NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 400

# TOXICOLOGY AND CARCINOGENESIS STUDIES OF 2,3-DIBROMO-1-PROPANOL

## (CAS NO. 96-13-9)

# IN F344/N RATS AND B6C3F$_1$ MICE

## (DERMAL STUDIES)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

## FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

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NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

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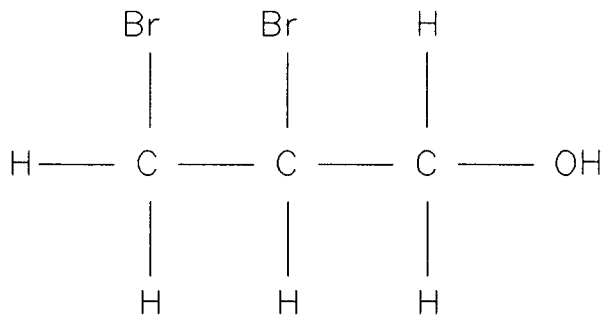
# ABSTRACT



**2,3-DIBROMO-1-PROPANOL**

CAS No. 96-13-9

Chemical Formula: $C_3H_6Br_2O$ Molecular Weight: 217.9

**Synonyms:** 2,3-dibromopropanol; 2,3-dibromopropyl alcohol


2,3-Dibromo-1-propanol, a colorless liquid, has been used as a flame retardant, as an intermediate in the preparation of the flame retardant tris(2,3-dibromopropyl) phosphate, and as an intermediate in the manufacture of pesticides and pharmaceutical preparations. Toxicology and carcinogenicity studies were conducted by applying 2,3-dibromo-1-propanol (approximately 98% pure) in ethanol to the subscapular area of the skin of male and female F344/N rats and B6C3F$_1$ mice 5 days per week for 16 days, 13 weeks, 48 to 51 weeks (male rats), 52 to 55 weeks (female rats), 36 to 39 weeks (male mice), or 39 to 42 weeks (female mice). Genetic toxicology studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, *Drosophila melanogaster*, mouse lymphoma cells, and mouse bone marrow cells.

## 16-Day Study in Rats

Groups of five male and five female rats received dermal applications of 0, 44, 88, 177, 375, or 750 mg/kg 2,3-dibromo-1-propanol 5 days per week for 16 days. One male and one female receiving 750 mg/kg died before the end of the study. The mean body weight gains and final mean body weights of dosed rats were similar to those of the controls. There were no clinical findings or gross lesions associated with chemical application.

## 16-Day Study in Mice

Groups of five male and five female mice received dermal applications of 0, 44, 88, 177, 375, or 750 mg/kg 2,3-dibromo-1-propanol 5 days per week for 16 days. Four males and one female receiving 750 mg/kg died before the end of the study. The mean body weight gains and final mean body weights of dosed mice were similar to those of the controls. There were no clinical findings or gross lesions associated with chemical application.

## 13-Week Study in Rats

Groups of 10 male and 10 female rats received dermal applications of 0, 44, 88, 177, 375, or 750 mg/kg 2,3-dibromo-1-propanol 5 days per week for 13 weeks. All rats survived until the end of the study. For rats in the 750 mg/kg groups, the mean body weight gain was 11% lower than that of the

controls for males and 13% lower for females. The mean liver weights and liver-weight-to-body-weight ratios of males receiving 375 or 750 mg/kg and of females receiving 750 mg/kg were increased.

Chemical-related lesions occurred in the kidney of male rats and in the liver of female rats. The average severity of nephropathy was slightly increased in males receiving dermal applications of 750 mg/kg, while individual cell necrosis was observed in the liver of all female rats in the 750 mg/kg group.

## 13-Week Study in Mice

Groups of 10 male and 10 female mice received dermal applications of 0, 44, 88, 177, 375, or 750 mg/kg 2,3-dibromo-1-propanol 5 days per week for 13 weeks. Eight male mice receiving 750 mg/kg died during the study, while all female mice survived. The final mean body weights of dosed and control mice were similar. The mean liver weights and liver-weight-to-body-weight ratios of males receiving 375 or 750 mg/kg and of females receiving 750 mg/kg were increased.

Chemical-related lesions occurred in the liver and lung of mice. Centrilobular hepatocellular necrosis occurred in all males in the 750 mg/kg group that died during the study, while individual cell necrosis was observed in the liver of females receiving 177, 375, or 750 mg/kg. Pleomorphism of the epithelium in pulmonary bronchioles occurred with a dose-related increased incidence in males and females. Necrosis of the bronchiolar epithelium was observed in males receiving 750 mg/kg.

## Long-Term Study in Rats

Originally planned to last for 2 years, the chronic study in rats was terminated early because of reduced survival in the high-dose groups related to chemical-induced neoplasms and because of the detection of antibodies to lymphocytic choriomeningitis virus in sentinel mice. Groups of 50 male and 50 female rats received dermal applications of 0, 188, or 375 mg/kg 2,3-dibromo-1-propanol 5 days per week for 48 to 51 weeks (males) or 52 to 55 weeks (females).

### *Survival, Body Weights, and Clinical Findings*

The survival of 375 mg/kg male and female rats was significantly lower than that of the controls (males: 50/50, 41/50, 16/50; females: 48/50, 38/50, 24/50). In the 375 mg/kg groups, the final mean body weight was 23% lower than that of the controls for males and 14% lower for females. There were no chemical-related clinical findings.

### *Pathology Findings*

Application of 2,3-dibromo-1-propanol to the skin produced significant dose-related increases in the incidences of neoplasms at numerous sites in male and female rats. Almost all dosed rats had malignant neoplasms; only one control male and one control female had malignant neoplasms. In male rats, the incidences of benign or malignant neoplasms of the skin, nose, Zymbal's gland, oral mucosa, esophagus, and small and large intestines were significantly increased in the low- and high-dose groups, while the incidences of neoplasms of the forestomach and liver were significantly increased only in the high-dose group. Neoplasms of the kidney, vascular neoplasms of the spleen, and mesotheliomas in males occurred with a significant positive trend. In female rats, the incidences of benign or malignant neoplasms of the nose, Zymbal's gland, oral mucosa, esophagus, large intestine, and liver were significantly increased in the low- and high-dose groups, while the incidences of neoplasms of the skin, forestomach, small intestine, mammary gland, and clitoral gland were significantly increased in the high-dose group only. Neoplasms of the kidney in females occurred with a significant positive trend.

## Long-Term Study in Mice

Originally planned to last for 2 years, the chronic study in mice was terminated early because of the detection of antibodies to lymphocytic choriomeningitis virus in sentinel mice. Groups of 50 male and 50 female mice received dermal applications of 0, 88, or 177 mg/kg 2,3-dibromo-1-propanol 5 days per week for 36 to 39 weeks (males) or 39 to 42 weeks (females).

### *Survival, Body Weights, and Clinical Findings*

All mice (except two low-dose females) survived until study termination. Mean body weights of control and

dosed mice were similar throughout the study, and there were no clinical findings attributed to 2,3-dibromo-1-propanol.

### *Pathology Findings*

Application of 2,3-dibromo-1-propanol to the skin produced significant dose-related increases in the incidences of neoplasms at several sites in male and female mice. Benign or malignant neoplasms were observed in 40% of the low-dose males, 66% of the high-dose males, 52% of the low-dose females, and 56% of the high-dose females. In control groups, neoplasms occurred in 6% of the males and 10% of the females. In male and female mice, the incidences of benign or malignant neoplasms of the forestomach were significantly increased in the low- and high-dose groups, while the incidences of neoplasms of the skin were significantly increased only in the high-dose groups. The incidences of liver and lung neoplasms were increased in high-dose males.

## GENETIC TOXICOLOGY

2,3-Dibromo-1-propanol was mutagenic in a variety of short-term tests, independent of exogenous metabolic activation (S9). It induced gene mutations in three strains of *Salmonella typhimurium* (TA98, TA100, and TA1535) and was positive in the mouse lymphoma assay for induction of trifluorothymidine resistance in L5178Y cells. 2,3-Dibromo-1-propanol induced sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells. In germ cells of male *Drosophila melanogaster*, 2,3-dibromo-1-propanol induced sex-linked recessive lethal mutations and reciprocal translocations. Results of an *in vivo* bone marrow micronucleus assay in male mice treated with 2,3-dibromo-1-propanol were negative.

## CONCLUSIONS

Under the conditions of these long-term dermal studies, there was *clear evidence of carcinogenic activity** of 2,3-dibromo-1-propanol in male F344/N rats based on increased incidences of neoplasms of the skin, nose, oral mucosa, esophagus, forestomach, small and large intestine, Zymbal's gland, liver, kidney, tunica vaginalis, and spleen. There was *clear evidence of carcinogenic activity* of 2,3-dibromo-1-propanol in female F344/N rats based on increased incidences of neoplasms of the skin, nose, oral mucosa, esophagus, forestomach, small and large intestine, Zymbal's gland, liver, kidney, clitoral gland, and mammary gland. There was *clear evidence of carcinogenic activity* of 2,3-dibromo-1-propanol in male B6C3F$_1$ mice based on increased incidences of neoplasms of the skin, forestomach, liver, and lung. There was *clear evidence of carcinogenic activity* of 2,3-dibromo-1-propanol in female B6C3F$_1$ mice based on increased incidences of neoplasms of the skin and the forestomach. The increased incidences of alveolar/bronchiolar adenomas in female mice may have been related to chemical administration.

In rats, 2,3-dibromo-1-propanol caused increased incidences of hyperkeratosis in the skin, forestomach, and esophagus, epithelial dysplasia in the nose, pleomorphism and basophilic and clear cell changes in the liver, and nuclear enlargement in the kidney. There were also chemical-related increases in the incidences of forestomach ulcers and acanthosis, angiectasis in the liver, and renal hyperplasia in male rats and epithelial dysplasia of the forestomach and bile duct hyperplasia in the liver in female rats. Chemical-related increases occurred in the incidences of hyperplasia in the skin, epithelial dysplasia of the forestomach, and bronchiolar epithelial pleomorphism and hyperplasia in male and female mice and in the incidence of eosinophilic cytoplasmic change in the liver in males.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

## Summary of the Long-Term Carcinogenesis and Genetic Toxicology Studies of 2,3-Dibromo-1-propanol

| Male F344/N Rats | Female F344/N Rats | Male $B6C3F_1$ Mice | Female $B6C3F_1$ Mice |
|---|---|---|---|
| **Doses** | | | |
| 0, 188, or 375 mg/kg | 0, 188, or 375 mg/kg | 0, 88, or 177 mg/kg | 0, 88, or 177 mg/kg |
| **Final body weights** | | | |
| High-dose group lower than controls | High-dose group lower than controls | Dosed groups similar to controls | Dosed groups similar to controls |
| **Survival rates**[a] | | | |
| 50/50, 41/50, 16/50 | 48/50, 38/50, 24/50 | 50/50, 50/50, 50/50 | 50/50, 48/50, 50/50 |
| **Nonneoplastic effects** | | | |
| Skin: hyperkeratosis (0/50, 1/50, 23/50) | Skin: hyperkeratosis (0/50, 0/50, 24/50) | Skin: hyperplasia (0/50, 7/50, 12/50) | Skin: hyperplasia (0/50, 8/50, 5/50) |
| Nose: epithelial dysplasia (0/50, 33/50, 49/50) | Nose: epithelial dysplasia (1/50, 49/50, 50/50) | Forestomach: epithelial dysplasia (0/50, 14/50, 33/49) | Forestomach: epithelial dysplasia (0/50, 16/49, 41/50) |
| Esophagus: hyperkeratosis (0/50, 18/50, 48/50) | Esophagus: hyperkeratosis (1/50, 20/50, 49/50) | Lung/bronchioles: epithelial pleomorphism (0/50, 50/50, 50/50); focal hyperplasia (0/50, 1/50, 6/50) | Lung/bronchioles: epithelial pleomorphism (0/50, 46/50, 50/50); focal hyperplasia (0/50, 6/50, 5/50) |
| Forestomach: hyperkeratosis (2/50, 6/50, 32/50); ulcer (0/50, 3/50, 5/50); acanthosis (0/50, 1/50, 6/50) | Forestomach: hyperkeratosis (0/50, 6/50, 30/50); epithelial dysplasia (0/50, 1/50, 8/50) | Liver: eosinophilic cytoplasmic change (0/50, 0/50, 11/50) | |
| Liver: pleomorphism (0/49, 0/50, 37/50); basophilic change (2/49, 28/50, 16/50); clear cell change (2/49, 15/50, 5/50); angiectasis (2/49, 27/50, 46/50) | Liver: pleomorphism (0/50, 0/50, 44/50); basophilic change (5/50, 27/50, 19/50); clear cell change (1/50, 8/50, 7/50); bile duct hyperplasia (1/50, 6/50, 37/50) | | |
| Kidney: nuclear enlargement (0/50, 0/50, 41/50); hyperplasia (0/50, 1/50, 5/50) | Kidney: nuclear enlargement (0/50, 6/50, 47/50) | | |
| **Neoplastic effects** | | | |
| Skin: squamous cell papilloma or carcinoma (1/50, 8/50, 8/50); basal cell tumor, sebaceous gland adenoma, or keratoacanthoma (0/50, 20/50, 31/50) | Skin: squamous cell papilloma or carcinoma (0/50, 0/50, 3/50); basal cell tumor, sebaceous gland adenoma, or keratoacanthoma (0/50, 3/50, 18/50) | Skin: squamous cell papilloma or carcinoma (0/50, 3/50, 11/50); sebaceous gland adenoma (0/50, 1/50, 8/50) | Skin: squamous cell papilloma or carcinoma (0/50, 1/50, 6/50); sebaceous gland adenoma (0/50, 3/50, 2/50) |
| Nose: adenoma (0/50, 48/50, 48/50) | Mammary gland: adeno-carcinoma (0/50, 0/50, 5/50) | Forestomach: squamous cell papilloma or carcinoma (0/50, 14/50, 21/49) | Forestomach: squamous cell papilloma or carcinoma (0/50, 18/49, 19/50) |

**Summary of the Long-Term Carcinogenesis and Genetic Toxicology Studies of 2,3-Dibromo-1-propanol** (continued)

| Male F344/N Rats | Female F344/N Rats | Male $B6C3F_1$ Mice | Female $B6C3F_1$ Mice |
|---|---|---|---|
| **Neoplastic effects** (continued) | | | |
| Oral mucosa: squamous cell papilloma or carcinoma (0/50, 47/50, 48/50) | Nose: adenoma (0/50, 44/50, 49/50) | Liver: hepatocellular adenoma or carcinoma (1/50, 2/50, 11/50) | |
| Esophagus: squamous cell papilloma (0/50, 19/50, 33/50) | Oral mucosa: squamous cell papilloma or carcinoma (0/50, 39/50, 49/50) | Lung: alveolar/bronchiolar adenoma (1/50, 1/50, 6/50) | |
| Forestomach: squamous cell papilloma (0/50, 1/50, 17/50) | Esophagus: squamous cell papilloma (0/50, 9/50, 38/50) | | |
| Small intestine: adeno-carcinoma (0/50, 8/50, 11/50) | Forestomach: squamous cell papilloma (1/50, 3/50, 23/50) | | |
| Large intestine: adenomatous polyp (1/50, 13/50, 29/50) | Small intestine: adeno-carcinoma (0/50, 3/50, 4/49) | | |
| Liver: neoplastic nodules or carcinoma (0/49, 4/50, 5/50) | Large intestine: adenomatous polyp (0/50, 12/50, 37/50) | | |
| Kidney: tubule cell adenoma (0/50, 0/50, 4/50) | Liver: neoplastic nodules or carcinoma (0/50, 11/50, 14/50) | | |
| Zymbal's gland: adenoma or adenocarcinoma (0/50, 9/50, 35/50) | Kidney: tubule cell adenoma (0/50, 1/50, 4/50) | | |
| Tunica vaginalis: mesothelioma (0/50, 1/50, 4/50) | Zymbal's gland: adenoma or adenocarcinoma (1/50, 9/50, 22/50) | | |
| Spleen: hemangioma or hemangiosarcoma (0/50, 0/50, 4/50) | Clitoral gland: adenoma or adenocarcinoma (0/50, 1/50, 6/50) | | |
| **Uncertain findings** | | | |
| None | None | None | Lung: alveolar/bronchiolar adenoma or carcinoma (1/50, 3/50, 4/50) |
| **Level of evidence of carcinogenic activity** | | | |
| Clear evidence | Clear evidence | Clear evidence | Clear evidence |

**Summary of the Long-Term Carcinogenesis and Genetic Toxicology Studies of 2,3-Dibromo-1-propanol** (continued)

| | |
|---|---|
| **Genetic toxicology** | |
| *Salmonella typhimurium* gene mutations: | Positive with and without S9 in strains TA98, TA100, and TA1535<br>Negative with and without S9 in strain TA1537 |
| L5178Y mouse lymphoma gene mutations: | Positive without S9 |
| Sister chromatid exchanges | |
| Chinese hamster ovary cells *in vitro*: | Positive with and without S9 |
| Chromosomal aberrations | |
| Chinese hamster ovary cells *in vitro*: | Positive with and without S9 |
| Sex-linked recessive lethal mutations | |
| *Drosophila melanogaster*: | Positive |
| Reciprocal translations | |
| *Drosophila melanogaster*: | Positive |
| Micronucleated erythrocytes | |
| Mouse bone marrow cells: | Negative |

[a] The studies were terminated during the following weeks: male rats, weeks 48-51; female rats, weeks 52-55; male mice, weeks 36-39; female mice, weeks 39-42.

# EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

# NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
## TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on 2,3-dibromo-1-propanol on June 23, 1992, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, panel members have five major responsibilities in reviewing NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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# SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On June 23, 1992, the draft Technical Report on the toxicology and carcinogenesis studies of 2,3-dibromo-1-propanol received public review by the National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. K.M. Abdo, NIEHS, introduced the toxicology and carcinogenesis studies of 2,3-dibromo-1-propanol by discussing the uses and rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplasms and nonneoplastic lesions in rats and mice. The proposed conclusions were *clear evidence of carcinogenic activity* in male and female F344/N rats and B6C3F$_1$ mice.

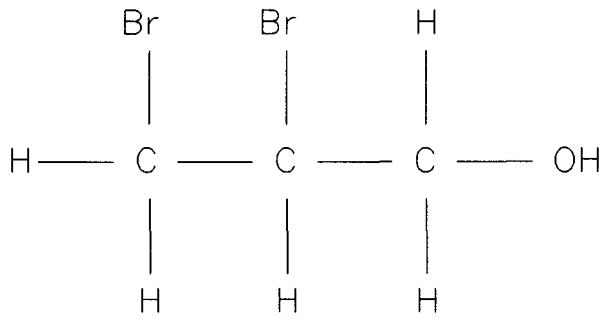
Dr. Zeise, a principal reviewer, agreed with the proposed conclusions. She asked if information including statistics could be provided for neoplasm sites that might have been of borderline significance, but were not discussed. Dr. J.K. Haseman, NIEHS, responded that because the study was terminated early there were few neoplasms occurring spontaneously. However, all neoplasms that occurred in sufficient numbers for meaningful analysis could be included in a table along with P values. (Editor's note: These values have been included in the tables in the results section.) Dr. Zeise said she would like to see an indication in the study rationale as to why the dermal route was selected. Dr. Abdo said the most common routes of human exposure were dermal and, to a lesser extent, inhalation.

Because Mr. Beliczky, the second principal reviewer, was unable to attend the meeting, Dr. L.G. Hart, NIEHS, read his review into the record. Mr. Beliczky agreed with the proposed conclusions. He noted the early termination of the chronic studies because of the presence of antibodies against lymphocytic choriomeningitis virus (LCM) in sentinel animals. Since the LCM virus also puts humans at risk, this action verifies the usefulness of the Sentinel Animal Program and the priority NTP places on the safety of laboratory personnel. Mr. Beliczky stated that since some carcinogenicity data on the chemical has been available since 1983, there should have been efforts by NTP and other Federal agencies to notify the public, industry, and workers.

Dr. Hayden asked whether it was usual NTP policy to terminate a long-term study when sentinel animals were diagnosed to be serologically positive for a potential human pathogen. Dr. S.L. Eustis, NIEHS, said this was the first such instance in his experience at NIEHS; however, in any future situation where there was a viral disease present that could be a hazard to humans the same action would be taken.

Dr. Zeise moved that the Technical Report on 2,3-dibromo-1-propanol be accepted with the revisions discussed and with the conclusions as written for male and female rats and mice, *clear evidence of carcinogenic activity.* Dr. Davis seconded the motion, which was accepted unanimously with seven votes.

# INTRODUCTION



**2,3-DIBROMO-1-PROPANOL**

CAS No. 96-13-9

Chemical Formula: $C_3H_6Br_2O$ Molecular Weight: 217.9

**Synonyms:** 2,3-dibromopropanol; 2,3-dibromopropyl alcohol

## CHEMICAL AND PHYSICAL PROPERTIES

2,3-Dibromo-1-propanol is a colorless liquid with a melting point of 6° C, a boiling point of 219° C, and a density of 2.12 g/mL. It is slightly soluble in water and is soluble in acetone, benzene, and diethyl ether (CRC, 1983). 2,3-Dibromo-1-propanol is prepared by a reaction of allyl alcohol with bromine in carbon tetrachloride (TOXNET, 1991).

## PRODUCTION, USE, AND HUMAN EXPOSURE

2,3-Dibromo-1-propanol has been used as an intermediate in the preparation of the flame retardant tris(2,3-dibromopropyl) phosphate, as an active flame retardant itself, and as a chemical intermediate for insecticide and pharmaceutical preparations (Fishbein, 1979). The U.S. Environmental Protection Agency has detected 2,3-dibromo-1-propanol in industrial effluent discharges at a concentration of $0.5 \times 10^{-3}$ g/L (Webb *et al.*, 1973; CEC, 1976). 2,3-Dibromo-1-propanol has been identified as a metabolite of tris(2,3-dibromopropyl) phosphate in humans wearing treated fabrics (Blum *et al.*, 1978). Prior to 1977, tris(2,3-dibromopropyl) phosphate was the most widely used flame retardant in synthetic fabrics, particularly polyester materials used in children's sleepwear. After studies showed that this flame retardant was mutagenic in bacteria (Prival *et al.*, 1977) and carcinogenic in rats and mice (NCI, 1978; Van Duuren *et al.*, 1978; Reznik *et al.*, 1979), the Consumer Product Safety Commission (CPSC) banned the sale of sleepwear containing this compound (CPSC, 1977a,b). In 1976, the production volume of 2,3-dibromo-1-propanol in the United States was greater than 10 million pounds (Fishbein, 1979). However, as a result of the ban of tris(2,3-dibromopropyl) phosphate by the CPSC, the production volume of 2,3-dibromo-1-propanol decreased drastically. Information on the current production level is not available.

## ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

### *Experimental Animals*

2,3-Dibromo-1-propanol has been detected in the urine of rats after absorption of tris(2,3-dibromopropyl) phosphate through the skin (St. John *et al.*, 1976) and after oral or intravenous injection (Lynn *et al.*, 1982; Nomeir and Matthews, 1983).

The possible metabolic pathways for tris(2,3-dibromopropyl) phosphate and 2,3-dibromo-1-propanol are shown in Figure 1. Marsden and Casida (1982) suggested that 2,3-dibromo-1-propanol and other haloalkanols undergo oxidation and dehydrohalogenation, with the formation of 2-haloacrolein as an unstable intermediate. Consistent with this hypothesis, these investigators identified haloacrylic acids in the urine of rats given dibromopropanol or dichloropropanol (10 μmol/kg body weight by intraperitoneal injection) at levels of 10% and 50% of the amounts resulting from direct haloacrylic acid administration.

2,3-Dibromo-1-propanol may also undergo oxidation to an epoxyhalopropane intermediate, 3-bromo-1,2-propane epoxide (Figure 1), which reacts with glutathione to form mercapturic acids. Jones and Fakhouri (1979) identified two acetylated cysteine-containing compounds in the urine of rats given each of four dihalopropanols. The two compounds were *N*-acetyl-*S*-(2,3-dihydroxypropyl)cysteine and *N,N'*-bis-acetyl-*S,S'*-(1,3-bis-cysteinyl)propan-2-ol. Moreover, these investigators also identified a β-halolactate (β-bromolactate or β-chlorolactate, depending on the dihalopropanol) in the urine of rats given the dihalopropanols; this finding suggests that the epoxyhalopropane may also undergo hydrolysis to the α-halohydrin and further oxidation to the β-halolactate and oxalic acid, in addition to direct conjugation with glutathione, to form the mercapturic acids.

β-Chlorohydrin administered to rats (Jones and Fakhouri, 1979) produced one mercapturic acid, *N*-acetyl-*S*-(2,3-dihydroxypropyl)cysteine, as a urinary metabolite; this is the same metabolite produced from α-chlorohydrin (Jones, 1973). To produce the same metabolite, both α- and β-chlorohydrin must be converted to the epoxide 2,3-epoxypropan-1-ol, providing further evidence of the obligatory formation of epoxides as intermediary metabolites.

Although 2,3-dibromo-1-propanol has been identified in the urine and tissues of rats given tris(2,3-dibromopropyl) phosphate, the major metabolite of this flame retardant compound in the plasma and bile of dosed rats is bis(2,3-dibromopropyl) phosphate (Lynn *et al.*, 1982). Nelson *et al.* (1984) have shown that 2-bromoacrolein and bis(2,3-dibromopropyl) phosphate are formed by oxidation of tris(2,3-dibromopropyl) phosphate, primarily at the C-1 position in an NADPH-dependent reaction by rat liver microsomes (see Figure 1). Consistent with these findings, 2-bromoacrylic acid has been identified in the urine of rats given tris(2,3-dibromopropyl) phosphate (Marsden and Casida, 1982).

### *Humans*

2,3-Dibromo-1-propanol, a metabolite of tris(2,3-dibromopropyl) phosphate, has been identified in the urine of children wearing sleepwear treated with the flame retardant (Blum *et al.*, 1978).

## TOXICITY

### *Experimental Animals*

Little is known about the toxic effects of 2,3-dibromo-1-propanol. It is more acutely toxic in rats and mice than is tris(2,3-dibromopropyl) phosphate. A single intraperitoneal injection of 200 mg/kg 2,3-dibromo-1-propanol to male Wistar rats killed all animals within 24 hours, whereas a single intraperitoneal injection of 750 mg/kg tris(2,3-dibromopropyl) phosphate was not lethal (Søderlund *et al.*, 1980). The intraperitoneal $LD_{50}$ of 2,3-dibromo-1-propanol in mice is 125 mg/kg (NIOSH, 1987), while the $LD_{50}$ of tris(2,3-dibromopropyl) phosphate in mice is 1.15 g/kg (Salamone and Katz, 1981). The oral $LD_{50}$ of tris(2,3-dibromopropyl) phosphate in Sprague-Dawley rats is 1.88 g/kg (Seabaugh *et al.*, 1981).

