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C02937	Calcium Cyanamide 156-62-7	REPORT 163 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C03805	Carbromal 77-65-6	REPORT 173 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C03770	4'-(Chloroacetyl)-Acetanilide 140-49-8	REPORT 177 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C02960	(2-Chloroethyl) Trimethylammonium Chloride 999-81-5	REPORT 158 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C03907	2-(Chloromethyl)Pyridine Hydrochloride 6959-47-3	REPORT 178 PUBLISHED	F344 B6C3F1	GAV		N	N	N	N
C00533	Chloropicrin 76-06-2	REPORT 65 PUBLISHED	OSU-MDL B6C3F1	GAV		I	I	N	N
C02040	3-Chloro-p-Toluidine 95-74-9	REPORT 145 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C01752	Chlorpropamide 94-20-2	REPORT 45 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C08662	Coumaphos 56-72-4	REPORT 96 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C00464	DDT 50-29-3	REPORT 131 PUBLISHED	OSU-MDL B6C3F1	FEED		N	N	N	N
C03269	Diarylanilide Yellow 6358-85-6	REPORT 30 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C08673	Diazinon 333-41-5	REPORT 137 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C03656A	Dibenzo-p-Dioxin 262-12-4	REPORT 122 PUBLISHED	OSU-MDL B6C3F1	FEED		N	N	N	N

C00673	Diazinon 333-41-5	REPORT 137 PUBLISH
C03656A	Dibenzo-p-Dioxin 262-12-4	REPORT PUBLISHED

C00124	Dieldrin 60-57-1	REPORT 22 PUBLISHED
C00135	Dimethoate 60-51-5	REPORT 4 PUBLISHED
C02255	2,4-Dimethoxyaniline Hydrochloride 54150-69-5	REPORT 171 PUBLISHED
C50055	Dimethyl Terephthalate 120-61-6	REPORT 121 PUBLISHED
C00395	Dioxathion 78-34-2	REPORT 125 PUBLISHED
C03974	EDTA Trisodium Salt (Trihydrate) 150-38-9	REPORT 11 PUBLISHED
C00566	Endosulfan 115-29-7	REPORT 62 PUBLISHED
C00157	Endrin 72-20-8	REPORT 12 PUBLISHED
C01694	Ethionamide 536-33-4	REPORT 46 PUBLISHED
C03010	Formulated Fenaminosulf 140-56-7	REPORT 101 PUBLISHED
C02653	Hexachlorophene 70-30-4	REPORT 40 PUBLISHED
C04568	Iodoform 75-47-8	REPORT 110 PUBLISHED
C02891	Lead Dimethyldithiocarbamate 19010-66-3	REPORT 151 PUBLISHED
C00204	Lindane 58-89-9	REPORT 14 PUBLISHED
C03861	Lithocholic Acid 434-13-9	REPORT 175 PUBLISHED
C00215A	Malathion 121-75-5	REPORT 24 PUBLISHED
C50000	dl-Menthol 89-78-1	REPORT 98 PUBLISHED
C00497	Methoxychlor 72-43-5	REPORT 35 PUBLISHED
C02971	Methyl Parathion 298-00-0	REPORT 157 PUBLISHED
C00544	Mexacarbate 315-18-4	REPORT 147 PUBLISHED

F344 B6C3F1	FEED	N	N	N	N
OSB-MDL B6C3F1	FEED	N	N	N	N

F344	FEED	N	N		
OSB-MDL B6C3F1	FEED	N	N	N	N
F344 B6C3F1	FEED	N	N	N	N
F344 B6C3F1	FEED	N	N	N	N
OSB-MDL B6C3F1	FEED	N	N	N	N
F344 B6C3F1	FEED	N	N	N	N
OSB-MDL B6C3F1	FEED	I	N	I	N
OSB-MDL B6C3F1	FEED	N	N	N	N
OSB-MDL B6C3F1	FEED	N	N	N	N
F344 B6C3F1	FEED	N	N	N	N
F344	FEED	N	N		
OSB-MDL B6C3F1	GAV	N	N	N	N
F344 B6C3F1	FEED	N	N	N	N
OSB-MDL B6C3F1	FEED	N	N	N	N
F344 B6C3F1	GAV	N	N	N	N
OSB-MDL B6C3F1	FEED	N	N	N	N
F344 B6C3F1	FEED	N	N	N	N
OSB-MDL B6C3F1	FEED	N	N	N	N
F344 B6C3F1	FEED	N	N	N	N
OSB-MDL B6C3F1	FEED	N	N	N	N

TABLE 7. NCL Carcinogen Bioassays with No Significant Evidence for Carcinogenicity (*continued*)