Although 2,3-dibromo-1-propanol is a urinary metabolite of tris(2,3-dibromopropyl) phosphate, it apparently is not responsible for the renal toxicity associated with the administration of tris(2,3-dibromopropyl) phosphate. Søderlund *et al.* (1980) demonstrated that intraperitoneal injection of single doses of 250 mg/kg or higher tris(2,3-dibromopropyl)

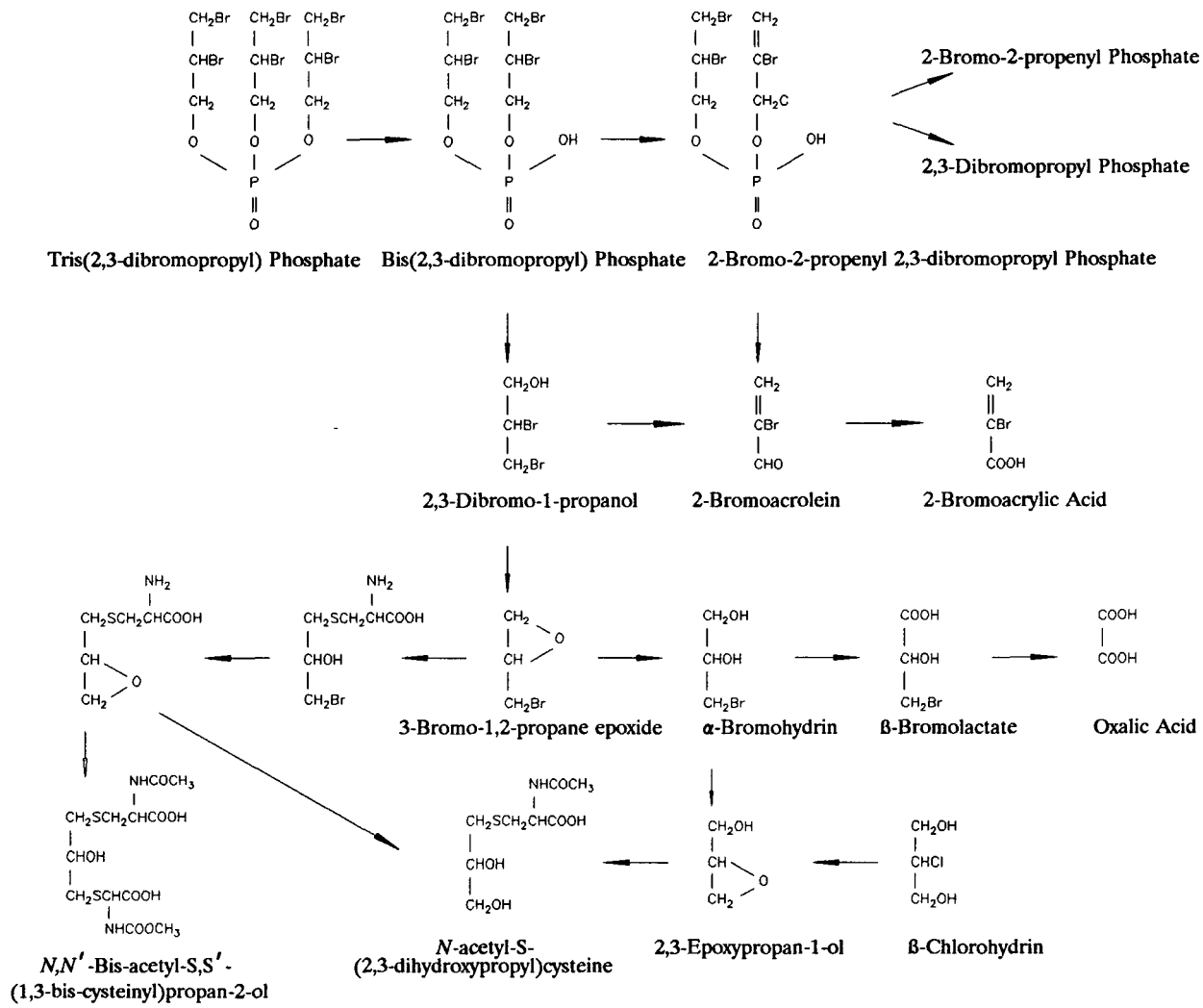



**FIGURE 1**
**Proposed Metabolic Pathways for 2,3-Dibromo-1-propanol and Relationship to Tris(2,3-dibromopropyl) Phosphate (Adapted from Jones and Fakhouri, 1979, and Marsden and Casida, 1982)**

phosphate to male Wistar rats resulted in necrosis of the proximal tubule epithelium and elevation of plasma urea and creatinine. Further, these investigators also showed that pretreatment of male rats with cobalt chloride, an agent that decreases cytochrome P-450 levels and increases tissue glutathione levels, reduced the extent of renal tubule necrosis caused by tris(2,3-dibromopropyl) phosphate. In contrast, single intraperitoneal doses of 100 mg 2,3-dibromo-1-propanol/kg body weight (one-half the lethal dose) did not produce renal tubule necrosis (Søderlund *et al.*, 1980). Similarly, Elliot *et al.* (1982) showed that an intraperitoneal dose of 61 mg 2,3-dibromo-1-propanol/kg body weight was not nephrotoxic in Sprague-Dawley rats, whereas an approximately equimolar dose of 154 mg tris(2,3-dibromopropyl) phosphate/kg body weight caused acute proximal tubule necrosis accompanied by elevated levels of serum urea and creatinine. Elliot *et al.* (1982) also demonstrated that bis(2,3-dibromopropyl) phosphate, another metabolite of tris(2,3-dibromopropyl) phosphate, caused more severe renal damage than did the parent compound and may be primarily responsible for the renal toxicity. In a follow-up study of their earlier work, Søderlund *et al.* (1982) showed that bis(2,3-dibromopropyl) phosphate and (2,3-dibromopropyl) phosphate caused more extensive renal lesions and higher levels of plasma urea and creatinine than did the parent compound.

### *Humans*

No information was available on the toxicity of 2,3-dibromo-1-propanol in humans.

## Reproductive and Developmental Toxicity

### *Experimental Animals*

Sperm morphology and vaginal cytology studies were conducted on F344/N rats exposed to 0, 188, or 375 mg/kg 2,3-dibromo-1-propanol for 13 weeks in the present NTP studies (Environmental Health Research and Testing, Inc., report dated April 1983, on file at NIEHS). Caudal, testicular, and epididymal weights of treated rats were significantly decreased. Sperm motility was not affected, but sperm density was reduced. 2,3-Dibromo-1-propanol did not alter the length of estrus or the relative frequency of various estrous stages. No other reproductive and developmental toxicity studies of 2,3-dibromo-1-propanol were found.

Dermal application of 2.27 g/kg tris(2,3-dibromopropyl) phosphate to the backs of male and female New Zealand albino rabbits once weekly for 3 months caused testicular atrophy in males, but no adverse effect in females (Osterberg *et al.*, 1977). Testicular atrophy and decreased epididymal sperm counts were dose-related effects observed in Sprague-Dawley rats that had been administered tris(2,3-dibromopropyl) phosphate by intraperitoneal injection three times per week for 72 days (Cochran and Wiedow, 1986). Whether the effects observed in these two studies were caused by the parent compound, bis(2,3-dibromopropyl) phosphate, or 2,3-dibromo-1-propanol is unknown.

No teratogenic effects were observed in Sprague-Dawley rats that were administered 0, 5, 25, or 125 mg/kg tris(2,3-dibromopropyl) phosphate by gavage daily on days 6 through 15 of gestation (Seabaugh *et al.*, 1981). Maternal body weight gain was marginally decreased during gestation in the 125 mg/kg dose group. No teratogenic effects were observed in Wistar rats after daily gavage administration of 25, 50, 100, or 200 mg/kg tris(2,3-dibromopropyl) phosphate on days 7 through 15 of gestation (Kawashima *et al.*, 1981).

### *Humans*

No information was available on the reproductive toxicity of 2,3-dibromo-1-propanol in humans.

## Carcinogenicity

### *Experimental Animals*

No studies have been reported on the carcinogenicity of 2,3-dibromo-1-propanol in laboratory animals. However, tris(2,3-dibromopropyl) phosphate given to F344/N rats at doses of 50 or 100 ppm and to B6C3F$_1$ mice at doses of 500 or 1,000 ppm in feed for 2 years induced renal tubule cell adenomas and carcinomas in both species (NCI, 1978a; Reznik *et al.*, 1979). These neoplasms appeared to originate from the proximal convoluted tubule epithelium. In addition, the incidences of benign and malignant neoplasms of the forestomach, lung, and liver were increased in dosed mice (NCI, 1978a). Dermal application of 10 or 30 mg of tris(2,3-dibromopropyl)

phosphate three times weekly for 67 to 71 weeks to the dorsal skin of ICR/Ha Swiss mice caused increased incidences of neoplasms of the skin, forestomach, oral cavity, and lung (Van Duuren *et al.*, 1978). Reznik *et al.* (1981) observed adenomas of the colon in F344/N rats administered 100 mg/kg tris(2,3-dibromopropyl) phosphate in corn oil by gavage 5 days a week for 52 weeks. Thus, tris(2,3-dibromopropyl) phosphate, the parent compound of 2,3-dibromo-1-propanol, is carcinogenic at multiple organ sites in laboratory animals. Whether the proximate carcinogen in these studies was tris(2,3-dibromopropyl) phosphate or one of its metabolites is unknown.

In NTP/National Cancer Institute (NCI) 2-year studies, neoplasms of the kidney in rats were most frequently produced by alkyl or alkenyl halide compounds (Kluwe *et al.*, 1984). These chemical-induced neoplasms occurred more commonly in rats than in mice and more commonly in males than in females. All of the halogenated three-carbon compounds previously tested by NTP/NCI were found to be carcinogenic. 1,2-Dibromo-3-chloropropane was carcinogenic in male and female rats and mice, causing increased incidences of forestomach squamous cell carcinomas. In female rats, it caused significantly increased incidences of mammary gland adenocarcinomas (NCI, 1978b). 1,2-Dichloropropane was not carcinogenic in male rats but caused marginally increased incidences of adenocarcinomas of the mammary gland in female rats. It was carcinogenic in male and female mice, causing increased incidences of hepatocellular neoplasms, primarily adenomas (NTP, 1986). 1,3-Dichloropropene was carcinogenic in male and female rats, causing increased incidences of squamous cell papillomas and carcinomas of the forestomach and increased incidences of neoplastic nodules in the liver of male rats. The study in male mice was considered inadequate because of poor survival in the control group. 1,3-Dichloropropene was carcinogenic in female mice, causing increased incidences of transitional cell carcinomas of the urinary bladder, alveolar/bronchiolar adenomas of the lung, and squamous cell papillomas and carcinomas of the forestomach (NTP, 1985).

### *Humans*

No epidemiology studies on the relationship between exposure to 2,3-dibromo-1-propanol and the incidence of cancer in humans have been reported. A mortality analysis of 628 male workers potentially exposed to tris(2,3-dibromo-propyl) phosphate at two manufacturing plants did not detect any significant, cause-specific, excessive mortality (Wong *et al.*, 1984). However, the exposure data were inadequate and the number of mortalities (36 deaths, with 7 due to cancer) was too small to draw definitive conclusions.

## GENETIC TOXICITY

2,3-Dibromo-1-propanol is mutagenic in *Salmonella typhimurium* strains TA98, TA100, and TA1535. The base-pair substitution strains, TA100 and TA1535, show a greater mutagenic response than does the frameshift strain, TA98 (Blum and Ames, 1977; Prival *et al.*, 1977; Carr and Rosenkranz, 1978; Nakamura *et al.*, 1979; Søderlund *et al.*, 1979; Lynn *et al.*, 1982; Haworth *et al.*, 1983; Holme *et al.*, 1983). The mutagenic activity of 2,3-dibromo-1-propanol was enhanced by the addition of S9 or microsomal metabolic activation systems. 2,3-Dibromo-1-propanol was also mutagenic in V79 Chinese hamster lung cells (Holme *et al.*, 1983) and germ cells of male *Drosophila melanogaster* (Yoon *et al.*, 1985). It induced unscheduled DNA repair synthesis in cultured rat hepatocytes (Holme *et al.*, 1983), elicited preferential growth inhibition in a DNA repair-deficient strain of *Escherichia coli* ($polA_1^-$) compared to the nondeficient strain ($polA^+$) (Hyman *et al.*, 1980), and caused reciprocal translocation (Yoon *et al.*, 1985) and chromosomal breakage (Zimmering, 1983) in germ cells of male *D. melanogaster*.

2-Bromoacrolein and 2,3-dibromopropanal, two related compounds and potential reactive metabolites of tris(2,3-dibromopropyl) phosphate and 2,3-dibromo-1-propanol, were mutagenic in *S. typhimurium* strain TA100 with and without rat liver microsomes, caused single strand breaks in the DNA of cultured hepatoma cells, and induced morphological transformation of Syrian hamster embryo cells (Gordon *et al.*, 1985).

2,3-Dibromo-1-propanol was a less potent mutagen than the parent compound, tris(2,3-dibromopropyl) phosphate, which is mutagenic in *S. typhimurium* strains TA100 and TA1535 when incubated with S9 or microsomal activation systems (Blum and Ames, 1977; Prival *et al.*, 1977; Nakamura *et al.*, 1979; Søderlund *et al.*, 1979; Brusick *et al.*, 1980; Lynn *et al.*, 1982; Zeiger *et al.*, 1982; Holme *et al.*, 1983). At concentrations of approximately 250 nmol/plate and higher, tris(2,3-dibromopropyl) phosphate does not require exogenous metabolic activation for its mutagenicity in *S. typhimurium* (Zeiger *et al.*, 1982). Tris(2,3-dibromopropyl) phosphate also induced mutations in V79 Chinese hamster lung cells and in L5178Y mouse lymphoma cells, morphological transformation in Syrian hamster embryo cells and in Balb/3T3 cells, and unscheduled DNA repair synthesis in cultured rat hepatocytes (Brusick *et al.*, 1980; Holme *et al.*, 1983; Søderlund *et al.*, 1985). In addition, tris(2,3-dibromopropyl) phosphate induced sister chromatid exchanges in Chinese hamster V79 cells and in L5178Y mouse lymphoma cells (Furukawa *et al.*, 1978; Nakanishi and Schneider, 1979; Brusick *et al.*, 1980), induced chromosomal aberrations in mouse bone marrow cells and L5178Y mouse lymphoma cells (Nakanishi and Schneider, 1979; Brusick *et al.*, 1980), increased the frequencies of abnormal sperm morphology and micronucleated polychromatic erythrocytes in $B6C3F_1$ mice (Salamone and Katz, 1981), caused strand breaks in DNA of cultured human cells (Gutter and Rosenkranz, 1977), and induced sex-linked recessive lethal mutations in *D. melanogaster* (Brusick *et al.*, 1980).

## STUDY RATIONALE

2,3-Dibromo-1-propanol was selected for long-term dermal toxicology and carcinogenesis studies as part of an organohalide class evaluation and because this compound is a metabolite of the flame retardant tris(2,3-dibromopropyl) phosphate, a known carcinogen in animals. Because the primary route of human exposure to flame retardants is through the skin, the dermal route of administration was chosen for the studies.

# MATERIALS AND METHODS

## PROCUREMENT AND CHARACTERIZATION

2,3-Dibromo-1-propanol was obtained from Great Lakes Chemical Corporation (Bayport, TX) in two lots. Lot 4-44-726 was used during the 16-day, 13-week, and a portion of the long-term studies, until it was depleted; thereafter, lot H1P was used. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) (Appendix G). Both lots of the bulk chemical, a clear, colorless, viscous liquid, were identified as 2,3-dibromo-1-propanol by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy.

The purity of lots 4-44-726 and H1P was approximately 98%, as determined by elemental analyses, Karl Fischer water analysis, titration of acidic components with sodium hydroxide, thin-layer chromatography, and gas chromatography. For both lots, elemental analyses for carbon, hydrogen, and bromine were in agreement with the theoretical values. Karl Fischer water analysis indicated no more than 0.07% water. Titration for acidic components indicated less than 25 ppm acid (hydrogen bromide). Thin-layer chromatography indicated only one trace impurity for each lot. Gas chromatography indicated up to five impurities which were present at a total area of approximately 1% and seven additional impurities with areas less than 0.1% for lot 4-44-726; up to five impurities with a total area of approximately 2% and 11 additional impurities with areas less than 0.1% for lot H1P.

Stability studies performed by the analytical chemistry laboratory using gas chromatography indicated that 2,3-dibromo-1-propanol is stable as a bulk chemical for at least 2 weeks at temperatures up to 60° C. Throughout the studies, the bulk chemical was stored in amber glass bottles at 0° to 6° C. The stability of the bulk chemical was monitored periodically by the study laboratory using gas chromatography. No degradation of the study material was observed throughout the studies.

## PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared by mixing 2,3-dibromo-1-propanol with ethanol (Table G1). Stability studies of the dose formulations conducted by the analytical chemistry laboratory using gas chromatography confirmed that the solutions were stable for at least 7 days when stored at room temperature. An additional stability study performed by the study laboratory using the same gas chromatographic system used by the analytical chemistry laboratory indicated that the dose formulations were stable for up to 8 weeks when stored at 0° to 8° C. During the studies, the dose formulations were stored at 2° to 6° C for up to 16 days; after the fourth month of the long-term studies, the dose formulations were stored protected from light.

The study laboratory conducted periodic analyses of the formulations using gas chromatography. Dose formulations were analyzed twice during the 13-week studies and approximately every 4 weeks during the long-term studies. During the 13-week studies, three of four dose formulations were within 10% of the target concentrations (Table G2). During the long-term studies, all samples were within 10% of the target concentrations (Table G3). Results of the periodic referee analyses performed by the analytical chemistry laboratory indicated good agreement with the results obtained by the study laboratory (Table G4).

## 16-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories (Portage, MI and Kingston, NY) and observed for 19 days before the studies began. Rats were 52 days old and mice were 59 days old at the beginning of the studies. Groups of five male and five female rats and mice were administered 0, 44, 88, 177, 375, or 750 mg/kg 2,3-dibromo-1-propanol in 95% ethanol applied to the subscapular skin (Table 1). The area of skin receiving the dose application was shaved

4 days prior to the first dose; rats were reshaved 8 days later. All groups were treated for 16 days, excluding weekends, for a total of 12 exposure days. Animals were housed five per cage; water and feed were available *ad libitum*. Animals were observed twice daily for signs of toxicity. Clinical observations were recorded on the day of necropsy. Animals were weighed initially, weekly, and at necropsy. Complete necropsies were performed on all animals. Further experimental details are presented in Table 1.

## 13-WEEK STUDIES

The 13-week studies were conducted to determine the cumulative toxic effects of repeated exposure to 2,3-dibromo-1-propanol and to determine appropriate concentrations for use in the long-term studies. Male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries (Indianapolis, IN) and were observed for 16 days (rats) or 9 to 16 days (mice) before the studies began. Rats were 48 days old and mice were 60 days old when the studies began. Groups of 10 male and 10 female rats and mice were administered 0, 44, 88, 177, 375, or 750 mg/kg 2,3-dibromo-1-propanol in 95% ethanol applied to the subscapular skin 5 days a week for 13 weeks. Animals were clipped initially at the site of dose application and were reclipped once or twice weekly. Rats and mice were housed five per cage; water and feed were available *ad libitum*. Animals were observed twice daily and clinical observations were recorded daily. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix I). Animals were weighed initially and weekly thereafter. Further experimental details are presented in Table 1.

Necropsies were performed on all animals. The liver of animals surviving to the end of the study was weighed at necropsy. Complete histopathology was performed on all control animals, all rats that received 750 mg/kg, all mice that received 375 mg/kg, and all mice receiving 750 mg/kg that survived to the end of the study. Tissues examined for rats in the 44, 88, 177, and 375 mg/kg groups were the kidney of males and liver of females. The liver and lung of all mice in the 44, 88, and 177 mg/kg groups and female mice in the 375 mg/kg group were also examined. Additional information is provided in Table 1.

## LONG-TERM STUDIES

### Study Design

The long-term studies were originally designed for 2 years. Groups of 50 male and 50 female rats and mice were administered 2,3-dibromo-1-propanol in 95% ethanol applied to the subscapular skin 5 days a week. Rats were administered 0, 188, or 375 mg/kg; mice were administered 0, 88, or 177 mg/kg. The studies were terminated early (rats at study weeks 48 to 51 for males and 52 to 55 for females; mice at study weeks 36 to 39 for males and 39 to 42 for females) to protect the health of workers performing these studies. Antibodies against lymphocytic choriomeningitis virus were detected in the sera of sentinel mice at 6 months and later in the sera of all groups of male mice. Lymphocytic choriomeningitis virus is a human pathogen and has been reported to cause serious illness (meningitis and death).

### Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Facility (Frederick, MD) for use in the long-term studies. Rats were quarantined 24 days and mice were quarantined 19 days. Five male and five female rats and mice were randomly selected and killed for parasite evaluation and gross observation of disease. Blood samples were collected for viral screens. Rats and mice were approximately 56 days old when the studies began. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program.

### Animal Maintenance

Rats and mice were housed five per cage. Feed and water were available *ad libitum*. Cages and racks were rotated every 2 weeks. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix H.

### Clinical Examinations and Pathology

All animals were observed twice daily and findings were recorded monthly or as necessary. Animals were weighed at study initiation, weekly for 13 weeks, and monthly thereafter.

Necropsies were performed on all animals. At necropsy, all organs and tissues were examined for gross lesions, and all major tissues were fixed and

preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination. Complete histopathology was performed on all animals. Tissues examined are listed in Table 1.

Upon completion of the microscopic evaluation by the study laboratory pathologist, the pathology data were entered into the Carcinogenesis Bioassay Data System. The microscope slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet-tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent pathology quality assessment laboratory. The clitoral and preputial glands, esophagus, kidney, large intestine, liver, nasal cavity, oral cavity, forestomach, small intestine, skin, and Zymbal's gland of male and female rats; the mammary gland of female rats; the lung, stomach, skin, and uterus of mice; and the liver of male mice were reviewed microscopically by the quality assessment pathologist for neoplasms or nonneoplastic lesions.

The quality assessment report and slides were submitted to the NTP Pathology Working Group (PWG) chair, who reviewed the selected tissues and any other tissues for which there was a disagreement in diagnosis between the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnosis between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chair to the PWG for review. These included examples of neoplasms of the skin, oral cavity, esophagus, forestomach, intestine, nasal cavity, preputial and clitoral glands, liver, and kidney in rats and skin, forestomach, liver, and lung in mice. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without knowledge of dose groups or previously rendered diagnoses. When the consensus opinion of the PWG differed from that of the laboratory pathologist, the diagnosis was changed. Thus, the final diagnoses represent a consensus of contractor pathologists and the PWG. Details of these review procedures have been described by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

## Statistical Methods

### *Survival Analyses*

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found dead of other than natural causes; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

### *Calculation of Incidence*

The incidences of neoplasms or nonneoplastic lesions as presented in Tables A1, A4, B1, B4, C1, C4, D1, and D4 are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms and all nonneoplastic lesions are given as the ratio of the number of affected animals to the number of animals with the site examined microscopically. However, when macroscopic examination was required to detect lesions in certain tissues (e.g., skin, intestine, harderian gland, and mammary gland) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed.

### *Analysis of Neoplasm and Nonneoplastic Lesion Incidences*

Because of infection with lymphocytic choriomeningitis virus, as well as chemical-related neoplasms at multiple sites in rats and mice, dosed and control animals were killed early and generally within a 4-week time frame. Mean survival differences among groups were generally only 0 to 2 weeks, with the largest difference being 6 weeks. Because of the similarity in survival times, it was deemed unnecessary to employ survival-adjusted analyses of neoplasm rates. Consequently, pairwise comparisons

were made by the Fisher exact test, and dose-response trends were assessed by the Cochran-Armitage trend test (Armitage, 1971; Gart *et al.*, 1979, Haseman, 1984). These same analyses were used to evaluate the incidences of selected non-neoplastic lesions.

### *Analysis of Continuous Variables*

Organ and body weight data, which have approximately normal distributions, were analyzed using the parametric multiple comparison procedures of Williams (1971, 1972) and Dunnett (1955). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of dose-response trends and to determine whether a trend-sensitive test (Williams' test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose response (Dunnett's test). Average nephropathy and necrosis severity values for the 13-week studies were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973).

### *Historical Control Data*

Although the concurrent control group is always the first and most appropriate control group used for evaluation, there are certain instances in which historical control data can be helpful in the overall assessment of neoplasm incidence (Haseman *et al.*, 1984, 1985). However, the NTP has no historical data for ethanol vehicle control dermal application studies for comparison with the treated groups in the 2,3-dibromo-1-propanol studies. Moreover, the 2,3-dibromo-1-propanol studies were terminated between 36 and 55 weeks. Nevertheless, historical control data for untreated F344/N rats and B6C3F$_1$ mice terminated between 35 and 62 weeks are provided in this report (Tables A3, B3, C3, and D3). These historical control data are from studies conducted during the same general period as the 2,3-dibromo-1-propanol studies. These historical control data are provided to give the reader perspective on the spontaneous rate of neoplasms in rats and mice at approximately 1 year of age.

## QUALITY ASSURANCE METHODS

The 13-week and long-term were conducted in compliance with FDA Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as study records were submitted to the NTP Archives, they were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and preliminary review draft of this NTP Technical Report were conducted. Audit procedures and findings are presented in the reports, which are on file at the NIEHS. The audit findings were reviewed and assessed by NTP staff so all had been resolved or were otherwise addressed during the preparation of this Technical Report.

## GENETIC TOXICOLOGY

The genetic toxicity of 2,3-dibromo-1-propanol was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, sex-linked recessive lethal mutations and reciprocal translocations in *Drosophila melanogaster*, and micronucleated erythrocytes in mouse bone marrow cells. The protocols for these studies and the test results are given in Appendix E.

The genetic toxicity studies of 2,3-dibromo-1-propanol are part of a larger effort by the NTP to develop a database that would permit the evaluation of carcinogenicity in experimental animals from the structure of the chemical and its responses in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms of chemically induced DNA damage and to predict carcinogenicity in animals, based on the electrophilic theory of chemical carcinogenesis and the somatic mutation theory (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other *in vitro* genetic toxicity tests do not correlate well with rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be

induced by the chemical being investigated. Data from NTP studies show that a positive response in *Salmonella* is currently the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens were rodent carcinogens), and that there is no complementarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. The predictivity for carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests is not yet defined.

TABLE 1
**Experimental Design and Materials and Methods in the Dermal Studies of 2,3-Dibromo-1-propanol**

| 16-Day Studies | 13-Week Studies | Long-Term Studies |
|---|---|---|
| **Study Laboratory** | | |
| Papanicolaou Cancer Research Institute at Miami, Inc. (Miami, FL) | Papanicolaou Cancer Research Institute at Miami, Inc. (Miami, FL) | Papanicolaou Cancer Research Institute at Miami, Inc. (Miami, FL) |
| **Strain and Species** | | |
| Rats: F344/N<br>Mice: $B6C3F_1$ | Rats: F344/N<br>Mice: $B6C3F_1$ | Rats: F344/N<br>Mice: $B6C3F_1$ |
| **Animal Source** | | |
| Charles River Breeding Laboratories (Portage, MI - rats; Kingston, NY - mice) | Harlan Industries (Indianapolis, IN) | Frederick Cancer Research Facility (Frederick, MD) |
| **Size of Study Groups** | | |
| 5 males and 5 females | 10 males and 10 females | 50 males and 50 females |
| **Doses** | | |
| 0, 44, 88, 177, 375, and 750 mg/kg 2,3-dibromo-1-propanol in 95% ethanol, applied to the subscapular skin | 0, 44, 88, 177, 375, and 750 mg/kg 2,3-dibromo-1-propanol in 95% ethanol, applied to the subscapular skin | Rats: 0, 188, and 375 mg/kg 2,3-dibromo-1-propanol in 95% ethanol, applied to the subscapular skin<br>Mice: 0, 88, and 177 mg/kg 2,3-dibromo-1-propanol in 95% ethanol, applied to the subscapular skin |
| **Time Held Before Study** | | |
| 19 days | Rats: 16 days<br>Mice: 9-16 days | Rats: 24 days<br>Mice: 19 days |
| **Age When Placed on Study** | | |
| Rats: 52 days<br>Mice: 59 days | Rats: 48 days<br>Mice: 60 days | Rats: 56 days<br>Mice: 56 days |
| **Date of First Dose** | | |
| 7 July 1980 | 22 September 1980 | Rats: 14 December 1981<br>Mice: 25 January 1982 |
| **Duration of Dosing** | | |
| 16 days, excluding weekends (total of 12 dosing days) | 13 weeks (5 days/week) | Male rats: 48-51 weeks (5 days/week)<br>Female rats: 52-55 weeks (5 days/week)<br>Male mice: 36-39 weeks (5 days/week)<br>Female mice: 39-42 weeks (5 days/week) |
| **Date of Last Dose** | | |
| 22 July 1980 | 19 December 1980 | Male rats: 9 December 1982<br>Female rats: 4 January 1983<br>Male mice: 26 October 1982<br>Female mice: 15 November 1982 |

TABLE 1
**Experimental Design and Materials and Methods in the Dermal Studies of 2,3-Dibromo-1-propanol**
(continued)

| 16-Day Studies | 13-Week Studies | Long-Term Studies |
|---|---|---|
| **Method of Sacrifice** | | |
| $CO_2$ | $CO_2$ | $CO_2$ |
| **Necropsy Date** | | |
| 30 July 1980 | 22-24 December 1980 | Male rats: 17 November 1982 - 10 December 1982<br>Female rats: 13 December 1982 - 6 January 1983<br>Male mice: 4-27 October 1982<br>Female mice: 27 October 1982 - 16 November 1982 |
| **Average Age at Necropsy** | | |
| Rats: 11 weeks<br>Mice: 12 weeks | Rats: 20-21 weeks<br>Mice: 22-23 weeks | Rats: 56-64 weeks<br>Mice: 44-50 weeks |
| **Method of Animal Distribution** | | |
| Animals were randomized by weight with a computer-generated randomization chart. | Animals were randomized by weight with a computer printout generated by Tracor-Jitco, Inc. (Rockville, MD). | Rats and female mice: same as 13-week studies. Male mice were randomized with a standard random number table. |
| **Animals per Cage** | | |
| 5 | 5 | 5 |
| **Method of Animal Identification** | | |
| Ear notch and india ink injection | Same as 16-day studies | Ear notch and toe notch |
| **Diet** | | |
| NIH-07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA), available *ad libitum* | Same as 16-day studies | Same as 16-day studies |
| **Water** | | |
| Tap water (city of Miami water supply) via outside-the-cage automatic watering system (Edstrom Industries, Inc., Waterford, WI), available *ad libitum* | Same as 16-day studies | Same as 16-day studies |
| **Cages** | | |
| Polycarbonate cages (Lab Products, Inc., Rochelle Park, NJ) | Same as 16-day studies | Same as 16-day studies |
| **Bedding** | | |
| Sani-Chip hardwood chips (P.J. Murphy, Forest Product Corp., Montville, NJ), changed twice weekly | Same as 16-day studies | BetaChips hardwood chips (Northeastern Products Corp., Warrensburg, NY); changed twice weekly |

TABLE 1
**Experimental Design and Materials and Methods in the Dermal Studies of 2,3-Dibromo-1-propanol**
(continued)

| 16-Day Studies | 13-Week Studies | Long-Term Studies |
|---|---|---|
| **Cage Filters** | | |
| Cerex spun nylon filters (Florida Filters, Miami, FL), changed every 2 weeks | Same as 16-day studies | Cerex spunbonded nylon filters (Monsanto Co., St. Louis, MO), changed every 2 weeks |
| **Racks** | | |
| Stainless steel racks (Lab Products, Inc., Rochelle Park, NJ), changed every 10 days | Stainless steel racks (Lab Products, Inc., Rochelle Park, NJ), changed every 2 weeks | Same as 13-week studies |
| **Animal Room Environment** | | |
| Temperature: 72°-76° F<br>Relative humidity: 40%-60%<br>Fluorescent light: 12 hours/day<br>Room air changes: 10-15/hour | Temperature: 72°-77° F<br>Relative humidity: 52%-67%<br>Fluorescent light: 12 hours/day<br>Room air changes: >15/hour | Temperature: 73.4° ± 1.8° F<br>Relative humidity: 59.9% ± 7.0%<br>Fluorescent light: 12 hours/day<br>Room air changes: 10-15/hour |
| **Type and Frequency of Observation** | | |
| Observed twice daily; weighed initially, weekly and at necropsy; clinical observations recorded at necropsy | Observed twice daily; weighed initially and weekly; clinical observations recorded daily | Observed twice daily; weighed initially, weekly for 13 weeks, and monthly thereafter; clinical observations recorded monthly |
| **Necropsy** | | |
| Necropsy was performed on all animals. | Necropsy was performed on all animals. The liver was weighed for all animals surviving to necropsy. | Necropsy was performed on all animals. |
| **Histopathology** | | |
| None | Complete histopathology on all control animals, all rats that received 750 mg/kg, all male mice that received 375 mg/kg, and all mice receiving 750 mg/kg that survived to the end of the studies. Tissues that were routinely examined microscopically included: adrenal gland, bile duct, bone marrow, brain, esophagus, heart, kidney, large intestine, liver, lung and bronchi, lymph nodes, ovary, pancreas, parathyroid gland, pituitary gland, prostate gland, salivary gland, small intestine, spleen, stomach, testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. The kidney of male rats and the liver of female rats in the 44, 88, 177, and 375 mg/kg groups were examined. The liver and lung of all mice receiving 44, 88, or 177 mg/kg and female mice receiving 375 mg/kg were examined. | Complete histopathology performed on all animals. Tissues that were routinely examined microscopically included: adrenal gland, bile duct, bone marrow, brain, esophagus, heart, kidney, large intestine, liver, lung and bronchi, lymph nodes, ovary, pancreas, parathyroid gland, pituitary gland, prostate gland, salivary gland, small intestine, spleen, stomach, testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. |

# RESULTS

## RATS

### 16-DAY STUDY

One male and one female rat in the 750 mg/kg groups died on day 2 of the study (Table 2). There were no significant differences in final mean body weights or body weight gains in dosed or control male and female rats. No treatment-related clinical findings or gross observations were noted.

TABLE 2
**Survival and Mean Body Weights of Rats in the 16-Day Dermal Study of 2,3-Dibromo-1-propanol**

| Concentration (mg/kg) | Survival[a] | Mean Body Weight[b] (g) | | | Final Weight Relative to Controls (%) |
|---|---|---|---|---|---|
| | | Initial | Final | Change | |
| **Male** | | | | | |
| 0 | 5/5 | 126 ± 7 | 219 ± 5 | 93 ± 3 | |
| 44 | 5/5 | 124 ± 6 | 219 ± 6 | 95 ± 2 | 100 |
| 88 | 4/4 | 130 ± 4 | 221 ± 7 | 91 ± 4 | 101 |
| 177 | 5/5 | 124 ± 6 | 221 ± 7 | 97 ± 4 | 101 |
| 375 | 5/5 | 127 ± 7 | 214 ± 5 | 88 ± 1 | 98 |
| 750 | 4/5[c] | 125 ± 7 | 221 ± 4 | 90 ± 3 | 101 |
| **Female** | | | | | |
| 0 | 5/5 | 100 ± 5 | 145 ± 5 | 45 ± 3 | |
| 44 | 5/5 | 101 ± 6 | 146 ± 4 | 44 ± 2 | 101 |
| 88 | 5/5 | 99 ± 4 | 148 ± 5 | 49 ± 3 | 102 |
| 177 | 5/5 | 99 ± 3 | 151 ± 4 | 52 ± 2 | 104 |
| 375 | 5/5 | 99 ± 4 | 144 ± 5 | 45 ± 2 | 99 |
| 750 | 4/5[c] | 102 ± 4 | 151 ± 4 | 49 ± 2 | 104 |

[a] Number of animals surviving at 16 days/number of animals initially in group. Differences from the control group were not significant by Williams' or Dunnett's test.
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies.
[c] Day of death: 2

## 13-WEEK STUDY

All rats survived to the end of the study (Table 3). Final mean body weights of male and female rats receiving 750 mg/kg were 94% of the control values. Mean body weight gains of males in the 750 mg/kg group and females in the 375 and 750 mg/kg groups were 89%, 92%, and 87% of control values, respectively. No biologically significant differences in these parameters were noted in other dose groups. Absolute and relative liver weights were increased in male rats receiving 375 mg/kg and male and female rats receiving 750 mg/kg (Table F1).

Dosed rats, especially in the 375 and 750 mg/kg groups, exhibited an unusual behavior pattern that was not observed in controls. After chemical application, dosed rats separated themselves from cagemates instead of huddling together as would be expected for group-housed rats. Recongregation typically occurred several hours later. No dose-related gross observations were noted at necropsy.

Lesions associated with dermal exposure to 2,3-dibromo-1-propanol were observed in the kidney of males and in the liver of females. Nephropathy was observed in most male rats, but the average severity was significantly increased in the 750 mg/kg group (Table 4). Nephropathy was characterized by a few scattered clusters of cortical tubules with slightly thickened basement membranes and basophilic epithelial cells (Plate 1). The interstitium surrounding these clusters of tubules generally contained increased collagen and occasional inflammatory cells. The nephropathy observed in control males was generally minimal in extent; only one or two foci were observed in the kidney sections. In the 750 mg/kg group, the average severity of nephropathy was mild, with three to five foci observed.

TABLE 3
**Survival and Mean Body Weights of Rats in the 13-Week Dermal Study of 2,3-Dibromo-1-propanol**

| Concentration (mg/kg) | Survival[a] | Mean Body Weight[b] (g) | | | Final Weight Relative to Controls (%) |
|---|---|---|---|---|---|
| | | Initial | Final | Change | |
| **Male** | | | | | |
| 0 | 10/10 | 124 ± 3 | 310 ± 5 | 187 ± 5 | |
| 44 | 10/10 | 123 ± 4 | 299 ± 9 | 176 ± 6 | 96 |
| 88 | 10/10 | 125 ± 4 | 310 ± 7 | 185 ± 6 | 100 |
| 177 | 10/10 | 122 ± 4 | 307 ± 10 | 185 ± 7 | 99 |
| 375 | 10/10 | 122 ± 4 | 301 ± 7 | 178 ± 4 | 97 |
| 750 | 10/10 | 125 ± 3 | 292 ± 3 | 167 ± 3* | 94 |
| **Female** | | | | | |
| 0 | 10/10 | 105 ± 2 | 181 ± 2 | 75 ± 2 | |
| 44 | 10/10 | 105 ± 2 | 181 ± 2 | 76 ± 2 | 100 |
| 88 | 10/10 | 105 ± 2 | 179 ± 2 | 73 ± 3 | 99 |
| 177 | 10/10 | 105 ± 2 | 184 ± 3 | 79 ± 3 | 102 |
| 375 | 10/10 | 105 ± 2 | 174 ± 4 | 69 ± 4 | 96 |
| 750 | 10/10 | 105 ± 2 | 170 ± 3* | 65 ± 2** | 94 |

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** (P≤0.01)
[a] Number of animals surviving at 13 weeks/number of animals initially in group
[b] Weights and weight changes are given as mean ± standard error

TABLE 4
**Incidences of Selected Nonneoplastic Lesions in Rats in the 13-Week Dermal Study of 2,3-Dibromo-1-propanol**

| | Vehicle Control | 44 mg/kg | 88 mg/kg | 177 mg/kg | 375 mg/kg | 750 mg/kg |
|---|---|---|---|---|---|---|
| **Male** | | | | | | |
| Kidney[a] | 10 | 10 | 10 | 10 | 10 | 10 |
| Nephropathy[b] | 6 (0.7)[c] | 6 (0.6) | 8 (0.9) | 10* (1.1) | 10* (1.4)* | 10* (1.8)** |
| **Female** | | | | | | |
| Liver | 10 | 0 | 0 | 0 | 10 | 10 |
| Hepatocellular necrosis | 0 (0.0) | – | – | – | 0 (0.0) | 10** (1.7)** |

* Significantly different (P≤0.05) from the control group by the Fisher exact test (rates) or Mann-Whitney U test (severity)
** P≤0.01
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Group average severity of lesion where 0=no lesion, 1=minimal, 2=mild

Individual hepatocyte necrosis was observed in all female rats in the 750 mg/kg group. In each of the 750 mg/kg female rats, there were from one to several randomly distributed necrotic hepatocytes that were sometimes surrounded by a few neutrophils, macrophages, or both (Plate 2).

*Dose Selection Rationale:* In rats receiving 750 mg/kg during the 13-week studies, hepatocellular lesions were seen in females, while the severity of nephropathy, a progressive, potentially life-threatening lesion, was increased in males. Therefore, dose levels selected for the long-term study were 188 and 375 mg/kg.

## LONG-TERM STUDY

### *Survival*

Estimates of survival probability for male and female rats are shown in Table 5 and in the Kaplan-Meier curves in Figure 2. The study was terminated early (weeks 48 to 51 for males and weeks 52 to 55 for females) because of the reduced survival of high-dose rats and because sentinel mice housed in the same room as the rats tested positive for lymphocytic choriomeningitis virus. Serum samples taken at necropsy from all rats were negative for the virus by complement fixation. Survival of male groups at week 48 was: control, 50/50; low-dose, 41/50; high-dose, 16/50 (Table 5 and Figure 2). Survival of female groups at week 52 was: 48/50, 38/50, 24/50. Most of the rats dying early were killed moribund because of the presence of large neoplasms, particularly of the oral cavity, Zymbal's gland, and mammary gland.

### *Body Weights and Clinical Findings*

The mean body weight of high-dose male rats was similar to that of the controls until week 28 (Table 6 and Figure 3). Thereafter, the mean body weight of high-dose males was lower than that of the controls, and at week 44, the last weighing period, the mean body weight of high-dose males was 23% lower. The mean body weight of high-dose female rats was within 10% of that of the controls until week 48, when it was 48% lower (Table 7).

There were no clinical findings directly attributable to 2,3-dibromo-1-propanol administration. Emaciation, dyspnea, and lethargy, which were observed in some treated rats, especially high-dose males, occurred as a result of neoplasms associated with the application of the chemical.

TABLE 5
**Survival in Rats in the Long-Term Dermal Study of 2,3-Dibromo-1-propanol**

| | Vehicle Control | 188 mg/kg | 375 mg/kg |
|---|---|---|---|
| **Male** | | | |
| Animals initially in study | 50 | 50 | 50 |
| Natural deaths or moribund kills | 0 | 9 | 34 |
| Animals surviving until study termination | 50 | 41 | 16 |
| Percent probability of survival at end of study[a] | 100 | 82 | 32 |
| Mean survival (weeks)[b] | 50 | 49 | 44 |
| Survival analysis[c] | P<0.001 | P=0.018 | P<0.001 |
| **Female** | | | |
| Animals initially in study | 50 | 50 | 50 |
| Natural deaths or moribund kills | 2 | 12 | 26 |
| Animals surviving until study termination | 48 | 38 | 24[d] |
| Percent probability of survival at end of study[a] | 96 | 76 | 48 |
| Mean survival (weeks)[b] | 53 | 51 | 49 |
| Survival analysis[c] | P<0.001 | P=0.011 | P<0.001 |

[a] Kaplan-Meier determinations
[b] Mean of all deaths (uncensored, censored, terminal sacrifice)
[c] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns.
[d] Includes three animals that died or were killed moribund during the terminal sacrifice period

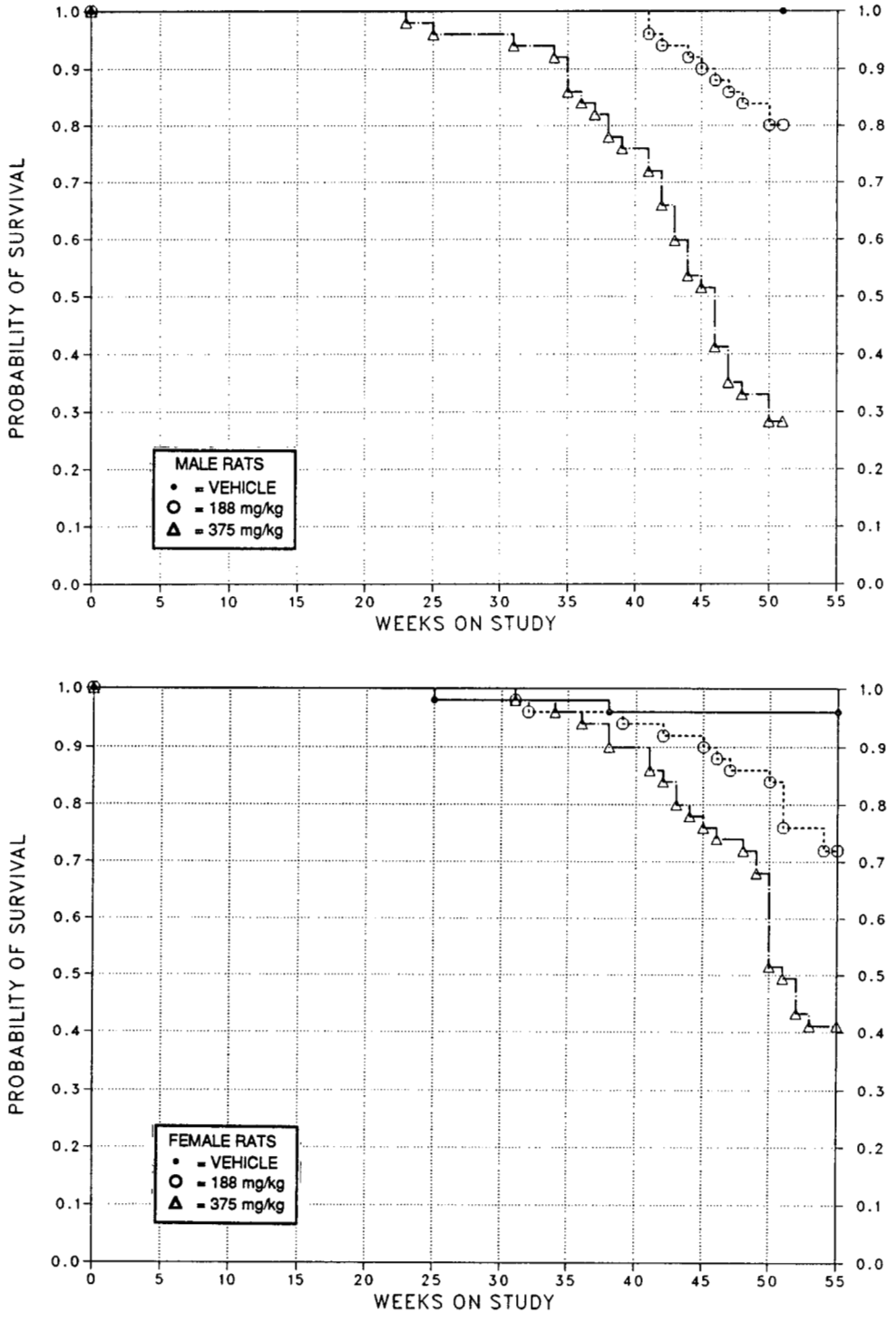



**FIGURE 2**
**Kaplan-Meier Survival Curves for Rats Administered 2,3-Dibromo-1-propanol by Dermal Application for 51 or 55 Weeks**

TABLE 6
**Mean Body Weights and Survival of Male Rats in the Long-Term Dermal Study of 2,3-Dibromo-1-propanol**

| Week on Study | Vehicle Control | | 188 mg/kg | | | 375 mg/kg | | |
|---|---|---|---|---|---|---|---|---|
| | Av. Wt. (g) | Number of Survivors | Av. Wt. (g) | Wt. (% of controls) | Number of Survivors | Av. Wt. (g) | Wt. (% of controls | Number of Survivors |
| 0 | 189 | 50 | 164 | 87 | 50 | 183 | 97 | 50 |
| 1 | 219 | 50 | 219 | 100 | 50 | 214 | 98 | 50 |
| 2 | 239 | 50 | 240 | 100 | 50 | 235 | 98 | 50 |
| 3 | 262 | 50 | 263 | 100 | 50 | 257 | 98 | 50 |
| 4 | 277 | 50 | 282 | 102 | 50 | 276 | 100 | 50 |
| 5 | 295 | 50 | 297 | 101 | 50 | 291 | 99 | 50 |
| 6 | 310 | 50 | 311 | 100 | 50 | 304 | 98 | 50 |
| 7 | 324 | 50 | 324 | 100 | 50 | 318 | 98 | 50 |
| 8 | 333 | 50 | 334 | 100 | 50 | 327 | 98 | 50 |
| 9 | 345 | 50 | 342 | 99 | 50 | 335 | 97 | 50 |
| 10 | 354 | 50 | 352 | 99 | 50 | 343 | 97 | 50 |
| 11 | 355 | 50 | 355 | 100 | 50 | 348 | 98 | 50 |
| 12 | 362 | 50 | 365 | 101 | 50 | 356 | 98 | 50 |
| 16 | 389 | 50 | 389 | 100 | 50 | 375 | 96 | 50 |
| 20 | 403 | 50 | 397 | 99 | 50 | 387 | 96 | 50 |
| 24 | 400 | 50 | 416 | 104 | 50 | 400 | 100 | 49 |
| 28 | 428 | 50 | 419 | 98 | 50 | 390 | 91 | 48 |
| 32 | 439 | 50 | 427 | 97 | 50 | 392 | 89 | 47 |
| 36 | 445 | 50 | 433 | 97 | 50 | 390 | 88 | 43 |
| 40 | 456 | 50 | 43[illegible] | 94 | 50 | 378 | 83 | 38 |
| 44 | 462 | 50 | 433 | 94 | 46 | 358 | 77 | 28 |
| 48 | 467 | 50 | 423 | 91 | 41 | 346 | 74 | 16 |
| **Mean for weeks** | | | | | | | | |
| 1-13 | 306 | | 307 | 100 | | 300 | 98 | |
| 14-44 | 428 | | 418 | 98 | | 384 | 90 | |

TABLE 7
**Mean Body Weights and Survival of Female Rats in the Long-Term Dermal Study of 2,3-Dibromo-1-propanol**

| Week on Study | Vehicle Control | | 188 mg/kg | | | 375 mg/kg | | |
|---|---|---|---|---|---|---|---|---|
| | Av. Wt. (g) | Number of Survivors | Av. Wt. (g) | Wt. (% of controls) | Number of Survivors | Av. Wt. (g) | Wt. (% of controls | Number of Survivors |
| 0 | 138 | 50 | 140 | 101 | 50 | 139 | 101 | 50 |
| 1 | 152 | 50 | 152 | 100 | 50 | 153 | 101 | 50 |
| 2 | 160 | 50 | 161 | 101 | 50 | 162 | 101 | 50 |
| 3 | 170 | 50 | 172 | 101 | 50 | 171 | 101 | 50 |
| 4 | 175 | 50 | 178 | 102 | 50 | 179 | 102 | 50 |
| 5 | 182 | 50 | 183 | 101 | 50 | 183 | 101 | 50 |
| 6 | 188 | 50 | 189 | 101 | 50 | 189 | 101 | 50 |
| 7 | 192 | 50 | 193 | 101 | 50 | 192 | 100 | 50 |
| 8 | 198 | 50 | 197 | 99 | 50 | 196 | 99 | 50 |
| 9 | 201 | 50 | 200 | 100 | 50 | 200 | 100 | 50 |
| 10 | 205 | 50 | 204 | 100 | 50 | 205 | 100 | 50 |
| 11 | 207 | 50 | 206 | 100 | 50 | 208 | 100 | 50 |
| 12 | 210 | 50 | 209 | 100 | 50 | 210 | 100 | 50 |
| 16 | 221 | 50 | 220 | 100 | 50 | 219 | 99 | 50 |
| 20 | 225 | 50 | 224 | 100 | 50 | 223 | 99 | 50 |
| 24 | 234 | 50 | 238 | 102 | 50 | 235 | 100 | 50 |
| 28 | 241 | 49 | 243 | 101 | 50 | 238 | 99 | 50 |
| 32 | 244 | 49 | 251 | 103 | 49 | 239 | 98 | 49 |
| 36 | 253 | 49 | 263 | 104 | 48 | 247 | 98 | 48 |
| 40 | 267 | 48 | 273 | 102 | 47 | 256 | 96 | 45 |
| 44 | 276 | 48 | 279 | 101 | 46 | 259 | 94 | 40 |
| 48 | 286 | 48 | 286 | 100 | 43 | 245 | 86 | 38 |
| **Mean for weeks** | | | | | | | | |
| 1-13 | 187 | | 187 | 100 | | 187 | 100 | |
| 14-48 | 250 | | 253 | 101 | | 240 | 96 | |

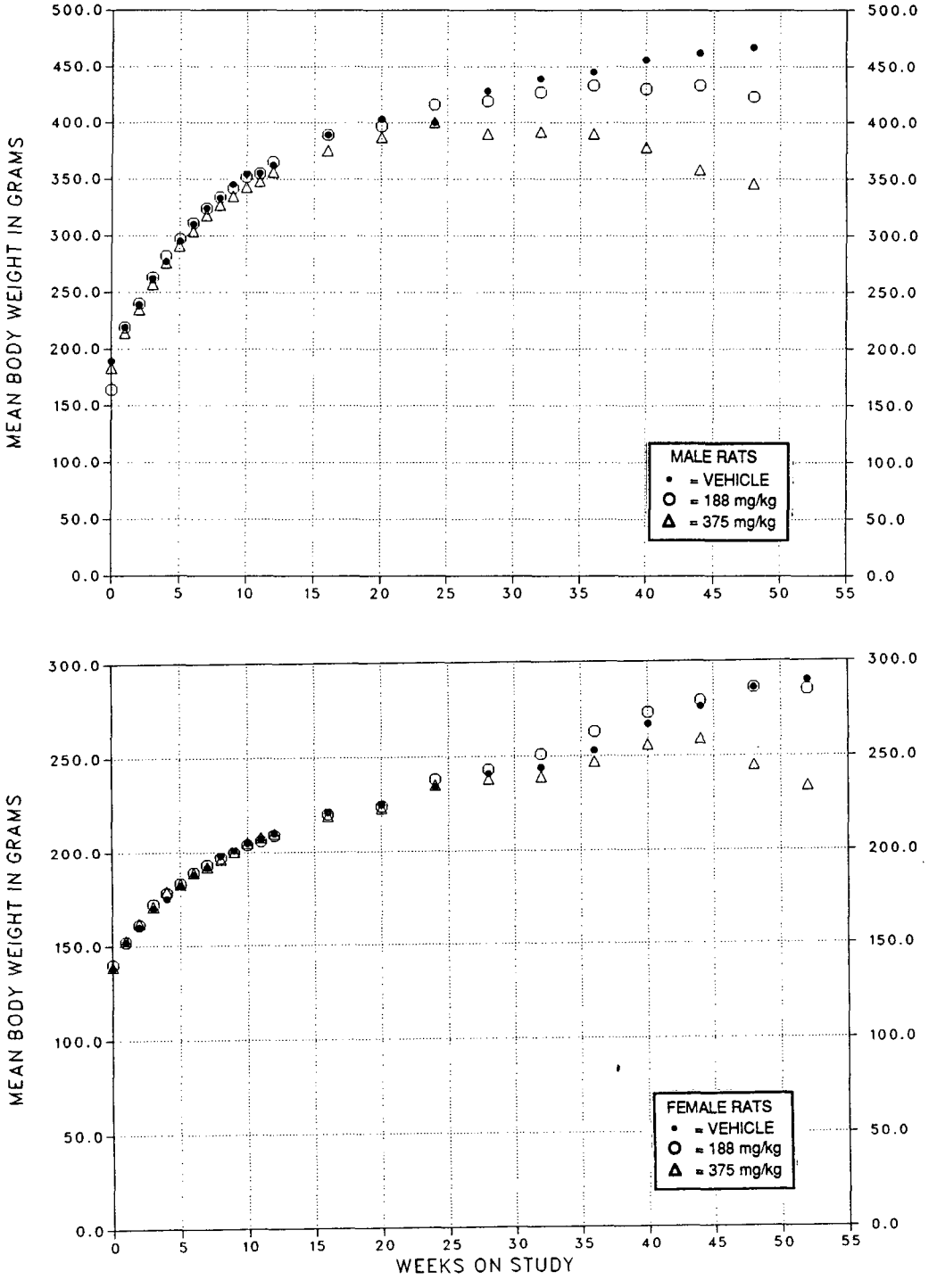



**FIGURE 3**
**Growth Curves for Rats Administered 2,3-Dibromo-1-propanol by Dermal Application for 51 or 55 Weeks**

### *Pathology and Statistical Evaluation*

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the skin (application site), gastrointestinal tract, nose, Zymbal's gland, kidney, liver, preputial and clitoral glands, mammary gland, mesothelium, and spleen. Summaries of the incidences of neoplasms and nonneoplastic lesions and individual animal tumor diagnoses are presented in Appendix A for male rats and Appendix B for female rats.