NCI NO.	CHEMICAL NAME CAS NUMBER	REPORT STATUS	ANIMAL STRAIN	ROUTE	ORGAN SITES	RAT M	RAT F	MOUSE M	MOUSE F
C03281	N-(1-Naphthyl)Ethylenediamino.2HCl 1465-25-4	REPORT 168 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C01945	4-Nitroanthranilic Acid 619-17-0	REPORT 109 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C01956	1-Nitronaphthalene 86-57-7	REPORT 64 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C03941	4-Nitro-o-Phenylenediamine 99-56-9	REPORT 180 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C02211	Beta-Nitrostyrene and Styrene 102-96-5 100-42-5	REPORT 170 PUBLISHED	F344 B6C3F1	GAV		N	N	N	N
C01445B	NTA Trisodium Salt.H2O 18662-53-8	REPORT 6 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C00419A	Pentachloronitrobenzene 82-68-8	REPORT 61 PUBLISHED	DSB-MDL B6C3F1	FEED		N	N	N	N
C01741	Phenformin 114-86-3	REPORT 7 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C03930	p-Phenylenediamine Dihydrochloride 624-18-0	REPORT 174 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C03952	1-Phenyl-3-Methyl-5-Pyrazolone 89-25-8	REPORT 141 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C02233	N-Phenyl-p-Phenylenediamine 101-54-2	REPORT 82 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C02017	1-Phenyl-2-Thiourea 103-85-5	REPORT 148 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C00599	Photodieldrin 13366-73-9	REPORT 17 PUBLISHED	DSB-MDL B6C3F1	FEED		N	N	N	N
C03612	Phthalamide 88-96-0	REPORT 161 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C03601	Phthalic Anhydride ...85-44-9	REPORT 159 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N
C02813	Piperonyl Butoxide 51-03-6	REPORT 120 PUBLISHED	F344 B6C3F1	FEED		N	N	N	N

C03601	Phthalic Anhydride	85-44-9
C02813	Piperonyl Butoxide	51-03-6
C01785	Pyrazinamide	98-96-4
C01683	Pyrimethamine	58-14-0
C02835	Sodium Diethyldithiocarbamate	148-18-5
C50022	Sulfisoxazole	127-69-5
C04557	3-Sulfolene	77-79-2
C03032	2,3,5,6-Tetrachloro-4-Nitroanisole	2438-88-2
C02959	Tetraethylthiuram Disulfide	97-77-8
C04240	Titanium Dioxide	13463-67-7 1309-63-3
C03327	Tolazamide	1156-19-0
C01763	Tolbutamide	64-77-7
C01832	2,5-Toluenediamine Sulfate	6369-59-1
C04637	Trichlorofluoromethane	75-69-4
C00260	Triphenyltin Hydroxide	76-87-9
C01729	L-Tryptophan	73-22-3

F344 = Fischer 344 rat
OSB-MDL = Osborne Mendel rat
SPR-DAW = Sprague Dawley rat
GAV = Gavage
IP/IJ = Intraperitoneal injection
N = Not shown to be carcinogenic
I = Inadequate test

REPORT 139 PUBLISHED	F344 B6C3F1	FEED				
REPORT 10 PUBLISHED	F344 B6C3F1	FEED	N	N	N	N

REPORT 48 PUBLISHED	F344 B6C3F1	FEED	N	N	N	I
REPORT 77 PUBLISHED	F344 B6C3F1	FEED	N	N	I	N
REPORT 172 PUBLISHED	F344 B6C3F1	FEED	N	N	N	N
REPORT 138 PUBLISHED	F344 B6C3F1	GAV	N	N	N	N
REPORT 102 PUBLISHED	OSB-MDL B6C3F1	GAV	N	N	N	N
REPORT 114 PUBLISHED	F344 B6C3F1	FEED	N	N	N	N
REPORT 166 PUBLISHED	F344 B6C3F1	FEED	N	N	N	N
REPORT 97 PUBLISHED	F344 B6C3F1	FEED	N	N	N	N
REPORT 51 PUBLISHED	F344 B6C3F1	FEED	N	N	N	N
REPORT 31 PUBLISHED	F344 B6C3F1	FEED	N	N	N	N
REPORT 126 PUBLISHED	F344 B6C3F1	FEED	N	N	N	N
REPORT 106 PUBLISHED	OSB-MDL B6C3F1	GAV	I	I	N	N
REPORT 139 PUBLISHED	F344 B6C3F1	FEED	N	N	N	N
REPORT 71 PUBLISHED	F344 B6C3F1	FEED	N	N	N	N