*Skin:* Hyperkeratosis of the skin at the site of 2,3-dibromo-1-propanol administration was observed in 2% of the low-dose male rats, 46% of the high-dose males, and 48% of the high-dose females, but not in the controls. Epithelial neoplasms of various histologic types were observed in the skin at or near the site of application in 44% of the low-dose males, 66% of the high-dose males, 6% of the low-dose females, and 36% of the high-dose females (Table 8). A squamous cell papilloma was observed in a single control male. The neoplasms in dosed rats frequently exhibited divergent differentiation, with varying numbers of basal cells, sebaceous cells, and/or squamous cells within an individual neoplasm, and the diagnosis was based on the predominant growth pattern and cell type.

The squamous cell papillomas were exophytic masses composed of irregular papillary fronds with fibrovascular cores covered by well-differentiated squamous epithelium and thick layers of keratin. Squamous cell carcinomas were poorly circumscribed, locally invasive masses composed of cords of squamous epithelium exhibiting dysplasia, atypical keratinization (keratin pearl formation), and numerous mitoses (Plate 3). The basal cell tumors were well-circumscribed endophytic masses consisting of cords and solid lobules of basal cells separated by dense collagenous connective tissue. The basal cells were relatively uniform in size and shape, with round nuclei and basophilic cytoplasm (Plate 4). In some basal cell tumors, small clusters of cells exhibited squamous or sebaceous differentiation; neoplasms exhibiting extensive sebaceous differentiation were designated sebaceous adenomas. Keratoacanthomas were invaginated, crateriform masses of stratified squamous epithelium continuous with the surface epithelium (Plate 5). The stratified epithelium formed papillary or nodular masses covered by thick layers of keratin which often filled the central cavity of the mass (Plate 6).

*Oral Mucosa (Tongue, Lip, Gum, Palate, Pharynx), Esophagus, and Forestomach:* Squamous cell papillomas or carcinomas of the oral mucosa occurred in nearly all low- and high-dose males and in almost all high-dose and most low-dose females; none were seen in the controls (Table 9). Moreover, many of the dosed rats had multiple oral neoplasms. The majority of neoplasms occurred on the dorsum of the tongue or on the pharynx, but a few were observed arising from the mucosa of the lip, palate, or gingiva.

Squamous cell papillomas of the esophagus and forestomach were also observed in many dosed rats (Table 9). In contrast to the frequent occurrence of squamous cell carcinomas of the tongue and pharynx, esophageal carcinomas were observed in only one low-dose male and one high-dose female, and no forestomach carcinomas occurred. Further, the incidence of squamous cell papillomas of the forestomach in each group was less than the incidence of squamous cell papillomas of the esophagus. The histologic appearance of the squamous cell papillomas (Plate 7) and carcinomas of the upper gastrointestinal tract was generally similar to those arising from the skin.

The incidences of hyperkeratosis of the esophageal epithelium were increased in low- and high-dose rats, while the incidences of hyperkeratosis of the forestomach epithelium were increased primarily in the high-dose groups (Table 9). Hyperkeratosis was characterized by a slight to moderate increase in the thickness of the keratin layer. While such an increase can be the result of increased keratin formation associated with hyperplasia, it may also result from a decrease in keratin loss because of reduced food intake and reduction in mechanical debridement.

Dysplasia of the forestomach epithelium was seen in a number of dosed male and female rats, but not in the controls. In females, the highest incidence was in the high-dose group, while in males the highest incidence was in the low-dose group (males: 0/50, 6/50, 1/50; females: 0/50, 1/50, 8/50). The dysplasia

TABLE 8
**Incidences of Neoplasms and Nonneoplastic Lesions of the Skin in Rats in the Long-Term Dermal Study of 2,3-Dibromo-1-propanol**

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | Vehicle Control | 188 mg/kg | 375 mg/kg | Vehicle Control | 188 mg/kg | 375 mg/kg |
| Hyperkeratosis | | | | | | |
| Overall rate[a] | 0/50 (0%) | 1/50 (2%) | 23/50 (46%) | 0/50 (0%) | 0/50 (0%) | 24/50 (48%) |
| Cochran-Armitage test[b] | P<0.001 | | | P<0.001 | | |
| Fisher exact test[b] | | P=0.500 | P<0.001 | | –[c] | P<0.001 |
| Squamous Cell Papilloma | | | | | | |
| Overall rate | 1/50 (2%) | 3/50[d] (6%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) | 2/50 (4%) |
| Cochran-Armitage test | P=0.378N | | | P=0.110 | | |
| Fisher exact test | | P=0.309 | P=0.500N | | – | P=0.247 |
| Squamous Cell Carcinoma | | | | | | |
| Overall rate | 0/50 (0%) | 5/50 (10%) | 8/50 (16%) | 0/50 (0%) | 0/50 (0%) | 1/50 (2%) |
| Cochran-Armitage test | P=0.004 | | | P=0.333 | | |
| Fisher exact test | | P=0.028 | P=0.003 | | – | P=0.500 |
| Squamous Cell Papilloma or Squamous Cell Carcinoma | | | | | | |
| Overall rate | 1/50 (2%) | 8/50 (16%) | 8/50 (16%) | 0/50 (0%) | 0/50 (0%) | 3/50 (6%) |
| Cochran-Armitage test | P=0.020 | | | P=0.036 | | |
| Fisher exact test | | P=0.015 | P=0.015 | | – | P=0.121 |
| Basal Cell Tumor | | | | | | |
| Overall rate | 0/50 (0%) | 13/50 (26%) | 21/50 (42%) | 0/50 (0%) | 3/50 (6%) | 12/50 (24%) |
| Cochran-Armitage test | P<0.001 | | | P<0.001 | | |
| Fisher exact test | | P<0.001 | P<0.001 | | P=0.121 | P<0.001 |
| Sebaceous Adenoma | | | | | | |
| Overall rate | 0/50 (0%) | 5/50 (10%) | 5/50 (10%) | 0/50 (0%) | 0/50 (0%) | 2/50 (4%) |
| Cochran-Armitage test | P=0.036 | | | P=0.110 | | |
| Fisher exact test | | P=0.028 | P=0.028 | | – | P=0.247 |
| Keratoacanthoma | | | | | | |
| Overall rate | 0/50 (0%) | 4/50 (8%) | 12/50 (24%) | 0/50 (0%) | 0/50 (0%) | 5/50 (10%) |
| Cochran-Armitage test | P<0.001 | | | P=0.004 | | |
| Fisher exact test | | P=0.059 | P<0.001 | | – | P=0.028 |
| Basal Cell Tumor, Sebaceous Adenoma, or Keratoacanthoma | | | | | | |
| Overall rate | 0/50 (0%) | 20/50 (40%) | 31/50 (62%) | 0/50 (0%) | 3/50 (6%) | 18/50 (36%) |
| Cochran-Armitage test | P<0.001 | | | P<0.001 | | |
| Fisher exact test | | P<0.001 | P<0.001 | | P=0.121 | P<0.001 |
| Epithelial Neoplasms (all types) | | | | | | |
| Overall rate | 1/50 (2%) | 22/50 (44%) | 33/50 (66%) | 0/50 (0%) | 3/50 (6%) | 18/50 (36%) |
| Cochran-Armitage test | P<0.001 | | | P<0.001 | | |
| Fisher exact test | | P<0.001 | P<0.001 | | P=0.121 | P<0.001 |

[a] Number of lesion-bearing animals/number of animals necropsied
[b] Beneath the control incidence are the P values associated with the trend test. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[c] Not applicable; no lesions in animal group
[d] Multiple occurrence of morphology in the same organ tissue is counted only once.

TABLE 9
**Incidences of Neoplasms and Nonneoplastic Lesions of the Digestive System in Rats in the Long-Term Dermal Study of 2,3-Dibromo-1-propanol**

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | Vehicle Control | 188 mg/kg | 375 mg/kg | Vehicle Control | 188 mg/kg | 375 mg/kg |
| **Oral Mucosa** | | | | | | |
| Squamous Cell Papilloma | | | | | | |
| Overall rate[a] | 0/50 (0%) | 40/50 (80%) | 33/50 (66%) | 0/50 (0%) | 27/50 (54%) | 41/50 (82%) |
| Cochran-Armitage test[b] | P<0.001 | | | P<0.001 | | |
| Fisher exact test[b] | | P<0.001 | P<0.001 | | P<0.001 | P<0.001 |
| Squamous Cell Carcinoma | | | | | | |
| Overall rate | 0/50 (0%) | 16/50 (32%) | 25/50 (50%) | 0/50 (0%) | 15/50 (30%) | 27/50 (54%) |
| Cochran-Armitage test | P<0.001 | | | P<0.001 | | |
| Fisher exact test | | P<0.001 | P<0.001 | | P<0.001 | P<0.001 |
| Squamous Cell Papilloma or Squamous Cell Carcinoma | | | | | | |
| Overall rate | 0/50 (0%) | 47/50 (94%) | 48/50 (96%) | 0/50 (0%) | 39/50 (78%) | 49/50 (98%) |
| Cochran-Armitage test | P<0.001 | | | P<0.001 | | |
| Fisher exact test | | P<0.001 | P<0.001 | | P<0.001 | P<0.001 |
| **Esophagus** | | | | | | |
| Hyperkeratosis | | | | | | |
| Overall rate[c] | 0/50 (0%) | 18/50 (36%) | 48/50 (96%) | 1/50 (2%) | 20/50 (40%) | 49/50 (98%) |
| Cochran-Armitage test | P<0.001 | | | P<0.001 | | |
| Fisher exact test | | P<0.001 | P<0.001 | | P<0.001 | P<0.001 |
| Squamous Cell Papilloma | | | | | | |
| Overall rate[c] | 0/50 (0%) | 19/50 (38%) | 33/50 (66%) | 0/50 (0%) | 9/50 (18%) | 38/50 (76%) |
| Cochran-Armitage test | P<0.001 | | | P<0.001 | | |
| Fisher exact test | | P<0.001 | P<0.001 | | P=0.001 | P<0.001 |
| Squamous Cell Carcinoma | | | | | | |
| Overall rate[c] | 0/50 (0%) | 1/50 (2%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) | 1/50 (2%) |
| Cochran-Armitage test | P=0.667 | | | P=0.333 | | |
| Fisher exact test | | P=0.500 | –[d] | | – | P=0.500 |
| Squamous Cell Papilloma or Squamous Cell Carcinoma | | | | | | |
| Overall rate[c] | 0/50 (0%) | 20/50 (40%) | 33/50 (66%) | 0/50 (0%) | 9/50 (18%) | 38/50 (76%) |
| Cochran-Armitage test | P<0.001 | | | P<0.001 | | |
| Fisher exact test | | P<0.001 | P<0.001 | | P=0.001 | P<0.001 |
| **Forestomach** | | | | | | |
| Hyperkeratosis | | | | | | |
| Overall rate[c] | 2/50 (4%) | 6/50 (12%) | 32/50 (64%) | 0/50 (0%) | 6/50 (12%) | 30/50 (60%) |
| Cochran-Armitage test | P<0.001 | | | P<0.001 | | |
| Fisher exact test | | P=0.134 | P<0.001 | | P=0.013 | P<0.001 |
| Epithelial Dysplasia | | | | | | |
| Overall rate[c] | 0/50 (0%) | 6/50 (12%) | 1/50 (2%) | 0/50 (0%) | 1/50 (2%) | 8/50 (16%) |
| Cochran-Armitage test | P=0.406 | | | P<0.001 | | |
| Fisher exact test | | P=0.013 | P=0.500 | | P=0.500 | P=0.003 |

(continued)

TABLE 9
**Incidences of Neoplasms and Nonneoplastic Lesions of the Digestive System in Rats in the Long-Term Dermal Study of 2,3-Dibromo-1-propanol** (continued)

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | Vehicle Control | 188 mg/kg | 375 mg/kg | Vehicle Control | 188 mg/kg | 375 mg/kg |
| **Forestomach** (continued) | | | | | | |
| Acanthosis | | | | | | |
| Overall rate[c] | 0/50 (0%) | 1/50 (2%) | 6/50 (12%) | 0/50 (0%) | 0/50 (0%) | 1/50 (2%) |
| Cochran-Armitage test | P=0.005 | | | P=0.333 | | |
| Fisher exact test | | P=0.500 | P=0.013 | | – | P=0.500 |
| Squamous Cell Papilloma | | | | | | |
| Overall rate[c] | 0/50 (0%) | 1/50 (2%) | 17/50 (34%) | 1/50 (2%) | 3/50 (6%) | 23/50 (46%) |
| Cochran-Armitage test | P<0.001 | | | P<0.001 | | |
| Fisher exact test | | P=0.500 | P<0.001 | | P=0.309 | P<0.001 |

[a] Number of lesion-bearing animals/number of animals necropsied, unless otherwise specified
[b] Beneath the control incidence are the P values associated with the trend test. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates.
[c] Number of lesion-bearing animals/number of animals with tissue examined microscopically
[d] Not applicable; no lesions in animal group

denoted intraepithelial foci of cellular atypia associated with increased thickness of the epithelium, often located near the junction of the glandular stomach and forestomach. Increased incidences of hyperplasia (diagnosed as acanthosis in males), characterized by focal to diffuse thickening of the stratum spinosum, and ulcers were also observed in dosed rats (Tables A4 and B4). The incidences of hyperplasia were 0/50, 1/50, and 6/50 in males and 0/50, 2/50, and 4/50 in females. The incidences of ulcers were 0/50, 3/50, and 5/50 in males and 0/50, 0/50, and 2/50 in females.

*Small Intestine:* The incidences of adenomatous polyps and adenocarcinomas of the small intestine in low- and high-dose males were significantly greater than those of the controls (Table 10). Adenocarcinomas of the small intestine also occurred in two low-dose and four high-dose females, and an adenomatous polyp occurred in another low-dose female. Although the incidences of these neoplasms in dosed groups of female rats were not significantly greater than those in the controls, they were considered to be chemical related because similar neoplasms occurred in the large intestine and a similar effect was observed in the small intestine of males.

Adenomatous polyps and adenocarcinomas constitute a morphologic continuum. The adenomatous polyps were focally elevated, pedunculated masses composed of a disordered array of irregular and often dilated glands. The glandular structures were lined by cuboidal to columnar epithelial cells which failed to show normal differentiation from the base of the crypts to the surface. The epithelial cells had large, round, hyperchromatic nuclei and basophilic cytoplasm. The adenocarcinomas were distinguished from polyps primarily on the basis of invasion of the submucosa or muscularis (Plate 8), although some also exhibited a cellular atypia and a scirrhous reaction. Formation of large, mucus-filled, cyst-like structures was also noted in some adenocarcinomas.

*Large Intestine:* The incidences of adenomatous polyps of the large intestine in low- and high-dose male and female rats were significantly greater than those in the controls (Table 10). Despite the high incidences of these benign neoplasms in the dosed groups, adenocarcinomas were observed in only one low-dose male and two high-dose males; none were observed in dosed or control females. The neoplasms of the large intestine were morphologically similar to those of the small intestine (Plates 9 and 10).

TABLE 10
**Incidences of Selected Neoplasms of the Small and Large Intestine in Rats in the Long-Term Dermal Study of 2,3-Dibromo-1-propanol**

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | Vehicle Control | 188 mg/kg | 375 mg/kg | Vehicle Control | 188 mg/kg | 375 mg/kg |
| **Small Intestine** | | | | | | |
| Adenomatous Polyp | | | | | | |
| Overall rate[a] | 0/50 (0%) | 1/50 (2%) | 3/50 (6%) | 0/50 (0%) | 1/50 (2%) | 0/49 (0%) |
| Cochran-Armitage test[b] | P=0.060 | | | P=0.667 | | |
| Fisher exact test[b] | | P=0.500 | P=0.121 | | P=0.500 | –[c] |
| Adenocarcinoma | | | | | | |
| Overall rate | 0/50 (0%) | 8/50 (16%) | 11/50 (22%) | 0/50 (0%) | 3/50 (6%) | 4/49 (8%) |
| Cochran-Armitage test | P<0.001 | | | P=0.027 | | |
| Fisher exact test | | P=0.003 | P<0.001 | | P=0.121 | P=0.056 |
| Adenomatous Polyp or Adenocarcinoma | | | | | | |
| Overall rate | 0/50 (0%) | 9/50 (18%) | 12/50 (24%) | 0/50 (0%) | 4/50 (8%) | 4/49 (8%) |
| Cochran-Armitage test | P<0.001 | | | P=0.035 | | |
| Fisher exact test | | P=0.001 | P<0.001 | | P=0.059 | P=0.056 |
| **Large Intestine** | | | | | | |
| Adenomatous Polyp | | | | | | |
| Overall rate[d] | 1/50 (2%) | 13/50 (26%) | 29/50 (58%) | 0/50 (0%) | 12/50 (24%) | 37/50 (74%) |
| Cochran-Armitage test | P<0.001 | | | P<0.001 | | |
| Fisher exact test | | P<0.001 | P<0.001 | | P<0.001 | P<0.001 |
| Adenocarcinoma | | | | | | |
| Overall rate[d] | 1/50 (2%) | 1/50 (2%) | 2/50 (4%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) |
| Cochran-Armitage test | P=0.267 | | | – | | |
| Fisher exact test | | P=0.753 | P=0.500 | | – | – |
| Adenomatous Polyp or Adenocarcinoma | | | | | | |
| Overall rate[d] | 2/50 (4%) | 14/50 (28%) | 30/50 (60%) | 0/50 (0%) | 12/50 (24%) | 37/50 (74%) |
| Cochran-Armitage test | P<0.001 | | | P<0.001 | | |
| Fisher exact test | | P<0.001 | P<0.001 | | P<0.001 | P<0.001 |

[a] Number of lesion-bearing animals/number of animals with tissue examined microscopically
[b] Beneath the control incidence are the P values associated with the trend test. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates.
[c] Not applicable; no neoplasms in animal group
[d] Number of lesion-bearing animals/number of animals necropsied or number of animals with tissue examined microscopically

*Nose:* Epithelial dysplasia occurred in almost all dosed male and female rats (males: 0/50, 33/50, 49/50; females: 1/50, 49/50, 50/50) (Tables A4 and B4). The term "dysplasia" encompasses several related lesions of the respiratory and olfactory epithelium, including hyperplasia (increased number of epithelial cell layers), squamous metaplasia of the respiratory epithelium, respiratory metaplasia of the olfactory epithelium, and loss of normal cellular and nuclear orientation (Plates 11-13).

Adenomas of the nasal mucosa also occurred in nearly all dosed male and female rats, while none were observed in the controls (Table 11).

TABLE 11
**Incidences of Neoplasms of the Nose in Rats in the Long-Term Dermal Study of 2,3-Dibromo-1-propanol**

| | Vehicle Control | 188 mg/kg | 375 mg/kg |
|---|---|---|---|
| **Male** | | | |
| Adenoma | | | |
| Overall rate[a] | 0/50 (0%) | 48/50 (96%) | 48/50 (96%) |
| Cochran-Armitage test[b] | P<0.001 | | |
| Fisher exact test[b] | | P<0.001 | P<0.001 |
| Adenocarcinoma | | | |
| Overall rate | 0/50 (0%) | 2/50 (4%) | 1/50 (2%) |
| Cochran-Armitage test | P=0.369 | | |
| Fisher exact test | | P=0.247 | P=0.500 |
| Adenoma or Adenocarcinoma | | | |
| Overall rate | 0/50 (0%) | 49/50 (98%) | 49/50 (98%) |
| Cochran-Armitage test | P<0.001 | | |
| Fisher exact test | | P<0.001 | P<0.001 |
| **Female** | | | |
| Adenoma | | | |
| Overall rate | 0/50 (0%) | 44/50 (88%) | 49/50 (98%) |
| Cochran-Armitage test | P<0.001 | | |
| Fisher exact test | | P<0.001 | P<0.001 |

[a] Number of lesion-bearing animals/number of animals necropsied
[b] Beneath the control incidence are the P values associated with the trend test. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates.

Adenocarcinomas were seen in two low-dose males and one high-dose male; none were observed in the females.The adenomas (Plates 14 and 15) and adenocarcinomas were sessile exophytic masses arising from the respiratory epithelium of the turbinates and septum and consisted of cuboidal to short columnar epithelium arranged in gland-like or tubular structures or cords of epithelium separated by a scant vascular stroma. The few adenocarcinomas exhibited greater heterogeneity in growth pattern, cellular pleomorphism and atypia, and invasion of the submucosa.

*Zymbal's Gland:* Adenomas or adenocarcinomas of the Zymbal's gland occurred in 18% of low-dose and 70% of high-dose males, and in 18% of low-dose and 44% of high-dose females (Table 12). The majority of the neoplasms in dosed rats were malignant (adenocarcinomas). One control female rat also had an adenocarcinoma, but none were observed in the control males. The combined incidence of adenoma or adenocarcinoma in each of the dosed groups was significantly greater than that in the controls.

Adenomas were well-circumscribed masses lacking normal lobular architecture. They consisted of well-differentiated sebaceous cells arranged in irregular, solid clusters, sometimes admixed with thick cords or islands of squamous epithelium. The adenocarcinomas were less well circumscribed and invaded surrounding soft tissues. They consisted of irregular acini or solid sheets of cells and frequently

TABLE 12
**Incidences of Neoplasms of the Zymbal's Gland in Rats in the Long-Term Dermal Study of 2,3-Dibromo-1-propanol**

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | Vehicle Control | 188 mg/kg | 375 mg/kg | Vehicle Control | 188 mg/kg | 375 mg/kg |
| Adenoma | | | | | | |
| Overall rate[a] | 0/50 (0%) | 1/50 (2%) | 7/50 (14%) | 0/50 (0%) | 7/50 (14%) | 3/50 (6%) |
| Cochran-Armitage test[b] | P=0.002 | | | P=0.158 | | |
| Fisher exact test[b] | | P=0.500 | P=0.006 | | P=0.006 | P=0.121 |
| Adenocarcinoma | | | | | | |
| Overall rate | 0/50 (0%) | 8/50 (16%) | 29/50 (58%) | 1/50 (2%) | 2/50 (4%) | 19/50 (38%) |
| Cochran-Armitage test | P<0.001 | | | P<0.001 | | |
| Fisher exact test | | P=0.003 | P<0.001 | | P=0.247 | P<0.001 |
| Adenoma or Adenocarcinoma | | | | | | |
| Overall rate | 0/50 (0%) | 9/50 (18%) | 35/50 (70%) | 1/50 (2%) | 9/50 (18%) | 22/50 (44%) |
| Cochran-Armitage test | P<0.001 | | | P<0.001 | | |
| Fisher exact test | | P=0.001 | P<0.001 | | P=0.001 | P<0.001 |

[a] Number of neoplasm-bearing animals/number of animals necropsied
[b] Beneath the control incidence are the P values associated with the trend test. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates.

contained cystic cavities filled with debris (sebum, keratin, and necrotic cells). The neoplastic cells varied from moderately well-differentiated sebaceous cells or squamous cells to pleomorphic, undifferentiated cells.

*Kidney:* Nuclear enlargement (karyomegaly) of renal tubule epithelial cells was observed in most high-dose rats and a few low-dose females (males: 0/50, 0/50, 41/50; females: 0/50, 6/50, 47/50) (Tables A4 and B4). Only a few scattered cells in the inner cortex and outer stripe of the outer medulla were affected in each section of kidney.

Renal tubule adenomas occurred in four high-dose males, one low-dose female, and four high-dose females, while none occurred in control rats (Table 13). The renal tubule adenomas occurred with significant positive trends in both males and females, but the incidence in each of the dosed groups was not significantly greater than that in the controls by pairwise comparisons. The adenomas in dosed rats are considered to be chemical related because a similar effect was observed in males and females and because the incidences of focal hyperplasia of the tubule epithelium were also increased, particularly in males.

Renal tubule cell hyperplasia and adenoma constitute a morphologic continuum. Hyperplasia was characterized by one or several adjacent tubule cross-sections with multiple layers of epithelium which partially or completely filled the tubule lumen(s). The adenomas were generally larger, greater than five tubules in diameter, and consisted of solid clusters or compact nests of cells.

TABLE 13
**Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Rats in the Long-Term Dermal Study of 2,3-Dibromo-1-propanol**

| | Vehicle Control | 188 mg/kg | 375 mg/kg |
|---|---|---|---|
| **Male** | | | |
| Hyperplasia | | | |
| Overall rate[a] | 0/50 (0%) | 1/50 (2%) | 5/50 (10%) |
| Cochran-Armitage test[b] | P=0.011 | | |
| Fisher exact test[b] | | P=0.500 | P=0.028 |
| Renal Tubule Adenoma | | | |
| Overall rate | 0/50 (0%) | 0/50 (0%) | 4/50 (8%) |
| Cochran-Armitage test | P=0.011 | | |
| Fisher exact test | | -[c] | P=0.059 |
| **Female** | | | |
| Hyperplasia | | | |
| Overall rate | 0/50 (0%) | 1/50 (2%) | 2/50 (4%) |
| Cochran-Armitage test | P=0.147 | | |
| Fisher exact test | | P=0.500 | P=0.247 |
| Renal Tubule Adenoma | | | |
| Overall rate | 0/50 (0%) | 1/50 (2%) | 4/50 (8%) |
| Cochran-Armitage test | P=0.023 | | |
| Fisher exact test | | P=0.500 | P=0.059 |

[a] Number of lesion-bearing animals/number of animals with tissue examined microscopically
[b] Beneath the control incidence are the P values associated with the trend test. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates.
[c] Not applicable; no neoplasms in animal group

*Liver:* Neoplastic nodules occurred with a significant positive trend in female rats, and the incidence in each of the dose groups was significantly greater than that in the controls (Table 14). Although hepatocellular carcinomas also occurred with a significant trend, only the incidence in the high-dose group was significantly greater than that in the controls. In male rats, there was a marginal increase in the incidence of neoplastic nodules or hepatocellular carcinomas (combined), but the incidence of neither neoplastic nodules nor hepatocellular carcinomas in the high-dose group was significantly greater than that in the controls (Table 14). Nevertheless, the hepatocellular neoplasms in males and females were considered chemical related because of their infrequent occurrence in historical control rats.

At the time the studies were performed, the diagnostic term "neoplastic nodule" was applied to proliferative lesions currently classified as hepatocellular adenoma. The neoplastic nodules were discrete masses usually larger than several hepatic lobules which slightly compressed the surrounding parenchyma. Normal lobular architecture was not apparent within the lesion, and the hepatic plates merged at abnormal angles with those of the normal adjacent tissue. The hepatocytes within neoplastic nodules were well-differentiated but were often larger than normal. Hepatocellular carcinomas were considerably larger than the neoplastic nodules and exhibited heterogenous growth patterns with the hepatocytes arranged in trabeculae or gland-like structures.

TABLE 14
**Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Rats in the Long-Term Dermal Study of 2,3-Dibromo-1-propanol**

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | Vehicle Control | 188 mg/kg | 375 mg/kg | Vehicle Control | 188 mg/kg | 375 mg/kg |
| Basophilic Cytoplasmic Change | | | | | | |
| Overall rate[a] | 2/49 (4%) | 28/50 (56%) | 16/50 (32%) | 5/50 (10%) | 27/50 (54%) | 19/50 (38%) |
| Cochran-Armitage test[b] | P=0.002 | | | P=0.002 | | |
| Fisher exact test[b] | | P<0.001 | P<0.001 | | P<0.001 | P<0.001 |
| Clear Cell Cytoplasmic Change | | | | | | |
| Overall rate | 2/49 (4%) | 15/50 (30%) | 5/50 (10%) | 1/50 (2%) | 8/50 (16%) | 7/50 (14%) |
| Cochran-Armitage test | P=0.253 | | | P=0.037 | | |
| Fisher exact test | | P<0.001 | P=0.226 | | P=0.015 | P=0.030 |
| Eosinophilic Cytoplasmic Change | | | | | | |
| Overall rate | 0/49 (0%) | 2/50 (10%) | 4/50 (8%) | 0/50 (0%) | 1/50 (2%) | 3/50 (6%) |
| Cochran-Armitage test | P=0.038 | | | P=0.060 | | |
| Fisher exact test | | P=0.253 | P=0.061 | | P=0.500 | P=0.121 |
| Cellular Pleomorphism | | | | | | |
| Overall rate | 0/49 (0%) | 0/50 (0%) | 37/50 (74%) | 0/50 (0%) | 0/50 (0%) | 44/50 (88%) |
| Cochran-Armitage test | P<0.001 | | | P<0.001 | | |
| Fisher exact test | | -[c] | P<0.001 | | - | P<0.001 |
| Angiectasis | | | | | | |
| Overall rate | 2/49 (4%) | 26/50 (52%) | 46/50 (92%) | 0/50 (0%) | 1/50 (2%) | 3/50 (6%) |
| Cochran-Armitage test | P<0.001 | | | P=0.060 | | |
| Fisher exact test | | P<0.001 | P<0.001 | | P=0.500 | P=0.121 |
| Periportal Bile Duct: Hyperplasia | | | | | | |
| Overall rate | 20/49 (40%) | 13/50 (26%) | 10/50 (20%) | 1/50 (2%) | 6/50 (12%) | 37/50 (74%) |
| Cochran-Armitage test | P=0.015N | | | P<0.001 | | |
| Fisher exact test | | P=0.088N | P=0.021N | | P=0.056 | P<0.001 |
| Neoplastic Nodule | | | | | | |
| Overall rate | 0/49 (0%) | 3/50 (6%) | 2/50 (4%) | 0/50 (0%) | 10/50 (20%) | 11/50 (22%) |
| Cochran-Armitage test | P=0.207 | | | P=0.001 | | |
| Fisher exact test | | P=0.125 | P=0.253 | | P<0.001 | P<0.001 |
| Hepatocellular Carcinoma | | | | | | |
| Overall rate | 0/49 (0%) | 1/50 (2%) | 3/50 (6%) | 0/50 (0%) | 2/50 (4%) | 6/50 (12%) |
| Cochran-Armitage test | P=0.061 | | | P=0.007 | | |
| Fisher exact test | | P=0.505 | P=0.125 | | P=0.247 | P=0.013 |
| Neoplastic Nodule or Hepatocellular Carcinoma | | | | | | |
| Overall rate | 0/49 (0%) | 4/50 (8%) | 5/50 (10%) | 0/50 (0%) | 11/50 (22%) | 14/50 (28%) |
| Cochran-Armitage test | P=0.031 | | | P<0.001 | | |
| Fisher exact test | | P=0.061 | P=0.030 | | P<0.001 | P<0.001 |

[a] Number of lesion-bearing animals/number of animals with tissue examined microscopically
[b] Beneath the control incidence are the P values associated with the trend test. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[c] Not applicable; no lesions in animal group

Increased incidences of foci of cytoplasmic change (basophilic, clear cell, and eosinophilic) and cellular pleomorphism were observed in dosed male and female rats. Dosed male rats also exhibited an increased incidence of angiectasis (Table 14). The incidence of bile duct hyperplasia was increased in dosed females, but not in males. Foci of cytoplasmic change were characterized by altered staining of the hepatocyte cytoplasm. The foci were generally smaller than three hepatic lobules in size, and the affected hepatocytes retained normal lobular arrangement. Pleomorphism consisted of panlobular cytomegaly (cellular enlargement) with some variation in nuclear size. "Angiectasis" referred to a change also known as cystic degeneration or spongiosis hepatis, and was characterized by focally dilated sinusoids forming cystic spaces filled with granular or flocculent material (protein) and variable numbers of erythrocytes. The bile duct hyperplasia in female rats was characterized by increased numbers of small, well-differentiated bile ducts in the portal areas, often accompanied by increased fibrous stroma.

*Preputial and Clitoral Glands:* Preputial glands in male rats and clitoral glands in female rats are specialized holocrine glands which function as homologous accessory sex organs. In dosed female rats, clitoral gland neoplasms (adenomas or adenocarcinomas) occurred with a significant positive trend, and the incidence in the high-dose group was significantly greater than that in the control group by pairwise comparison (Table 15). The incidence of preputial gland adenomas in low-dose males was slightly greater than that in the controls, but the difference was not significant.

*Mammary Gland:* Adenocarcinomas of the mammary gland occurred in five high-dose females; none were seen in the low-dose or control groups (Table 15). The Cochran-Armitage trend test was significant and the incidence in the high-dose group was significantly greater than that in the controls by pairwise comparison.

*Mesothelium:* Mesotheliomas of the testicular tunica vaginalis occurred in one low-dose male and four high-dose males; none were observed in the controls (Table 15). The trend test was significant, but the pairwise comparisons were not. Nevertheless, because of the low spontaneous occurrence of mesotheliomas in NTP historical control rats, these neoplasms are considered chemical related.

*Spleen:* Hemangiomas of the spleen occurred in three high-dose male rats and a hemangiosarcoma occurred in another high-dose male; none were seen in the controls (Table 15). Although the trend test was significant, the incidence of vascular neoplasms (benign or malignant, combined) in the high-dose group was not significantly greater than that in the controls.

TABLE 15
**Incidences of Selected Neoplasms of the Preputial or Clitoral Gland, Spleen, Mesothelium, and Mammary Gland in Rats in the Long-Term Dermal Study of 2,3-Dibromo-1-propanol**

| | Vehicle Control | 188 mg/kg | 375 mg/kg |
|---|---|---|---|
| **Male** | | | |
| **Preputial Gland** | | | |
| Adenoma | | | |
| Overall rate[a] | 2/50 (4%) | 6/50 (12%) | 3/50 (6%) |
| Cochran-Armitage test[b] | P=0.424 | | |
| Fisher exact test[b] | | P=0.134 | P=0.500 |
| **Tunica Vaginalis** | | | |
| Mesothelioma | | | |
| Overall rate | 0/50 (0%) | 1/50 (2%) | 4/50 (8%) |
| Cochran-Armitage test | P=0.023 | | |
| Fisher exact test | | P=0.500 | P=0.059 |
| **Spleen** | | | |
| Hemangioma | | | |
| Overall rate[c] | 0/50 (0%) | 0/50 (0%) | 3/50 (6%) |
| Cochran-Armitage test | P=0.036 | | |
| Fisher exact test | | | P=0.121 |
| Hemangiosarcoma | | | |
| Overall rate[c] | 0/50 (0%) | 0/50 (0%) | 1/50 (2%) |
| Cochran-Armitage test | P=0.333 | | |
| Fisher exact test | | | P=0.500 |
| Hemangioma or Hemangiosarcoma | | | |
| Overall rate[c] | 0/50 (0%) | 0/50 (0%) | 4/50 (8%) |
| Cochran-Armitage test | P=0.011 | | |
| Fisher exact test | | –[d] | P=0.059 |
| **Female** | | | |
| **Clitoral Gland** | | | |
| Adenoma | | | |
| Overall rate[a] | 0/50 (0%) | 1/50 (2%) | 3/50 (6%) |
| Cochran-Armitage test | P=0.060 | | |
| Fisher exact test | | P=0.500 | P=0.121 |
| Adenocarcinoma | | | |
| Overall rate | 0/50 (0%) | 0/50 (0%) | 3/50 (6%) |
| Cochran-Armitage test | P=0.036 | | |
| Fisher exact test | | – | P=0.121 |
| Adenoma or Adenocarcinoma | | | |
| Overall rate | 0/50 (0%) | 1/50 (2%) | 6/50 (12%) |
| Cochran-Armitage test | P=0.005 | | |
| Fisher exact test | | P=0.500 | P=0.013 |
| **Mammary Gland** | | | |
| Adenocarcinoma | | | |
| Overall rate | 0/50 (0%) | 0/50 (0%) | 5/50 (10%) |
| Cochran-Armitage test | P=0.004 | | |
| Fisher exact test | | – | P=0.028 |

[a] Number of neoplasm-bearing animals/number of animals necropsied, unless otherwise specified
[b] Beneath the control incidence are the P values associated with the trend test. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates.
[c] Number of neoplasm-bearing animals/number of animals with tissue examined microscopically
[d] Not applicable; no neoplasms in animal group

# MICE

## 16-DAY STUDY

Four male mice in the 750 mg/kg group died on day 2 and one female in the 750 mg/kg group died on day 3 of the study (Table 16). There were no biologically significant differences in final mean body weights or body weight gains in dosed males or females. No chemical-related clinical findings or gross observations were noted in dosed male or female mice.

TABLE 16
**Survival and Mean Body Weights of Mice in the 16-Day Dermal Study of 2,3-Dibromo-1-propanol**

| Concentration (mg/kg) | Survival[a] | Mean Body Weight[b] (g) | | | Final Weight Relative to Controls (%) |
|---|---|---|---|---|---|
| | | Initial | Final | Change | |
| **Male** | | | | | |
| 0 | 5/5 | 25.7 ± 0.7 | 29.8 ± 0.8 | 4.2 ± 1.0 | |
| 44 | 5/5 | 25.9 ± 0.6 | 28.5 ± 0.6 | 2.6 ± 0.3 | 96 |
| 88 | 5/5 | 25.9 ± 0.9 | 29.2 ± 0.6 | 3.3 ± 1.1 | 98 |
| 177 | 5/5 | 25.5 ± 0.9 | 30.2 ± 0.5 | 4.7 ± 0.6 | 101 |
| 375 | 5/5 | 25.6 ± 1.1 | 30.0 ± 0.7 | 4.5 ± 0.7 | 101 |
| 750 | 1/5[c] | 26.0 ± 1.1 | 30.5 | 5.4 | 102 |
| **Female** | | | | | |
| 0 | 5/5 | 17.8 ± 0.7 | 19.6 ± 0.5 | 1.8 ± 0.3 | |
| 44 | 5/5 | 17.6 ± 0.6 | 19.8 ± 0.1 | 2.2 ± 0.5 | 101 |
| 88 | 5/5 | 17.9 ± 0.5 | 20.0 ± 0.3 | 2.1 ± 0.6 | 102 |
| 177 | 5/5 | 17.6 ± 0.8 | 19.8 ± 0.2 | 2.2 ± 0.7 | 101 |
| 375 | 5/5 | 17.8 ± 0.8 | 21.0 ± 0.7 | 3.2 ± 0.9 | 107 |
| 750 | 4/5[d] | 18.2 ± 0.9 | 21.8 ± 0.7** | 3.7 ± 0.4 | 111 |

** Significantly different (P≤0.01) from the control group by Williams' or Dunnett's test
[a] Number of animals surviving at 16 days/number of animals initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies. No standard error was calculated for groups with high mortality.
[c] Day of death: all deaths occurred on day 2
[d] Day of death: 3

## 13-WEEK STUDY

Eight male mice receiving 750 mg/kg died during the first four days of the study (Table 17). There were no other deaths. Final mean body weights of dosed mice were similar to those of the controls. Final mean body weight gains of male mice that received 177 mg/kg were 85% of control values. Final mean body weight gains of females in the 177, 375, and 750 mg/kg groups were 88%, 75% and 88% of control values, respectively. Final mean body weight gains of other dosed groups were similar to those of the controls. Absolute and relative liver weights of males receiving 375 or 750 mg/kg and females receiving 750 mg/kg were higher than those of the controls (Table F2). Male mice that received 750 mg/kg, especially those that died, were observed to be lethargic and weak. The post-exposure "separation" behavior previously described for rats in the 13-week

study occurred sporadically in 750 mg/kg males and 375 or 750 mg/kg females. No treatment-related gross observations were noted at necropsy.

Necrosis of the pulmonary bronchial and bronchiolar epithelium (Plate 16) and centrilobular hepatocellular necrosis (Plate 17) were observed in many male mice receiving 750 mg/kg that died at the beginning of the study. Pleomorphism of the bronchial and bronchiolar epithelium also occurred with dose-related increased incidences in males and females, and was considered to be directly related to chemical administration (Table 18). The decreased incidence noted in males that received 750 mg/kg was probably related to the high mortality. Bronchiolar epithelial pleomorphism was characterized by a loss of nuclear and cellular polarity, cytomegaly with karyomegaly, and atypia and syncytia formation (Plate 18). An alveolar/bronchiolar adenoma was noted in a 375 mg/kg female. Hepatocellular necrosis occurred with increased incidences in the liver of dosed female mice, and was also observed in one male receiving 750 mg/kg that survived to the end of the study. This lesion consisted of coagulative necrosis of scattered individual hepatocytes or small clusters of hepatocytes, with or without accumulation of a few mononuclear cells, neutrophils, or both.

*Dose Selection Rationale:* Based on lung and liver lesions observed during the 13-week studies, dose levels selected for the long-term study were 88 and 177 mg/kg.

TABLE 17
**Survival and Mean Body Weights of Mice in the 13-Week Dermal Study of 2,3-Dibromo-1-propanol**

| Concentration (mg/kg) | Survival[a] | Mean Body Weight[b] (g) | | | Final Weight Relative to Controls (%) |
|---|---|---|---|---|---|
| | | Initial | Final | Change | |
| **Male** | | | | | |
| 0 | 10/10 | 22.3 ± 0.5 | 27.6 ± 0.6 | 5.3 ± 0.5 | |
| 44 | 10/10 | 22.2 ± 0.4 | 28.1 ± 0.4 | 5.9 ± 0.2 | 102 |
| 88 | 10/10 | 22.4 ± 0.4 | 27.6 ± 0.7 | 5.3 ± 0.4 | 100 |
| 177 | 10/10 | 22.5 ± 0.5 | 27.0 ± 0.6 | 4.5 ± 0.6 | 98 |
| 375 | 10/10 | 22.1 ± 0.4 | 27.9 ± 0.7 | 5.8 ± 0.6 | 101 |
| 750 | 2/10[c] | 22.4 ± 0.5 | 27.9 ± 0.9 | 6.4 ± 0.7 | 101 |
| **Female** | | | | | |
| 0 | 10/10 | 18.9 ± 0.4 | 24.5 ± 0.5 | 5.6 ± 0.4 | |
| 44 | 10/10 | 19.1 ± 0.5 | 24.5 ± 0.7 | 5.4 ± 0.3 | 100 |
| 88 | 10/10 | 19.0 ± 0.5 | 25.0 ± 0.8 | 6.0 ± 0.4 | 102 |
| 177 | 10/10 | 18.7 ± 0.4 | 23.6 ± 0.5 | 4.9 ± 0.4 | 96 |
| 375 | 10/10 | 18.9 ± 0.5 | 23.1 ± 0.8 | 4.2 ± 0.4 | 94 |
| 750 | 10/10 | 19.1 ± 0.4 | 24.1 ± 0.5 | 4.9 ± 0.3 | 98 |

[a] Number of animals surviving at 13 weeks/number of animals initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies.
[c] Week of death: all deaths occurred during week 1

TABLE 18
**Incidences of Selected Lesions in Mice in the 13-Week Dermal Study of 2,3-Dibromo-1-propanol**

| | Vehicle Control | 44 mg/kg | 88 mg/kg | 177 mg/kg | 375 mg/kg | 750 mg/kg |
|---|---|---|---|---|---|---|
| **Male** | | | | | | |
| Lung[a] | 9 | 10 | 10 | 10 | 10 | 9 |
| Bronchiole pleomorphism[b] | 0 (0.0)[c] | 2 (0.2) | 6** (0.6) | 10** (1.0) | 8** (1.0) | 2 (0.4) |
| Necrosis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 5* (2.0) |
| Liver | 9 | 0 | 0 | 0 | 0 | 10 |
| Hepatocellular necrosis | 0 (0.0) | – | – | – | – | 1 (0.1) |
| Centrilobular necrosis | 0 (0.0) | – | – | – | – | 8** (2.4) |
| **Female** | | | | | | |
| Lung | 10 | 10 | 10 | 10 | 10 | 10 |
| Bronchiole pleomorphism[b] | 0 (0.0) | 1 (0.1) | 1 (0.2) | 2 (0.2) | 5* (0.6) | 10** (1.7) |
| Alveolar/bronchiolar adenoma | 0 | 0 | 0 | 0 | 1 | 0 |
| Liver | 10 | 10 | 10 | 10 | 10 | 10 |
| Hepatocellular necrosis | 0 (0.0) | 2 (0.2) | 1 (0.2) | 7** (1.0) | 5* (0.6) | 5* (0.8) |

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion; the diagnostic term used by the study pathologist for bronchiole pleomorphism was "metaplasia, NOS"
[c] Group average severity of lesion, where 0=no lesion, 1=minimal, 2=mild, 3=moderate, 4=marked

## LONG-TERM STUDY

### *Survival*

At 6 months, sera from sentinel mice housed in the same room as the study animals were found to be positive for antibodies to lymphocytic choriomeningitis virus by complement fixation and immunofluorescent antibody tests. Because of the potential for workers at the laboratory to contract the virus, the study was terminated early (weeks 36 to 39 for male mice and weeks 39 to 42 for female mice). All male mice in each of the groups survived until week 36, while all but two low-dose female mice survived until week 39 (Table 19). Serum samples taken from mice in the study at necropsy or moribund sacrifice were also tested for antibodies to lymphocytic choriomeningitis using complement fixation. Although none of the samples from female mice were clearly positive, samples from 9 of 49 control, 7 of 50 low-dose, and 24 of 50 high-dose males were positive. Despite the serological evidence of infection with lymphocytic choriomeningitis virus, no clinical signs of illness or histological lesions were observed.

### *Body Weights and Clinical Findings*

Mean body weights of control and dosed mice were similar throughout the study (Tables 20 and 21 and Figure 4). No treatment-related clinical findings were observed.

TABLE 19
**Survival in Mice in the Long-Term Dermal Study of 2,3-Dibromo-1-propanol**

| | Vehicle Control | 88 mg/kg | 177 mg/kg |
|---|---|---|---|
| **Male** | | | |
| Animals initially in study | 50 | 50 | 50 |
| Animals surviving until study termination | 50 | 50[a] | 50 |
| Percent probability of survival at end of study[b] | 100 | 100 | 100 |
| Mean survival (weeks)[c] | 38 | 38 | 38 |
| **Female** | | | |
| Animals initially in study | 50 | 50 | 50 |
| Natural deaths or moribund kills | 0 | 2 | 0 |
| Animals surviving until study termination | 50 | 48 | 50 |
| Percent probability of survival at end of study[b] | 100 | 96 | 100 |
| Mean survival (weeks)[c] | 41 | 40 | 41 |
| Survival analysis[d] | P=1.000 | P=0.475 | P=1.000 |

[a] Includes one animal that was killed moribund during the terminal sacrifice period
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns.