TABLE 8. NCI Carcinogen Bioassays That Are Inadequate

NCI NO.	CHEMICAL NAME CAS NUMBER	REPORT STATUS	ANIMAL STRAIN	ROUTE
C02108	Acetamide 60-35-5	NO TECH RPT; INCONCLUSIVE	F344 B6C3F1	FEED
C02095	Adipamide 628-94-4	NO TECH RPT; INCONCLUSIVE	F344 B6C3F1	FEED
C01514	Adriamycin 23214-92-8	NO TECH RPT; INCONCLUSIVE	F344 B6C3F1	IP/IJ
C02120	l-Arginine Glutamate 4320-30-3	NO TECH RPT; INCONCLUSIVE	F344 B6C3F1	FEED
C02131	N-Butylurea 592-31-4	NO TECH RPT; INCONCLUSIVE	F344 B6C3F1	FEED
C04591A	Carbon Disulfide 75-15-0	NO TECH RPT; INCONCLUSIVE	OSB-MDL B6C3F1	GAV
C01821	N,N-Dimethyl-p-Nitrosoaniline 138-89-6	NO TECH RPT; INCONCLUSIVE	F344 B6C3F1	FEED
C01605	Emetine 483-18-1	REPORT 43 PUBLISHED	SPR-DAW B6C3F1	IP/IJ
C50259	Hexamethylmelamine 645-05-6	NO TECH RPT; INCONCLUSIVE	F344 B6C3F1	IP/IJ
C02142	Hexanamide 628-02-4	NO TECH RPT; INCONCLUSIVE	F344 B6C3F1	FEED
C03190	Methansulfon-m-Anisidide, 4'-(9-Acridinyl-amino)-, monohydrochloride UNK0579	NO TECH RPT; INCONCLUSIVE	F344 B6C3F1	IP/IJ
C02084	Nitrous Acid, Sodium Salt 7632-00-0	NO TECH RPT; INCONCLUSIVE	 B6C3F1	FEED
C02153	p-Tolylurea 622-51-5	NO TECH RPT; INCONCLUSIVE	F344 B6C3F1	FEED
C04626A	1,1,1-Trichloroethane 71-55-6	REPORT 3 PUBLISHED	OSB-MDL B6C3F1	GAV
C02119	Urea 57-13-6	NO TECH RPT; INCONCLUSIVE	F344 B6C3F1	FEED

F344 = Fischer 344 rat
OSB-MDL = Osborne Mendel rat
SPR-DAW = Sprague Dawley rat
GAV = Gavage
IP/IJ = Intraperitoneal injection

incidences higher than 10% when there are no tumors in the control group; as a consequence, negative results do not necessarily mean that the test chemical is not a carcinogen. (4) Any substance that is deemed to be a carcinogen or a suspected carcinogen is a potential hazard to humans unless proved otherwise. The extent of the health risk to humans may be a matter for further research.

These premises are scientific issues. Increasing knowledge about chemical carcinogenesis may validate, alter, or eliminate any of them. As a consequence, the design, conduct, and evaluation of the carcinogen bioassay will undergo an evolutionary process. We hope that the procedures described in this paper will serve as discussion points for further developments of rodent bioassays.

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NCI-TR-15. 1978. Bioassay of captan for possible carcinogenicity. *Carcinogenesis Tech. Rep. Ser. 15, DHEW Publ. 77-815.*

NCI-TR-17. 1977. Bioassay of photodieldrin for possible carcinogenicity. *Carcinogenesis Tech. Rep. Ser. 17, DHEW Publ. 78-828.*

NCI-TR-24. 1978. Bioassay of malathion for possible carcinogenicity. *Carcinogenesis Tech. Rep. Ser. 24, DHEW Publ. 78-828.*

NCI-TR-25. 1978. Bioassay of chloramben for possible carcinogenicity. *Carcinogenesis Tech. Rep. Ser. 25, DHEW Publ. 78-828.*

NCI-TR-28. 1978. Bioassay of dibromochloropropane for possible carcinogenicity. *Carcinogenesis Tech. Rep. Ser. 28, DHEW Publ. 78-828.*

NCI-TR-30. 1978. Bioassay of diarylanilide yellow for possible carcinogenicity. *Carcinogenesis Tech. Rep. Ser. 30, DHEW Publ. 78-828.*

NCI-TR-43. 1978. Bioassay of emetine for possible carcinogenicity. *Carcinogenesis Tech. Rep. Ser. 43, DHEW Publ. 78-828.*

NCI-TR-45. 1978. Bioassay of chlorpropamide for possible carcinogenicity. *Carcinogenesis Tech. Rep. Ser. 45, DHEW Publ. 78-845.*

F344 = Fischer 344 rat
OSB-MDL = Osborne Mendel rat
SPR-DAW = Sprague Dawley rat
GAV = Gavage
IP/IJ = Intraperitoneal injection

NCI-TR-54. 1978. Bioassay of 2,4-dinitrotoluene for possible carcinogenicity. *Carcinogenesis Tech. Rep. Ser. 54, DHEW Publ. 78-828.*

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