TABLE 20
**Mean Body Weights and Survival of Male Mice in the Long-Term Dermal Study of 2,3-Dibromo-1-propanol**

| Week on Study | Vehicle Control | | 88 mg/kg | | | 177 mg/kg | | |
|---|---|---|---|---|---|---|---|---|
| | Av. Wt. (g) | Number of Survivors | Av. Wt. (g) | Wt. (% of controls) | Number of Survivors | Av. Wt. (g) | Wt. (% of controls | Number of Survivors |
| 0 | 23.6 | 50 | 24.3 | 103 | 50 | 24.7 | 104 | 50 |
| 1 | 25.8 | 50 | 25.3 | 98 | 50 | 26.8 | 104 | 50 |
| 2 | 26.9 | 50 | 26.9 | 100 | 50 | 27.4 | 102 | 50 |
| 3 | 27.9 | 50 | 27.7 | 99 | 50 | 28.7 | 103 | 50 |
| 4 | 29.0 | 50 | 28.9 | 100 | 50 | 29.7 | 102 | 50 |
| 5 | 30.3 | 50 | 30.0 | 99 | 50 | 30.8 | 102 | 50 |
| 6 | 30.3 | 50 | 30.5 | 101 | 50 | 31.7 | 105 | 50 |
| 7 | 31.5 | 50 | 30.9 | 98 | 50 | 31.9 | 101 | 50 |
| 8 | 32.3 | 50 | 32.0 | 99 | 50 | 32.8 | 101 | 50 |
| 9 | 32.8 | 50 | 32.6 | 99 | 50 | 33.6 | 102 | 50 |
| 10 | 33.4 | 50 | 32.9 | 98 | 50 | 34.1 | 102 | 50 |
| 11 | 33.5 | 50 | 33.6 | 100 | 50 | 35.0 | 104 | 50 |
| 12 | 33.7 | 50 | 33.6 | 100 | 50 | 35.5 | 105 | 50 |
| 16 | 36.5 | 50 | 34.7 | 95 | 50 | 37.2 | 102 | 50 |
| 20 | 39.1 | 50 | 38.2 | 98 | 50 | 39.3 | 101 | 50 |
| 24 | 40.7 | 50 | 39.9 | 98 | 50 | 40.5 | 100 | 50 |
| 28 | 43.0 | 50 | 41.7 | 97 | 50 | 41.2 | 96 | 50 |
| 32 | 43.4 | 50 | 42.1 | 97 | 50 | 42.6 | 98 | 50 |
| **Mean for weeks** | | | | | | | | |
| 1-13 | 30.6 | | 30.4 | 99 | | 31.5 | 103 | |
| 14-32 | 40.5 | | 39.3 | 97 | | 40.2 | 99 | |

TABLE 21
**Mean Body Weights and Survival of Female Mice in the Long-Term Dermal Study of 2,3-Dibromo-1-propanol**

| Week on Study | Vehicle Control | | 88 mg/kg | | | 177 mg/kg | | |
|---|---|---|---|---|---|---|---|---|
| | Av. Wt. (g) | Number of Survivors | Av. Wt. (g) | Wt. (% of controls) | Number of Survivors | Av. Wt. (g) | Wt. (% of controls | Number of Survivors |
| 0 | 17.8 | 50 | 18.2 | 102 | 50 | 18.2 | 102 | 50 |
| 1 | 19.1 | 50 | 19.3 | 101 | 50 | 19.9 | 104 | 50 |
| 2 | 20.4 | 50 | 20.5 | 101 | 50 | 20.2 | 99 | 50 |
| 3 | 21.2 | 50 | 20.9 | 99 | 49 | 21.6 | 102 | 50 |
| 4 | 21.8 | 50 | 21.8 | 100 | 49 | 22.0 | 101 | 50 |
| 5 | 22.3 | 50 | 22.8 | 102 | 49 | 22.6 | 101 | 50 |
| 6 | 23.0 | 50 | 22.9 | 100 | 49 | 23.3 | 101 | 50 |
| 7 | 23.5 | 50 | 23.3 | 99 | 49 | 23.2 | 99 | 50 |
| 8 | 24.0 | 50 | 23.6 | 98 | 49 | 23.9 | 100 | 50 |
| 9 | 24.2 | 50 | 24.2 | 100 | 49 | 25.1 | 104 | 50 |
| 10 | 24.5 | 50 | 24.2 | 99 | 49 | 24.6 | 100 | 50 |
| 11 | 24.8 | 50 | 24.6 | 99 | 49 | 25.1 | 101 | 50 |
| 12 | 25.3 | 50 | 25.3 | 100 | 49 | 25.0 | 99 | 50 |
| 16 | 26.3 | 50 | 25.5 | 97 | 49 | 26.1 | 99 | 50 |
| 20 | 28.2 | 50 | 27.5 | 97 | 48 | 27.9 | 99 | 50 |
| 24 | 29.1 | 50 | 28.3 | 97 | 48 | 29.0 | 99 | 50 |
| 28 | 30.8 | 50 | 29.8 | 97 | 48 | 30.5 | 99 | 50 |
| 32 | 32.3 | 50 | 30.3 | 94 | 48 | 31.6 | 98 | 50 |
| 36 | 34.0 | 50 | 33.0 | 97 | 48 | 33.5 | 99 | 50 |
| **Mean for weeks** | | | | | | | | |
| 1-13 | 22.8 | | 22.8 | 100 | | 23.0 | 101 | |
| 14-36 | 30.1 | | 29.1 | 97 | | 29.8 | 99 | |

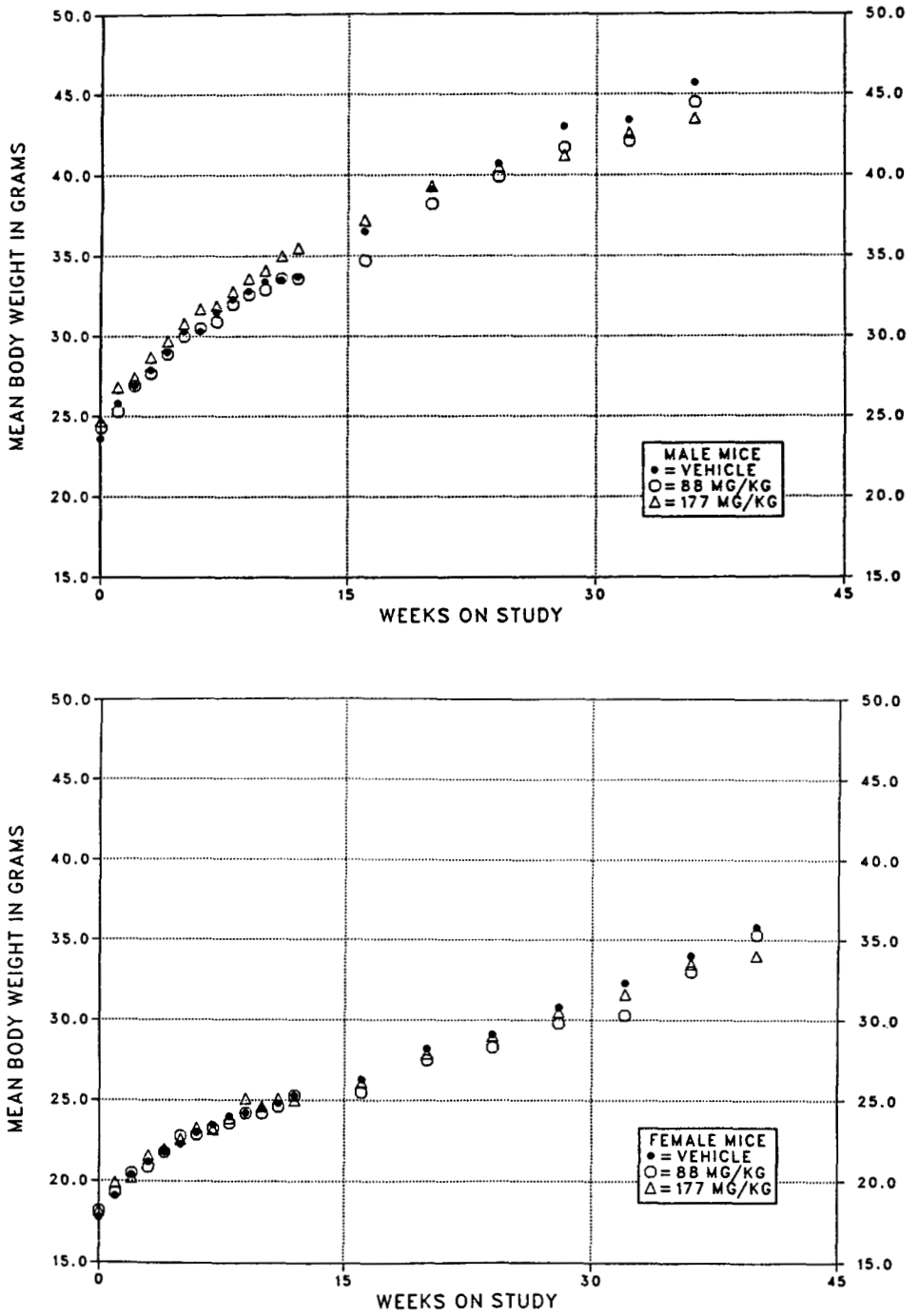



**FIGURE 4**
**Growth Curves for Mice Administered 2,3-Dibromo-1-propanol by Dermal Application for 39 or 42 Weeks**

### *Pathology and Statistical Evaluation*

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the skin (site of application), forestomach, lung, and liver. Summaries of the incidences of neoplasms and nonneoplastic lesions and individual animal tumor diagnoses are presented in Appendix C for male mice and Appendix D for female mice.

*Skin:* Epithelial neoplasms were observed in the skin at or near the site of application in 8% of the low-dose male and female mice, 36% of the high-dose males, and 18% of the high-dose females (Table 22). No neoplasms of the skin occurred in the controls. Although the incidences of some individual histologic types in the low- and high-dose groups were not significantly greater than those in the controls, they were considered chemical related because they were all epithelial in origin, exhibited histologic similarities, and were supported by increased incidences of hyperplasia (Table 22).

Epithelial hyperplasia was characterized by focal thickening and folding of the stratified squamous epithelium due to increased cell layers, whereas sebaceous hyperplasia consisted of enlargement and increased cellularity of the sebaceous glands. The squamous cell papillomas and carcinomas and sebaceous gland adenomas (Plate 19) were morphologically similar to those observed in dosed rats. Some of the neoplasms were complex, with exophytic papillary structures lined by stratified squamous epithelium as well as small lobules of sebaceous cells extending into the dermis. The diagnosis applied to these neoplasms was based on the predominant histological component.

*Forestomach:* Dysplasia of the forestomach epithelium occurred with dose-related increases in male and female mice, and the incidence in each of the dose groups was significantly greater than that in the controls (Table 23). Squamous cell papillomas or carcinomas were seen in 28% of the low-dose males, 43% of the high-dose males, 37% of the low-dose females, and 38% of the high-dose females; none were seen in the controls (Table 23). The incidence of squamous cell neoplasms in each of the dose groups was significantly greater than that in the controls. Although the majority of these neoplasms were benign (papillomas), a larger proportion of the neoplasms in females were malignant than in males.

Epithelial dysplasia denoted thickening of the epithelium, due primarily to increased numbers of basal cells, with slight cellular atypia, loss of cellular orientation, and formation of blunt rete peglike downgrowths. The squamous cell neoplasms (Plate 20) were morphologically similar to those in rats.

*Lung:* Pleomorphism of the bronchiolar epithelium occurred in nearly all dosed mice, but not in the controls (Table 24). Further, the incidences of focal hyperplasia of the alveolar epithelium in high-dose males and low- and high-dose females were significantly greater than those in the controls.

Alveolar/bronchiolar neoplasms occurred more frequently in the dosed groups, but the incidences were not significantly greater than those in the controls (Table 24). Nevertheless, the chemical-related increased incidences of hyperplasia suggest that the marginal increase in alveolar/bronchiolar neoplasms is also chemical related.

Pleomorphism occurred primarily in the bronchi and bronchioles and was characterized by variation in cell and nuclear size and shape, karyomegaly, cytoplasmic vacuolation, nuclear hyperchromasia, and in a few mice, formation of papillary fronds. Focal hyperplasia of the alveolar/bronchiolar epithelium, alveolar/bronchiolar adenoma, and alveolar/bronchiolar carcinoma constitute a morphologic continuum. Hyperplasia was characterized by foci of alveolar septa lined by increased numbers of low cuboidal epithelial cells; normal alveolar architecture was maintained. The alveolar/bronchiolar adenomas were generally larger and exhibited distortion and loss of normal alveolar architecture. They consisted of single layers of uniform cuboidal to columnar epithelial cells overlying a delicate vascular stroma and arranged in irregular glandular or papillary structures. The carcinomas usually exhibited heterogeneous growth patterns and cellular atypia and pleomorphism.

TABLE 22
**Incidences of Neoplasms and Nonneoplastic Lesions of the Skin in Mice in the Long-Term Dermal Study of 2,3-Dibromo-1-propanol**

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | Vehicle Control | 88 mg/kg | 177 mg/kg | Vehicle Control | 88 mg/kg | 177 mg/kg |
| Sebaceous Gland Hyperplasia | | | | | | |
| Overall rate[a] | 0/50 (0%) | 1/50 (2%) | 9/50 (18%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) |
| Cochran-Armitage test[b] | P<0.001 | | | –[c] | | |
| Fisher exact test[b] | | P=0.500 | P=0.001 | | – | – |
| Epithelial Hyperplasia | | | | | | |
| Overall rate | 0/50 (0%) | 6/50 (12%) | 3/50 (6%) | 0/50 (0%) | 3/50 (6%) | 2/50 (4%) |
| Cochran-Armitage test | P=0.146 | | | P=0.203 | | |
| Fisher exact test | | P=0.013 | P=0.121 | | P=0.121 | P=0.247 |
| Hyperplasia, NOS | | | | | | |
| Overall rate | 0/50 (0%) | 1/50 (2%) | 9/50 (18%) | 0/50 (0%) | 5/50 (10%) | 3/50 (6%) |
| Cochran-Armitage test | P<0.001 | | | P=0.133 | | |
| Fisher exact test | | P=0.500 | P=0.001 | | P=0.028 | P=0.121 |
| Squamous Cell Papilloma | | | | | | |
| Overall rate | 0/50 (0%) | 3/50 (6%) | 9/50 (18%) | 0/50 (0%) | 1/50 (2%) | 5/50 (10%) |
| Cochran-Armitage test | P<0.001 | | | P=0.011 | | |
| Fisher exact test | | P=0.121 | P=0.001 | | P=0.500 | P=0.028 |
| Squamous Cell Carcinoma | | | | | | |
| Overall rate | 0/50 (0%) | 0/50 (0%) | 2/50 (4%) | 0/50 (0%) | 0/50 (0%) | 1/50 (2%) |
| Cochran-Armitage test | P=0.110 | | | P=0.333 | | |
| Fisher exact test | | – | P=0.247 | | – | P=0.500 |
| Squamous Cell Papilloma or Squamous Cell Carcinoma | | | | | | |
| Overall rate | 0/50 (0%) | 3/50 (6%) | 11/50 (22%) | 0/50 (0%) | 1/50 (2%) | 6/50 (12%) |
| Cochran-Armitage test | P<0.001 | | | P=0.005 | | |
| Fisher exact test | | P=0.121 | P<0.001 | | P=0.500 | P=0.013 |
| Sebaceous Gland Adenoma | | | | | | |
| Overall rate | 0/50 (0%) | 1/50 (2%) | 8/50 (16%) | 0/50 (0%) | 3/50 (6%) | 2/50 (4%) |
| Cochran-Armitage test | P<0.001 | | | P=0.203 | | |
| Fisher exact test | | P=0.500 | P=0.003 | | P=0.121 | P=0.247 |
| Epithelial Neoplasms (all types) | | | | | | |
| Overall rate | 0/50 (0%) | 4/50 (8%) | 18/50 (36%) | 0/50 (0%) | 4/50 (8%) | 9/50 (18%) |
| Cochran-Armitage test | P<0.001 | | | P<0.001 | | |
| Fisher exact test | | P=0.059 | P<0.001 | | P=0.059 | P=0.001 |

[a] Number of lesion-bearing animals/number of animals necropsied
[b] Beneath the control incidence are the P values associated with the trend test. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates.
[c] Not applicable; no lesions in animal group

TABLE 23
**Incidences of Neoplasms and Nonneoplastic Lesions of the Forestomach in Mice in the Long-Term Dermal Study of 2,3-Dibromo-1-propanol**

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | Vehicle Control | 88 mg/kg | 177 mg/kg | Vehicle Control | 88 mg/kg | 177 mg/kg |
| Epithelial Dysplasia | | | | | | |
| Overall rate[a] | 0/50 (0%) | 14/50 (28%) | 33/49 (67%) | 0/50 (0%) | 16/49 (32%) | 41/50 (82%) |
| Cochran-Armitage test[b] | P<0.001 | | | P<0.001 | | |
| Fisher exact test[b] | | P<0.001 | P<0.001 | | P<0.001 | P<0.001 |
| Squamous Cell Papilloma | | | | | | |
| Overall rate | 0/50 (0%) | 12/50 (24%) | 20/49 (41%) | 0/50 (0%) | 12/49 (24%) | 17/50 (34%) |
| Cochran-Armitage test | P<0.001 | | | P<0.001 | | |
| Fisher exact test | | P<0.001 | P<0.001 | | P<0.001 | P<0.001 |
| Squamous Cell Carcinoma | | | | | | |
| Overall rate | 0/50 (0%) | 2/50 (4%) | 1/49 (2%) | 0/50 (0%) | 7/49 (14%) | 6/50 (12%) |
| Cochran-Armitage test | P=0.357 | | | P=0.026 | | |
| Fisher exact test | | P=0.247 | P=0.495 | | P=0.006 | P=0.013 |
| Squamous Cell Papilloma or Squamous Cell Carcinoma | | | | | | |
| Overall rate | 0/50 (0%) | 14/50 (28%) | 21/49 (43%) | 0/50 (0%) | 18/49 (37%) | 19/50 (38%) |
| Cochran-Armitage test | P<0.001 | | | P<0.001 | | |
| Fisher exact test | | P<0.001 | P<0.001 | | P<0.001 | P<0.001 |

[a] Number of lesion-bearing animals/number of animals with tissue examined microscopically
[b] Beneath the control incidence are the P values associated with the trend test. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates.

TABLE 24
**Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Mice in the Long-Term Dermal Study of 2,3-Dibromo-1-propanol**

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | Vehicle Control | 88 mg/kg | 177 mg/kg | Vehicle Control | 88 mg/kg | 177 mg/kg |
| Focal Hyperplasia | | | | | | |
| Overall rate[a] | 0/50 (0%) | 1/50 (2%) | 6/50 (12%) | 0/50 (0%) | 6/50 (12%) | 5/50 (10%) |
| Cochran-Armitage test[b] | P=0.004 | | | P=0.042 | | |
| Fisher exact test[b] | | P=0.500 | P=0.013 | | P=0.013 | P=0.028 |
| Pleomorphism (Lung/bronchiole) | | | | | | |
| Overall rate | 0/50 (0%) | 50/50 (100%) | 50/50 (100%) | 0/50 (0%) | 46/50 (92%) | 50/50 (100%) |
| Cochran-Armitage test | P<0.001 | | | P<0.001 | | |
| Fisher exact test | | P<0.001 | P<0.001 | | P<0.001 | P<0.001 |
| Alveolar/bronchiolar Adenoma | | | | | | |
| Overall rate | 1/50 (2%) | 1/50 (2%) | 6/50 (12%) | 0/50 (0%) | 3/50 (6%) | 4/50 (8%) |
| Cochran-Armitage test | P=0.022 | | | P=0.049 | | |
| Fisher exact test | | P=0.753 | P=0.056 | | P=0.121 | P=0.059 |
| Alveolar/bronchiolar Carcinoma | | | | | | |
| Overall rate | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) | 1/50 (2%) | 0/50 (0%) | 0/50 (0%) |
| Cochran-Armitage test | –[c] | | | P=0.333N | | |
| Fisher exact test | | – | – | | P=0.500N | P=0.500N |
| Alveolar/bronchiolar Adenoma or Carcinoma | | | | | | |
| Overall rate | 1/50 (2%) | 1/50 (2%) | 6/50 (12%) | 1/50 (2%) | 3/50 (6%) | 4/50 (8%) |
| Cochran-Armitage test | P=0.022 | | | P=0.133 | | |
| Fisher exact test | | P=0.753 | P=0.056 | | P=0.309 | P=0.181 |

[a] Number of lesion-bearing animals/number of animals with tissue examined microscopically
[b] Beneath the control incidence are the P values associated with the trend test. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[c] Not applicable; no lesions in animal group

*Liver:* The incidence of eosinophilic cytoplasmic change in high-dose male mice was significantly greater than that in the controls (Table 25). Moreover, basophilic cytoplasmic change occurred in one low-dose and two high-dose males, but not in the controls (Table C4). The incidence of hepatocellular adenoma or carcinoma (combined) in high-dose males was also significantly greater than that in the controls (Table 25). Chemical-related increases in the incidences of foci of cytoplasmic change or hepatocellular neoplasms did not occur in female mice (Tables D1 and D4).

TABLE 25
**Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Male Mice in the Long-Term Dermal Study of 2,3-Dibromo-1-propanol**

| | Vehicle Control | 88 mg/kg | 177 mg/kg |
|---|---|---|---|
| Eosinophilic Cytoplasmic Change | | | |
| Overall rate[a] | 0/50 (0%) | 0/50 (0%) | 11/50 (22%) |
| Cochran-Armitage test[b] | P<0.001 | | |
| Fisher exact test[b] | | –[c] | P<0.001 |
| Hepatocellular Adenoma | | | |
| Overall rate | 1/50 (2%) | 2/50 (4%) | 9/50 (18%) |
| Cochran-Armitage test[b] | P=0.003 | | |
| Fisher exact test[b] | | P=0.500 | P=0.008 |
| Hepatocellular Carcinoma | | | |
| Overall rate | 0/50 (0%) | 0/50 (0%) | 3/50 (6%) |
| Cochran-Armitage test | P=0.036 | | |
| Fisher exact test | | – | P=0.121 |
| Hepatocellular Adenoma or Carcinoma | | | |
| Overall rate | 1/50 (2%) | 2/50 (4%) | 11/50 (22%) |
| Cochran-Armitage test | P<0.001 | | |
| Fisher exact test | | P=0.500 | P=0.002 |

[a] Number of lesion-bearing animals/number of animals with tissue examined microscopically
[b] Beneath the control incidence are the P values associated with the trend test. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates.
[c] Not applicable; no lesions in animal group

## GENETIC TOXICOLOGY

2,3-Dibromo-1-propanol was mutagenic in all but one of the short-term tests conducted by the NTP. It induced gene mutations in three strains of *Salmonella typhimurium* (TA98, TA100, and TA1535) when tested in a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9; no clearly positive response was observed in strain TA1537 (Table E1; Haworth *et al.*, 1983). 2,3-Dibromo-1-propanol produced a positive response in the absence of S9 activation in the mouse lymphoma assay for induction of trifluorothymidine resistance in L5178Y cells; it was not tested with S9 (Table E2). Increases in sister chromatid exchanges and chromosomal aberrations were induced in cultured Chinese hamster ovary cells both with and without Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Tables E3 and E4). 2,3-Dibromo-1-propanol induced significant increases in sex-linked recessive lethal mutations and reciprocal translocations in male germ cells of *Drosophila melanogaster* (Tables E5 and E6; Yoon *et al.*, 1985). Intraperitoneal injection (25 to 100 mg/kg) of 2,3-dibromo-1-propanol, administered three times at 24-hour intervals, did not increase the frequency of micronucleated polychromatic erythrocytes in the bone marrow of male $B6C3F_1$ mice sampled 24 hours after the third injection. Also, the percentages of polychromatic erythrocytes among the total erythrocyte population were not affected by 2,3-dibromo-1-propanol administration, indicating no toxicity in the bone marrow.

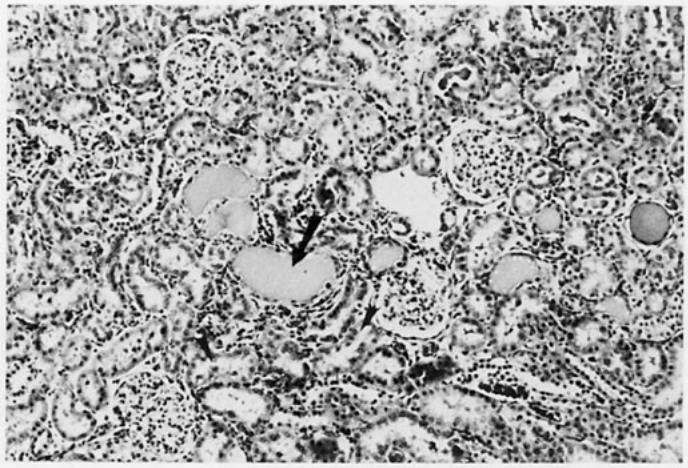


**PLATE 1**
Nephropathy of the kidney in a male F344/N rat receiving 750 mg/kg 2,3-dibromo-1-propanol in the 13-week dermal study. Note the hyaline casts (arrow), tubules lined by small basophilic epithelial cells (arrow head), and interstitial cellular infiltrate. H&E, 120X

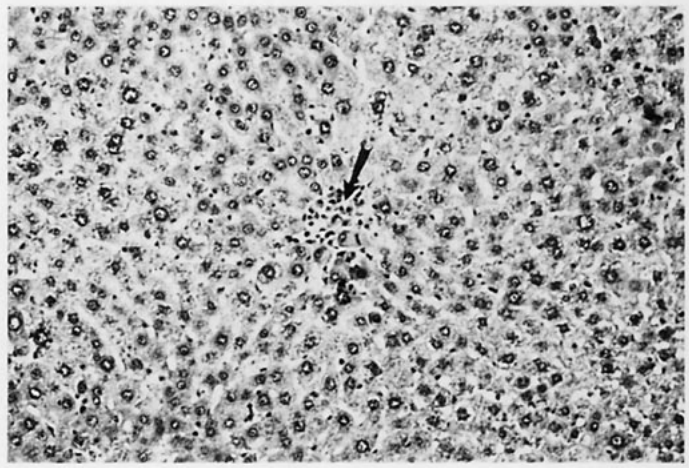


**PLATE 2**
Liver of a female F344/N rat receiving 750 mg/kg 2,3-dibromo-1-propanol in the 13-week dermal study. Note the focal accumulation of inflammatory cells surrounding individual necrotic hepatocytes (arrow). H&E, 25X

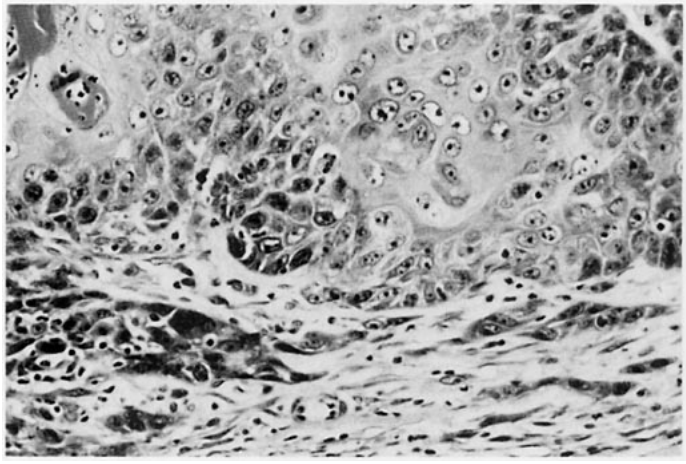


**PLATE 3**
Squamous cell carcinoma of the skin in a male F344/N rat receiving 375 mg/kg 2,3-dibromo-1-propanol in the long-term dermal study. Note the cellular atypia, disordered pattern of differentiation, and invasion by anaplastic cells. H&E, 80X

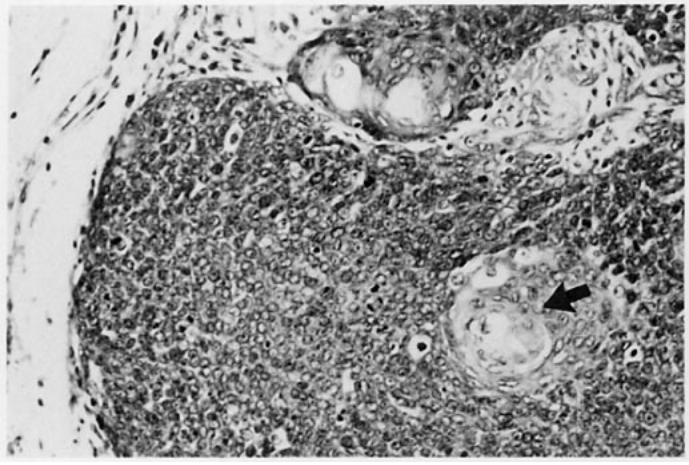


**PLATE 4**
Basal cell tumor of the skin in a male F344/N rat receiving 375 mg/kg 2,3-dibromo-1-propanol in the long-term dermal study. The neoplastic cells typically have scant, basophilic cytoplasm although small foci of squamous differentiation may be present (arrow). H&E, 80X

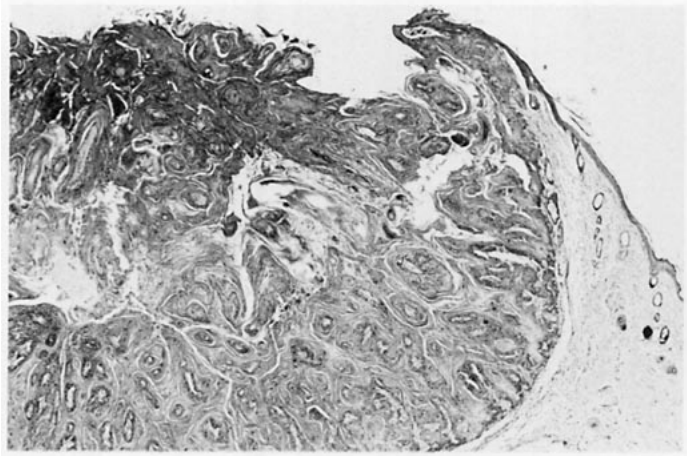


**PLATE 5**
Keratoacanthoma of the skin in a male F344/N rat receiving 375 mg/kg 2,3-dibromo-1-propanol in the long-term dermal study. Note how the tumor extends below the surface of the skin to form a crateriform mass within the dermis and subcutis. H&E, 10X

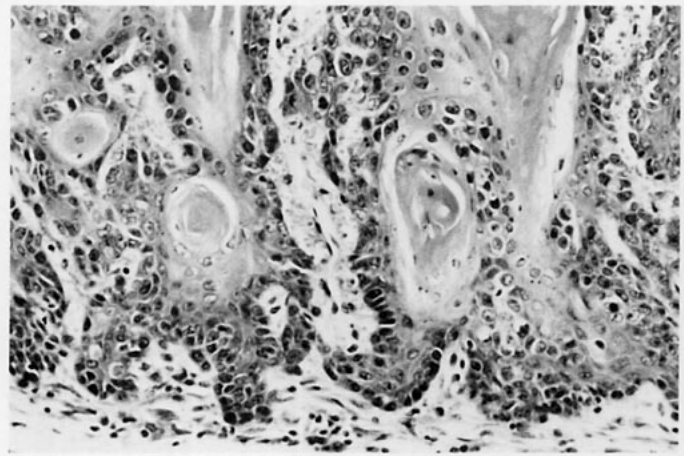


**PLATE 6**
High magnification of the keratoacanthoma in Plate 5 showing the keratinized, stratified squamous epithelium comprising the wall of the neoplasm. H&E, 80X

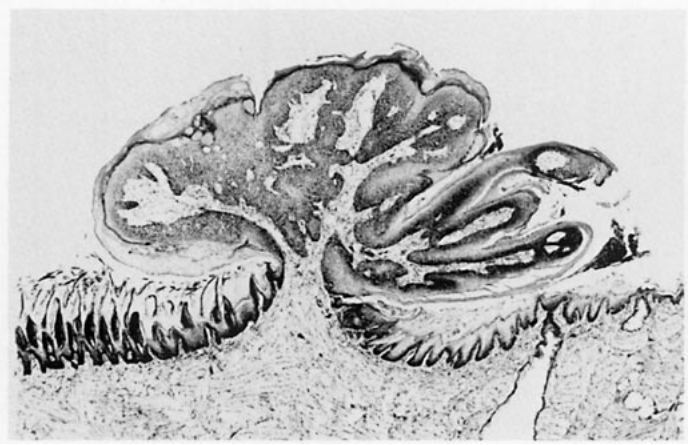


**PLATE 7**
Squamous cell papilloma of the tongue in a male F344/N rat receiving 188 mg/kg 2,3-dibromo-1-propanol in the long-term dermal study. H&E, 30X

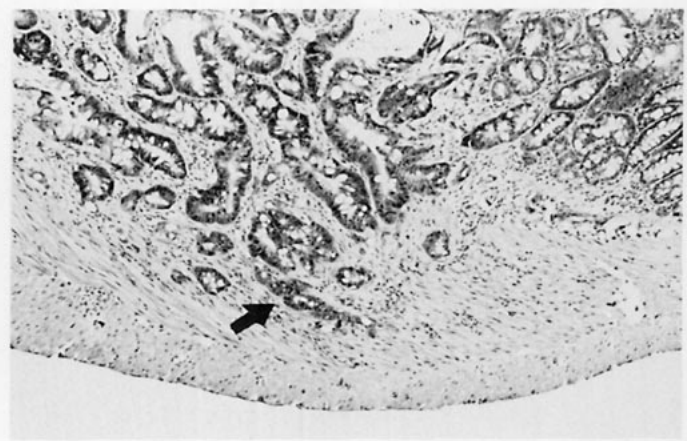


**PLATE 8**
Adenocarcinoma of the jejunum in a male F344/N rat receiving 375 mg/kg 2,3-dibromo-1-propanol in the long-term dermal study. Note the invasion of the submucosa and tunica muscularis (arrow). H&E, 80X

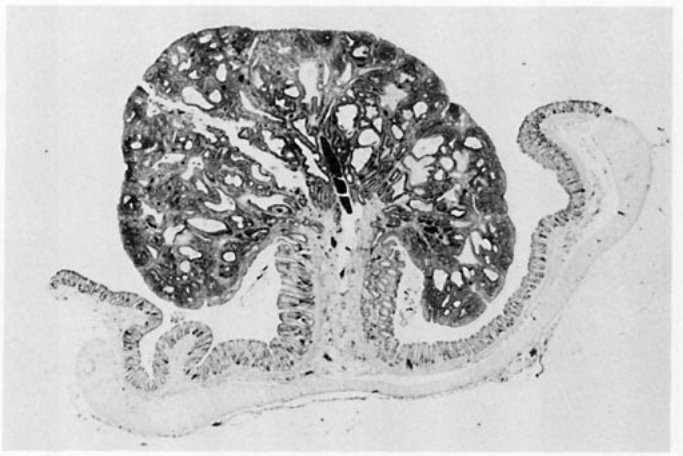


**PLATE 9**
Adenomatous polyp of the colon in a male F344/N rat receiving 188 mg/kg 2,3-dibromo-1-propanol in the long-term dermal study. H&E, 12X

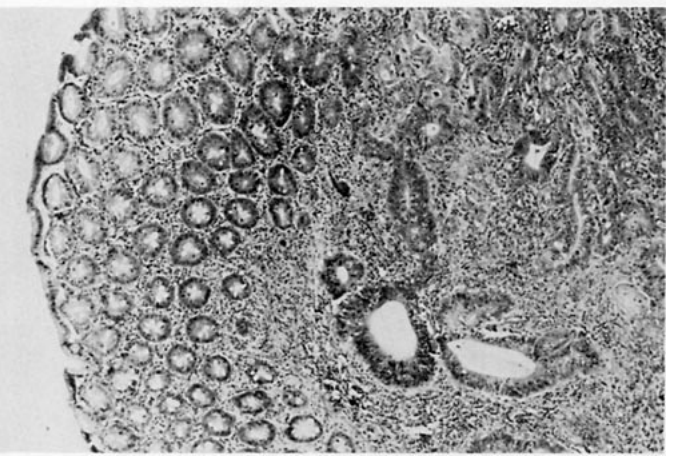


**PLATE 10**
Adenocarcinoma of the cecum in a male F344/N rat receiving 375 mg/kg 2,3-dibromo-1-propanol in the long-term dermal study. Irregular glands and tubules lined by poorly differentiated epithelium invade the submucosa. H&E, 25X

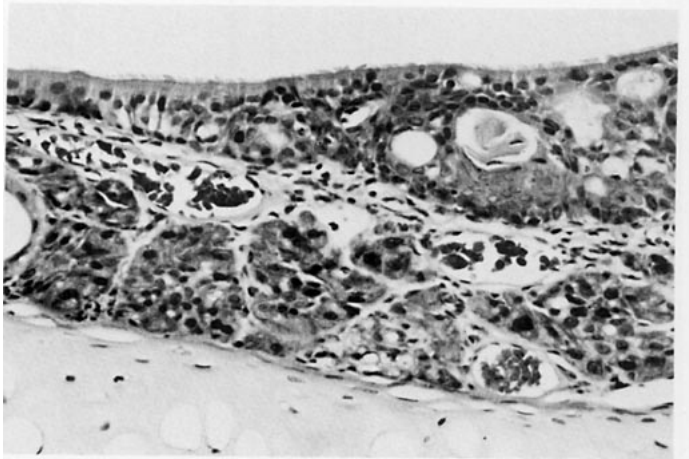


**PLATE 11**
Dysplasia of the respiratory epithelium in the dorsal aspect of the nasal septum in a male F344/N rat receiving 375 mg/kg 2,3-dibromo-1-propanol in the long-term dermal study. Note the proliferation of basal cells and squamous metaplasia. H&E, 80X

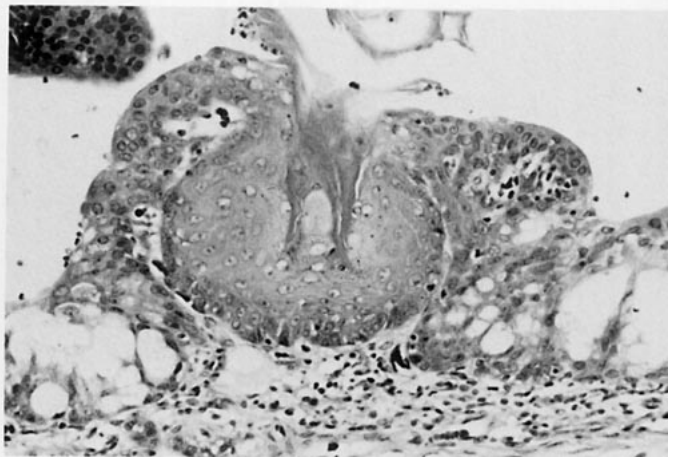


**PLATE 12**
Prominent focus of squamous metaplasia of the respiratory epithelium on the nasal septum in a male F344/N rat receiving 375 mg/kg 2,3-dibromo-1-propanol in the long-term dermal study. H&E, 80X

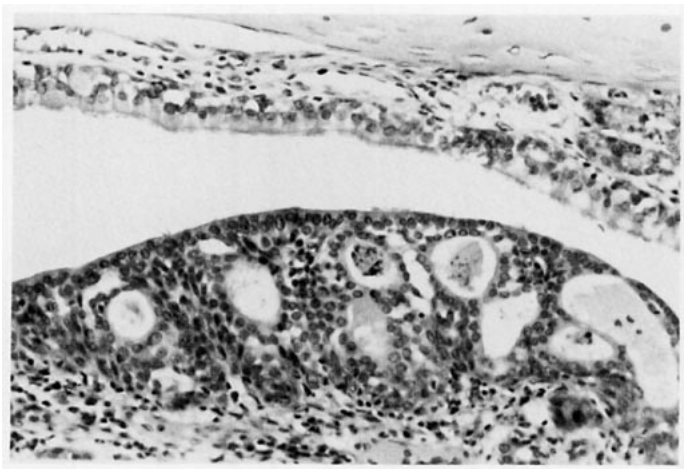


**PLATE 13**
Proliferation of basal cells on the lateral aspect of nasoturbinate near junction of respiratory and olfactory epithelium in a male F344/N rat receiving 375 mg/kg 2,3-dibromo-1-propanol in the long-term dermal study. H&E, 80X

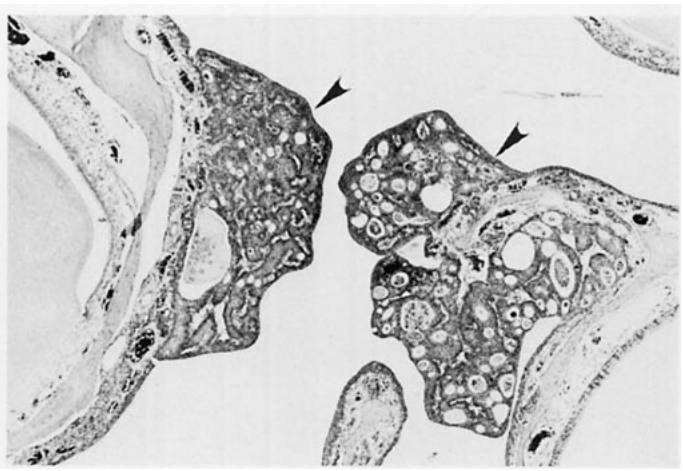


**PLATE 14**
Adenomas (arrowheads) of the nasal cavity in a male F344/N rat receiving 188 mg/kg 2,3-dibromo-1-propanol in the long-term dermal study. H&E, 40X

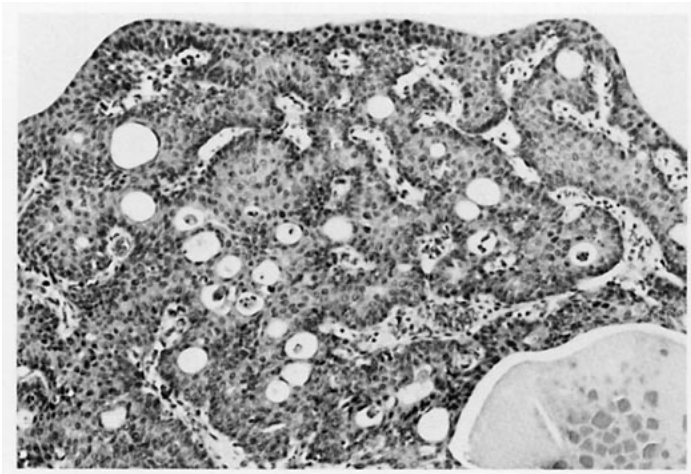


**PLATE 15**
Adenoma of the nasal epithelium in a male F344/N rat receiving 375 mg/kg 2,3-dibromo-1-propanol in the long-term dermal study. H&E, 50X

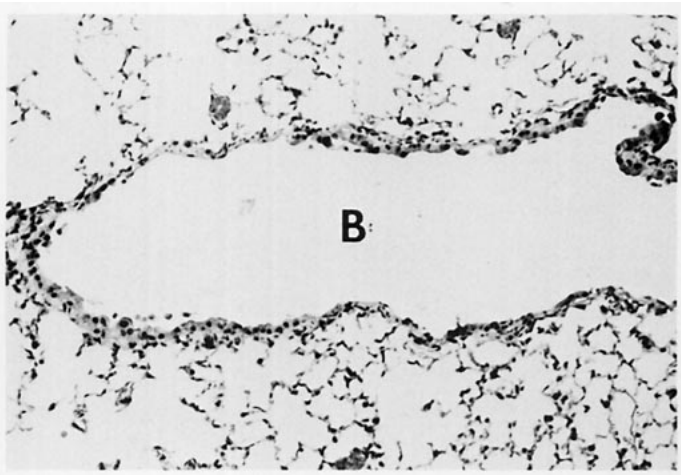



**PLATE 16**
Lung of a male B6C3F$_1$ mouse receiving 750 mg/kg 2,3-dibromo-1-propanol in the 13-week dermal study. The epithelium of the bronchiole (B) is reduced in cellularity and consists of flattened cells of varying size as a result of necrosis. H&E, 25X

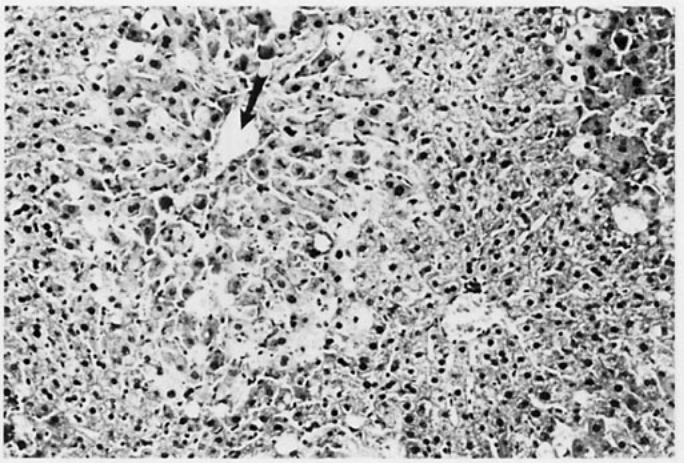


**PLATE 17**
Centrilobular hepatocellular necrosis of the liver in a male B6C3F$_1$ mouse that died after receiving 750 mg/kg 2,3-dibromo-1-propanol during the 13-week dermal study. The necrotic hepatocytes surrounding the central venule (arrow) have hyaline, eosinophilic cytoplasm, and pyknotic nuclei. H&E, 25X

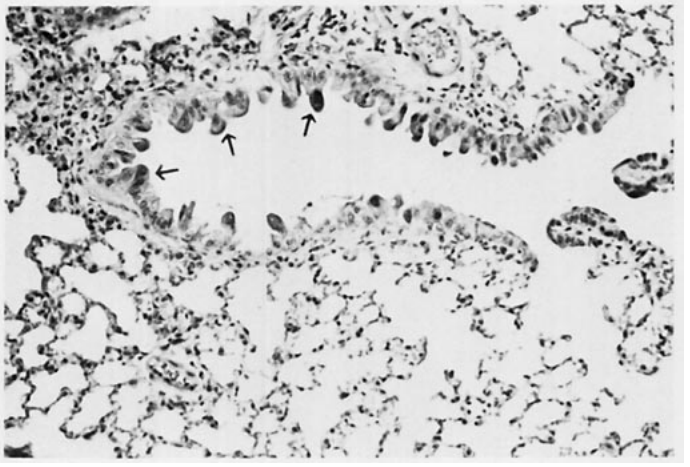


**PLATE 18**
Lung of a female B6C3F$_1$ mouse receiving 750 mg/kg 2,3-dibromo-1-propanol in the 13-week dermal study. The bronchiolar epithelium (arrows) consists of enlarged, pleomorphic cells with hyperchromatic, karyomegalic nuclei. H&E, 25X

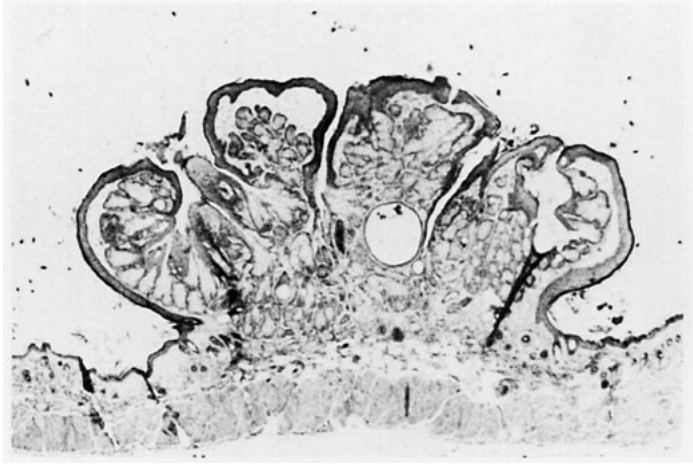


**PLATE 19**
Sebaceous gland adenoma of the skin (site of application) in a male B6C3F$_1$ mouse receiving 177 mg/kg 2,3-dibromo-1-propanol in the long-term dermal study. H&E, 30X

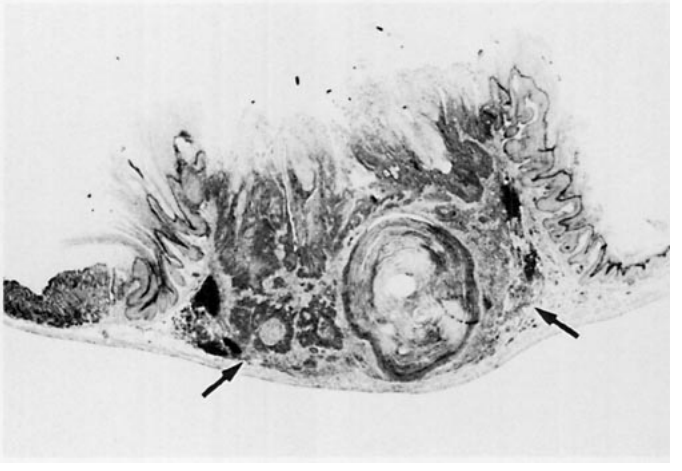


**PLATE 20**
Squamous cell carcinoma of the forestomach in a female B6C3F$_1$ mouse receiving 177 mg/kg 2,3-dibromo-1-propanol in the long-term dermal study. Note the invasion (arrows) into underlying mucosa. H&E, 15X

# DISCUSSION AND CONCLUSIONS

2,3-Dibromo-1-propanol has been used as a flame retardant, as an intermediate in the preparation of other flame retardants including tris(2,3-dibromopropyl) phosphate, and as an intermediate in the preparation of insecticides and pharmaceutical preparations (Fishbein, 1979). 2,3-Dibromo-1-propanol was nominated by the National Cancer Institute (NCI) for toxicology and carcinogenicity testing as part of organohalide class studies and because it is a metabolite of tris(2,3-dibromopropyl) phosphate, previously shown to be a mutagen and a carcinogen in animals (NCI, 1978a). Toxicology and carcinogenicity studies were conducted by applying the chemical to the skin of male and female F344/N rats and B6C3F$_1$ mice. Comparative single-dose gavage and skin-paint studies showed that 2,3-dibromo-1-propanol, at doses ranging from 88 to 1,500 mg/kg body weight in ethanol, was well absorbed from the skin of rats and mice (Appendix J). The absorption efficiency for skin relative to gavage was 68% for rats and 37% for mice. Because the primary route of human exposure to flame retardants is through the skin, the dermal route of administration was chosen for the studies.

Male mice were more sensitive to the acute toxic effects of this chemical than were rats or female mice. Eight of 10 male mice receiving dermal applications of 750 mg/kg died during the 13-week study, but there were no deaths in rats or female mice receiving up to 750 mg/kg 2,3-dibromo-1-propanol for 13 weeks. Male mice dying as a result of treatment with 2,3-dibromo-1-propanol had generalized centrilobular necrosis of the liver. The regional specificity of the necrosis in male mice is consistent with the zonal differences in hepatic enzymes and the postulated metabolic pathway of 2,3-dibromo-1-propanol. The centrilobular region of the liver lobule (zone 3 of the liver acinus) is believed to be the region most susceptible to injury by certain chemicals because of its higher content of cytochrome P-450, epoxide hydrolase, and glutathione transferase (Gumucio and Miller, 1982). The centrilobular hepatocellular necrosis produced by bromobenzene is believed to be determined, in part, by the relative rates of conversion to a reactive epoxide intermediate by microsomal enzymes and subsequent reaction with glutathione transferase and epoxide hydrolase (Mitchell *et al.*, 1976). Similar to bromobenzene, 2,3-dibromo-1-propanol is believed to be metabolized by microsomal cytochrome P-450 to reactive intermediates (Jones and Fakhouri, 1979; Marsden and Casida, 1982). Whether the postulated metabolites of 2,3-dibromo-1-propanol, 2-bromoacrolein and 3-bromo-1,2-propane epoxide, are the direct cause of cellular injury leading to hepatocellular necrosis is unknown.

In contrast to male mice, female mice and female rats receiving dermal applications of 750 mg/kg 2,3-dibromo-1-propanol exhibited slight individual cell necrosis in the liver. The lesion consisted of a very small number of necrotic hepatocytes, sometimes associated with small numbers of inflammatory cells, in the liver sections. The differences in the distribution and severity of the liver lesions between male mice and those in female rats and female mice may be determined, in part, by the effective dose of the critical metabolites (possibly 3-bromo-1,2-propane epoxide or 2-bromoacrolein) at the target site(s) within the hepatocyte. Thus, generalized centrilobular hepatocellular necrosis might have occurred in female rats and female mice, and perhaps male rats, at higher dose levels of 2,3-dibromo-1-propanol.

Liver lesions have been observed in humans exposed to 1,2-dichloropropane (Larcan *et al.*, 1977) and in laboratory animals, including rats and mice, exposed to short-chain halogenated hydrocarbons such as carbon tetrachloride, chloroform, trichloroethylene, 1,1,2-trichloroethane (Plaa, 1986), 1,2,3-trichloropropane, and perchloroethylene (Sidorenko *et al.*, 1976). Necrosis has been observed in the lung and liver of rats exposed to 1,3-dichloropropene by inhalation (Torkelson and Oyen, 1977) and in the liver of female F344/N rats and B6C3F$_1$ mice administered 1,2-dichloropropane by gavage (NTP, 1986).

Lung lesions also occured in mice in the 13-week study. Five of the eight male mice receiving 750 mg/kg that died during the 13-week study had necrosis of the bronchial and bronchiolar epithelium, while males and females exhibited cytologic alterations (pleomorphism) in the distal airway epithelium. Because there may have been some volatilization of 2,3-dibromo-1-propanol after dermal application, inhalation exposure in the group-housed mice may have contributed to the lesions in the pulmonary airways. It is unknown why the intrapulmonary airways were more sensitive to 2,3-dibromo-1-propanol than the nasal and tracheal epithelium, but the secondary bronchi and bronchioles contain fewer goblet cells and a higher proportion of Clara cells, which are known to contain microsomal cytochrome P-450. The differences in cell population and in airflow pattern and velocity are thought to contribute to the regional specificity of airway lesions caused by chemicals.

The cytologic alterations in the epithelium of distal airways of male and female mice receiving dermal applications of 2,3-dibromo-1-propanol consisted of changes in cell size and shape (pleomorphism) and nuclear enlargement (karyomegaly). Whether this lesion is also caused by the formation of an epoxide intermediate or 2-bromoacrolein merits further study. Similar cytologic alterations have been observed in male and female mice exposed by inhalation to 1,2-dibromo-3-chloropropane (NTP, 1982a), 1,2-dibromoethane (NTP, 1982b), and 1,2-dichloropropane (NTP, 1986), and by gavage to 1,2,3-trichloropropane in NTP 13-week studies (NTP, 1993).

Although the body weight gain of rats receiving dermal applications of 750 mg/kg was 11% lower than that of the controls for males and 13% lower for females in the 13-week study, only slight histopathologic effects were observed. In male rats there was a slight increase in the severity of nephropathy, primarily in the 750 mg/kg group. Although it is apparent that 2,3-dibromo-1-propanol has some effect on the kidneys, these findings confirm previous studies indicating that 2,3-dibromo-1-propanol is not the primary metabolite responsible for the acute renal tubule necrosis associated with the administration of tris(2,3-dibromopropyl) phosphate to rats (Søderlund *et al.*, 1980). Chemical-induced nephrotoxicity in rats and mice in NTP/NCI studies has been associated with exposure to many short-chain halogenated hydrocarbons, but no consistent sex- or species-related differences in response were found (Kluwe *et al.*, 1984). In general, however, rats seem to be more susceptible to the nephrotoxic effects of these compounds than mice, and male rats appear to be more susceptible than female rats.

The highest dose selected for the planned 2-year dermal study in rats was 375 mg/kg because of the significant reduction in body weight gain and slight histopathologic effects observed in rats receiving 750 mg/kg in the 13-week study. Primarily because of the high mortality and hepatocellular necrosis in male mice receiving dermal applications of 750 mg/kg in the 13-week study, the highest dose selected for the planned 2-year study in mice was 177 mg/kg. The planned 2-year studies were terminated early after serological evidence of infection with lymphocytic choriomeningitis (LCM) virus was found in mice. This virus can infect humans, occasionally producing severe meningitis and death, thus posing a hazard to laboratory workers. Moreover, the early mortality in male rats receiving dermal applications of 350 mg/kg was an indication that the chemical is a potent carcinogen.

The viral infection in mice in the NTP long-term study was asymptomatic and no histologic evidence of disease was observed. The source of the infection is unknown, but could possibly have resulted from exposure to feral mice (Lehmann-Grube, 1982). Although *in utero* or perinatal infection can be a source of persistently infected mice, there was no evidence of infection in the breeding colony from which the study animals were obtained. The LCM virus has been shown to depress humoral and/or cellular immunity and to inhibit neoplasm induction by viruses such as polyoma virus and mammary tumor virus in mice (National Research Council, 1991). Nevertheless, it is unlikely that the LCM infection had any influence on the outcome of these long-term studies as it relates to the carcinogenic potential of this chemical, because a) the infection occurred in only 13% of the mice tested, b) the infection occurred in both dosed and control mice, c) the incidence of neoplasms in the control mice was very low and was within the expected range for historical controls of that age, d) the induced neoplasms in dosed mice occurred with very high incidences and short latency, and e) a

similar strong carcinogenic response occurred in the rats, which were not infected with LCM virus.

In the long-term study, the decreased final mean body weights of rats receiving 2,3-dibromo-1-propanol, particularly the high-dose groups, were largely due to impaired feed consumption resulting from chemical-related neoplasms of the oral mucosa. The significantly reduced survival of dosed rats was the result of aggressive moribund sacrifices necessitated by these neoplasms in dosed rats. In contrast, neither the final mean body weights nor the survival of mice was affected by 2,3-dibromo-1-propanol administration.

2,3-Dibromo-1-propanol caused significant dose-related increases in the incidences of neoplasms at numerous sites in male and female rats and, to a lesser extent, in mice in the long-term dermal studies. The total numbers of male and female rats with benign and malignant neoplasms, as well as the total numbers of these neoplasms, were significantly greater in the low- and high-dose groups than in the controls. Nearly all dosed rats, but only 2% of the control rats, had malignant neoplasms. The organs or tissues with significantly increased incidences of neoplasms included the skin, nose, oral mucosa, esophagus, forestomach, small and large intestine, liver, and Zymbal's gland of male and female rats as well as the mammary gland and clitoral gland of females. Marginally increased incidences of neoplasms also occurred in the kidney of male and female rats and in the tunica vaginalis mesothelium and spleen of male rats. No neoplasms were observed in control rats at any of these sites, with the exception of one control male that had a squamous cell papilloma of the skin. Accordingly, the increased incidence of neoplasms observed at various sites was considered to be clearly related to 2,3-dibromo-1-propanol administration.

The pattern of neoplasm response in the stratified squamous epithelium of the upper gastrointestinal tract of rats suggests that the chemical induction of neoplasms in the oral mucosa, esophagus, and forestomach may be related to oral exposure through grooming behavior rather than from dermal absorption. The incidences of squamous cell neoplasms and the proportion of malignant to benign neoplasms decreased as the distance from the oral cavity increased (Figure 5). Of these three sites, the incidence of squamous cell neoplasms and the proportion of carcinomas was highest in the oral mucosa. The incidence of squamous cell neoplasms in the esophagus was intermediate between those of the oral cavity and forestomach, and few carcinomas were observed. The lowest incidence of neoplasms occurred in the forestomach, and no carcinomas were observed. Exposure by inhalation may also have contributed to the induction of neoplasms of the nasal mucosa.

There were some differences between male and female rats in response to the carcinogenic activity of 2,3-dibromo-1-propanol, including lower incidences of liver neoplasms and higher incidences of adenocarcinomas of the small intestine in dosed males than in dosed females. Although there was a small difference in the duration of treatment between sexes (4 weeks), it seems unlikely that this difference contributed substantively to the differences in neoplasm incidence at these sites. The lower incidences of adenocarcinomas of the small intestine in exposed female rats than in males may be related to the later appearance of this neoplasm in females. The first adenocarcinoma was observed at week 25 for males and at week 48 for females.

Dermal exposure of mice to a concentration of 2,3-dibromo-1-propanol similar to that received by rats induced neoplasms at fewer sites and lower overall incidences. Chemical-induced neoplasms were observed at the site of application (the skin) as well as the forestomach, liver, and lung of males and the forestomach of females. A slight increase in lung neoplasms in female mice may also have been chemical induced. The duration of exposure in mice was about 12 weeks less than in rats; this shorter duration may have contributed to the differences in carcinogenic response between rats and mice. Nevertheless, based on the greater number of neoplasm sites observed in dosed rats compared to dosed mice (11 sites for male rats, 12 for female rats, 4 for male mice, and 2 for female mice), rats appear to be more sensitive to the carcinogenic effect of 2,3-dibromo-1-propanol.

The results of these studies showed that 2,3-dibromo-1-propanol is a multiple-organ carcinogen in rats and mice, as are its parent compound tris(2,3-dibromopropyl) phosphate (NCI, 1978a; Reznick *et al.*,

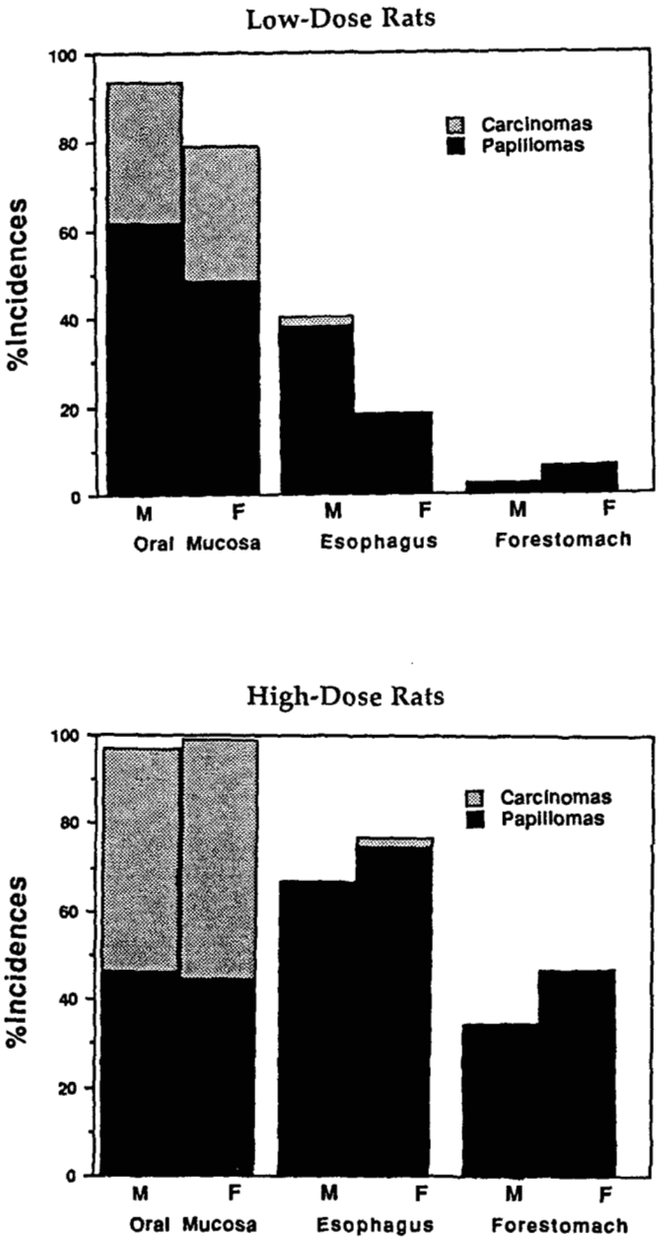



FIGURE 5
**Neoplasms of the Upper Gastrointestinal Tract in Rats Administered 2,3-Dibromo-1-propanol by Dermal Application for 51 or 55 Weeks**

1981) and the structurally related halogenated three-carbon compounds, 1,2-dibromo-3-chloropropane (NCI, 1978b; NTP, 1982a), 1,2-dichloropropane (NTP, 1986), and 1,3-dichloropropene (NTP, 1985). However, the number of sites affected by the dermal application of 2,3-dibromo-1-propanol was greater than the number of sites affected by the dosed feed or gavage administration of tris(2,3-dibromopropyl) phosphate and other halogenated three-carbon compounds (Tables 26 and 27). Although differences in dose level, strains of animals, route of administration, and duration of dose employed in the various studies could have contributed to the variation in response to these chemicals, the results suggest that 2,3-dibromo-1-propanol is the most potent carcinogen of these chemicals.

Among the short-chain hydrocarbons, including the halogenated hydrocarbons, are chemicals that are direct-acting carcinogens, such as epoxides and halo ethers, and others that are considered indirect-acting carcinogens, which require metabolic activation to the ultimate carcinogen in tissues such as the liver, stomach, lung, or kidney (Van Duuren, 1977). Epoxide intermediates are demonstrated metabolites of trichloroethylene (epoxy-1,1,2-trichloroethane), allyl chloride (epichlorohydrin and glycidaldehyde) (Van Duuren, 1977), and 1,2-dibromo-3-chloropropane (1,2-epoxypropane) (Jones and Gibson, 1980). 2,3-Dibromo-1-propanol is a direct-acting mutagen, producing gene mutations in *Salmonella typhimurium* and gene mutation and chromosomal damage in cultured mammalian cells (Appendix E). It also produced sex-linked recessive lethal mutations and reciprocal translocations in germ cells of *Drosophila melanogaster.* Moreover, the metabolism of 2,3-dibromo-1-propanol also appears to involve the formation of reactive intermediates including 2-bromoacrolein, 2,3-dibromopropanal (Marsden and Casida, 1982), and 3-bromo-1,2-propane epoxide (Jones and Fakhouri, 1979). The first two intermediates are direct mutagens in *S. typhimurium* and are potent inducers of DNA single-strand breaks in rat hepatoma cells (Gordon *et al.*, 1985). This mutagenic and chemical profile is consistent with the pattern of carcinogenic activity observed in these studies, that is, the induction of an early onset of neoplasms at multiple sites.

**TABLE 26**
**Comparison of Neoplasm Sites in Rats Exposed to 2,3-Dibromo-1-propanol and Structurally Related Compounds**

| Compound/ Technical Report | Strain | Exposure Route and Duration | Dose | Neoplasm Site | |
|---|---|---|---|---|---|
| | | | | Male | Female |
| Tris(2,3-dibromopropyl) phosphate NTP TR 76 | F344/N | Dosed feed for 2 years | 50 or 100 ppm (2.5 or 5 mg/kg per day) | Kidney | Kidney |
| 1,2-Dibromo-3-chloropropane NTP TR 28 | Osborne-Mendel | Corn oil gavage for 2 years | 15 or 29 mg/kg per day | Forestomach | Forestomach<br>Mammary gland |
| 1,2-Dibromo-3-chloropropane NTP TR 206 | F344/N | Inhalation for 76-103 weeks (6 hours/day, 5 days/week) | 0.6 or 3.0 ppm | Nose<br>Tongue | Nose<br>Tongue<br>Adrenal gland<br>Mammary gland |
| 1,3-Dichloropropene NTP TR 269 | F344/N | Corn oil gavage for 2 years | 25 or 50 mg/kg per day | Forestomach<br>Liver | Forestomach |
| 1,2-Dichloropropane NTP TR 263 | F344/N | Corn oil gavage for 2 years | Males 125 or 250 mg/kg per day; females 62 or 125 mg/kg per day | None | None |
| 2,3-Dibromo-1-propanol NTP TR 400 | F344/N | Dermal for 48-55 weeks | 188 or 375 mg/kg per day | Skin<br>Nose<br>Oral mucosa<br>Esophagus<br>Forestomach<br>Small intestine<br>Large intestine<br>Liver<br>Kidney<br>Tunica vaginalis<br>Zymbal's gland | Skin<br>Nose<br>Oral mucosa<br>Esophagus<br>Forestomach<br>Small intestine<br>Large intestine<br>Liver<br>Kidney<br>Mammary gland<br>Clitoral gland<br>Zymbal's gland |

TABLE 27
**Comparison of Neoplasm Sites in Mice Exposed to 2,3-Dibromo-1-propanol and Structurally Related Compounds**

| Compound/ Technical Report | Strain | Exposure Route and Duration | Dose | Neoplasm Site | |
|---|---|---|---|---|---|
| | | | | Male | Female |
| Tris(2,3-dibromopropyl) phosphate NCI TR 76 | B6C3F$_1$ | Dosed feed for 2 years | 500 or 1,000 ppm (65 or 130 mg/kg per day) | Kidney Forestomach Lung | Kidney Forestomach Lung Liver |
| Tris(2,3-dibromopropyl) phosphate Van Duuren *et al.*, 1978 | ICR/Ha Swiss | Dermal for 67-71 weeks | 10 or 30 mg/kg per day | Skin Forestomach Oral cavity Lung | Skin Forestomach Oral cavity Lung |
| 1,2-Dibromo-3-chloropropane NCI TR 28 | B6C3F$_1$ | Corn oil gavage for 2 years | 110 or 220 mg/kg per day | Forestomach | Forestomach |
| 1,2-Dibromo-3-chloropropane NTP TR 206 | B6C3F$_1$ | Inhalation for 76-103 weeks (6 hours/day, 5 days/week) | 0.6 or 3.0 ppm | Nose Lung | Nose Lung |
| 1,3-Dichloropropene[a] NTP TR 269 | B6C3F$_1$ | Corn oil gavage for 2 years | 50 or 100 mg/kg per day | Inadequate study | Urinary bladder Forestomach Lung |
| 1,2-Dichloropropane NTP TR 263 | B6C3F$_1$ | Corn oil gavage for 2 years | 125 or 250 mg/kg per day | Liver | Liver |
| 2,3-Dibromo-1-propanol NTP TR 400 | B6C3F$_1$ | Dermal for 36-42 weeks | 88 or 177 mg/kg per day | Skin Forestomach Liver Lung | Skin Forestomach |

[a] Low survival in male control group

## CONCLUSIONS

Under the conditions of these long-term dermal studies, there was *clear evidence of carcinogenic activity** of 2,3-dibromo-1-propanol in male F344/N rats based on increased incidences of neoplasms of the skin, nose, oral mucosa, esophagus, forestomach, small and large intestine, Zymbal's gland, liver, kidney, tunica vaginalis, and spleen. There was *clear evidence of carcinogenic activity* of 2,3-dibromo-1-propanol in female F344/N rats based on increased incidences of neoplasms of the skin, nose, oral mucosa, esophagus, forestomach, small and large intestine, Zymbal's gland, liver, kidney, clitoral gland, and mammary gland. There was *clear evidence of carcinogenic activity* of 2,3-dibromo-1-propanol in male B6C3F$_1$ mice based on increased incidences of neoplasms of the skin, forestomach, liver, and lung. There was *clear evidence of carcinogenic activity* of 2,3-dibromo-1-propanol in female B6C3F$_1$ mice based on increased incidences of neoplasms of the skin and the forestomach. The increased incidences of alveolar/bronchiolar adenomas in female mice may have been related to chemical administration.

In rats, 2,3-dibromo-1-propanol caused increased incidences of hyperkeratosis in the skin, forestomach, and esophagus, epithelial dysplasia in the nose, pleomorphism and basophilic and clear cell changes in the liver, and nuclear enlargement in the kidney. There were also chemical-related increases in the incidences of forestomach ulcers and acanthosis, angiectasis in the liver, and renal hyperplasia in male rats and epithelial dysplasia of the forestomach and bile duct hyperplasia in the liver in female rats. Chemical-related increases occurred in the incidences of hyperplasia in the skin, epithelial dysplasia of the forestomach, and bronchiolar epithelial pleomorphism and hyperplasia in male and female mice and in the incidence of eosinophilic cytoplasmic change in the liver in males.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

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# APPENDIX A
# SUMMARY OF LESIONS IN MALE RATS IN THE 51-WEEK DERMAL STUDY OF 2,3-DIBROMO-1-PROPANOL


| | | |
|---|---|---|
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TABLE A1
**Summary of the Incidence of Neoplasms in Male Rats in the 51-Week Dermal Study of 2,3-Dibromo-1-propanol**

| | Vehicle Control | 188 mg/kg | 375 mg/kg |
|---|---|---|---|
| **Disposition Summary** | | | |
| Animals initially in study | 50 | 50 | 50 |
| Early deaths | | | |
| Natural deaths | | 2 | 4 |
| Moribund | | 7 | 30 |
| Survivors | | | |
| Terminal sacrifice | 50 | 41 | 16 |
| Animals necropsied | 50 | 50 | 50 |
| Animals examined histopathologically | 50 | 50 | 50 |
| **Integumentary System** | | | |
| Skin[a] | (50) | (50) | (50) |
| Squamous cell papilloma | 1 (2%) | 3 (6%)[b] | |
| Squamous cell carcinoma | | 5 (10%) | 8 (16%) |
| Basal cell tumor | | 13 (26%) | 21 (42%) |
| Sebaceous adenoma | | 5 (10%) | 5 (10%) |
| Keratoacanthoma | | 4 (8%) | 12 (24%) |
| Subcutaneous tissue, fibroma | 1 (2%) | | |
| **Respiratory System** | | | |
| Lung[c] | (50) | (50) | (50) |
| Carcinoma, NOS[d], metastatic | | | 1 (2%) |
| Alveolar/bronchiolar adenoma | | | 2 (4%) |
| Alveolar/bronchiolar carcinoma | 1 (2%) | | |
| Adenocarcinoma, metastatic | | | 1 (2%) |
| Nasal cavity[a] | (50) | (50) | (50) |
| Adenocarcinoma, NOS | | 2 (4%) | 1 (2%) |
| Adenoma, NOS | | 48 (96%) | 48 (96%) |
| **Hematopoietic System** | | | |
| Spleen[c] | (50) | (50) | (50) |
| Hemangioma | | | 3 (6%) |
| Hemangiosarcoma | | | 1 (2%) |
| **Circulatory System** | | | |
| None | | | |
| **Digestive System** | | | |
| Oral cavity, NOS[a] | (50) | (50) | (50) |
| Squamous cell papilloma | | 1 (2%) | |
| Palate[a] | (50) | (50) | (50) |
| Squamous cell papilloma | | 3 (6%) | |
| Lip[a] | (50) | (50) | (50) |
| Squamous cell papilloma | | | 1 (2%) |

TABLE A1
**Summary of the Incidence of Neoplasms in Male Rats in the 51-Week Dermal Study of 2,3-Dibromo-1-propanol** (continued)

| | Vehicle Control | 188 mg/kg | 375 mg/kg |
|---|---|---|---|
| **Digestive System** (continued) | | | |
| Tongue[a] | (50) | (50) | (50) |
| Squamous cell papilloma | | 38 (76%) | 29 (58%) |
| Squamous cell carcinoma | | 15 (30%) | 25 (50%) |
| Keratoacanthoma | | | 1 (2%) |
| Tooth[a] | (50) | (50) | (50) |
| Odontoma, NOS | | | 1 (2%) |
| Gum[a] | (50) | (50) | (50) |
| Squamous cell papilloma | | | 1 (2%) |
| Liver[c] | (49) | (50) | (50) |
| Neoplastic nodule | | 3 (6%) | 2 (4%) |
| Hepatocellular carcinoma | | 1 (2%) | 3 (6%) |
| Hemangiosarcoma, metastatic | | | 1 (2%) |
| Pharynx[a] | (50) | (50) | (50) |
| Squamous cell papilloma | | 10 (20%) | 10 (20%) |
| Squamous cell carcinoma | | 1 (2%) | 4 (8%) |
| Esophagus[c] | (50) | (50) | (50) |
| Squamous cell papilloma | | 19 (38%) | 33 (66%) |
| Squamous cell carcinoma | | 1 (2%) | |
| Forestomach[c] | (50) | (50) | (50) |
| Squamous cell papilloma | | 1 (2%) | 17 (34%) |
| Jejunum[c] | (50) | (50) | (50) |
| Adenocarcinoma, NOS | | 8 (16%) | 9 (18%) |
| Adenomatous polyp, NOS | | 1 (2%) | 2 (4%) |
| Ileum[c] | (50) | (50) | (50) |
| Adenocarcinoma, NOS | | | 2 (4%) |
| Adenomatous polyp, NOS | | | 1 (2%) |
| Cecum[c] | (50) | (50) | (50) |
| Adenocarcinoma, NOS | 1 (2%) | | |
| Colon[c] | (50) | (50) | (50) |
| Adenocarcinoma, NOS | | 1 (2%) | 2 (4%) |
| Adenomatous polyp, NOS | 1 (2%) | 13 (26%) | 28 (56%) |
| Rectum[a] | (50) | (50) | (50) |
| Adenomatous polyp, NOS | | | 1 (2%) |
| **Urinary System** | | | |
| Kidney[c] | (50) | (50) | (50) |
| Tubular-cell adenoma | | | 4 (8%) |
| **Endocrine System** | | | |
| Anterior pituitary[c] | (50) | (50) | (48) |
| Adenoma, NOS | 2 (4%) | 1 (2%) | |
| Adrenal[c] | (50) | (50) | (50) |
| Cortical adenoma | 1 (2%) | | |
| Adrenal medulla[c] | (50) | (50) | (50) |
| Pheochromocytoma | 1 (2%) | | 1 (2%) |
| Thyroid[c] | (50) | (50) | (50) |
| C-cell adenoma | | | 1 (2%) |

TABLE A1
**Summary of the Incidence of Neoplasms in Male Rats in the 51-Week Dermal Study of 2,3-Dibromo-1-propanol** (continued)

| | Vehicle Control | 188 mg/kg | 375 mg/kg |
|---|---|---|---|
| **Reproductive System** | | | |
| Preputial gland[a] | (50) | (50) | (50) |
| Adenoma, NOS | 2 (4%) | 6 (12%) | 3 (6%) |
| Testis[c] | (50) | (50) | (50) |
| Interstitial-cell tumor | 8 (16%) | 17 (34%) | 2 (4%) |
| Tunica vaginalis[a] | (50) | (50) | (50) |
| Mesothelioma, NOS | | 1 (2%) | 4 (8%) |
| **Nervous System** | | | |
| Brain[c] | (50) | (50) | (50) |
| Astrocytoma | | 1 (2%) | 1 (2%) |
| **Special Sense Organs** | | | |
| Ear canal[a] | (50) | (50) | (50) |
| Squamous cell papilloma | | 1 (2%) | |
| Zymbal's gland[a] | (50) | (50) | (50) |
| Adenoma, NOS | | 1 (2%) | 7 (14%) |
| Adenocarcinoma, NOS | | 8 (16%) | 29 (58%) |
| **Musculoskeletal System** | | | |
| None | | | |
| **All Other Systems** | | | |
| Multiple organs[a] | (50) | (50) | (50) |
| Leukemia, mononuclear cell | | | 1 (2%) |
| **Neoplasm Summary** | | | |
| Total animals with primary neoplasms[e] | 16 | 50 | 50 |
| Total primary neoplasms | 17 | 239 | 332 |
| Total animals with benign neoplasms | 15 | 48 | 46 |
| Total benign neoplasms | 16 | 143 | 185 |
| Total animals with malignant neoplasms | 1 | 50 | 50 |
| Total malignant neoplasms | 1 | 91 | 136 |
| Total animals with metastatic neoplasms | | | 3 |
| Total metastatic neoplasms | | | 3 |
| Total animals with neoplasms uncertain-benign or malignant | | 4 | 8 |
| Total uncertain neoplasms | | 5 | 11 |

[a] Number of animals necropsied
[b] Multiple occurrence of morphology in the same organ tissue is counted only once.
[c] Number of animals with tissue examined microscopically
[d] NOS=not specified
[e] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 51-Week Dermal Study of 2,3-Dibromo-1-propanol: Vehicle Control**

| Animal Number | 0 1 | 0 2 | 0 3 | 0 4 | 0 5 | 0 6 | 0 7 | 0 8 | 0 9 | 1 0 | 1 1 | 1 2 | 1 3 | 1 4 | 1 5 | 1 6 | 1 7 | 1 8 | 1 9 | 2 0 | 2 1 | 2 2 | 2 3 | 2 4 | 2 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Weeks on Study** | 0 4 9 | 0 4 9 | 0 4 9 | 0 4 9 | 0 4 9 | 0 5 1 | 0 5 1 | 0 5 1 | 0 5 1 | 0 5 1 | 0 4 8 | 0 4 8 | 0 4 8 | 0 4 8 | 0 4 8 | 0 5 1 | 0 5 1 | 0 5 1 | 0 5 1 | 0 5 1 | 0 4 9 | 0 4 9 | 0 4 9 | 0 4 9 | 0 4 9 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | X | | | | | | | | | | | | | |
| Fibroma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | X | | | | | |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Nasal cavity | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Circulatory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Digestive System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Oral cavity | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Bile duct | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenocarcinoma, NOS | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Adenomatous polyp, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |

+: Tissue examined microscopically
–: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
m: Multiple occurrences of morphology
NOS: Not specified
Blank: No tissue information submitted due to protocol
C: Necropsy, no histology
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 51-Week Dermal Study of 2,3-Dibromo-1-propanol: Vehicle Control** (continued)

| Animal Number | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Weeks on Study | 05 | 05 | 05 | 05 | 05 | 05 | 05 | 05 | 05 | 05 | 04 | 04 | 04 | 04 | 04 | 05 | 05 | 05 | 05 | 05 | 05 | 05 | 05 | 05 | 05 | Total Tissues/ Tumors |
| | 11 | 11 | 11 | 11 | 11 | 10 | 00 | 00 | 00 | 00 | 09 | 09 | 09 | 09 | 09 | 00 | 00 | 00 | 00 | 00 | 00 | 00 | 00 | 00 | 00 | |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Fibroma | | | | | | | | | | | | | | | | | | | | | | | X | | | 1 |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Nasal cavity | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Circulatory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Digestive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Oral cavity | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenocarcinoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Adenomatous polyp, NOS | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 51-Week Dermal Study of 2,3-Dibromo-1-propanol: Vehicle Control** (continued)

| Animal Number | 0 1 | 0 2 | 0 3 | 0 4 | 0 5 | 0 6 | 0 7 | 0 8 | 0 9 | 1 0 | 1 1 | 1 2 | 1 3 | 1 4 | 1 5 | 1 6 | 1 7 | 1 8 | 1 9 | 2 0 | 2 1 | 2 2 | 2 3 | 2 4 | 2 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Weeks on Study** | 0 4 9 | 0 4 9 | 0 4 9 | 0 4 9 | 0 4 9 | 0 5 1 | 0 5 1 | 0 5 1 | 0 5 1 | 0 5 1 | 0 4 8 | 0 4 8 | 0 4 8 | 0 4 8 | 0 4 8 | 0 5 1 | 0 5 1 | 0 5 1 | 0 5 1 | 0 5 1 | 0 4 9 | 0 4 9 | 0 4 9 | 0 4 9 | 0 4 9 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma, NOS | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Cortical adenoma | | | | | | | | | | | | | | | | | | | | | | | | X | |
| Pheochromocytoma | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Reproductive System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Testis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Interstitial-cell tumor | | | | | | X | | | | | | | X | | X | X | | | | | | | | | |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Preputial gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Adenoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tunica vaginalis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Sense Organs** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear canal | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Zymbal's gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **All Other Systems** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 51-Week Dermal Study of 2,3-Dibromo-1-propanol: Vehicle Control** (continued)

| Animal Number | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Weeks on Study | 051 | 051 | 051 | 051 | 051 | 050 | 050 | 050 | 050 | 050 | 049 | 049 | 049 | 049 | 049 | 050 | 050 | 050 | 050 | 050 | 050 | 050 | 050 | 050 | 050 | Total Tissues/ Tumors |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | X | | 2 |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Cortical adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pheochromocytoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Reproductive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Testis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Interstitial-cell tumor | X | | | | | | | | | | | | | | X | | | | | | X | | X | | | 8 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Preputial gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| Adenoma, NOS | X | | | | | X | | | | | | | | | | | | | | | | | | | | 2 |
| Tunica vaginalis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Sense Organs** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear canal | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| Zymbal's gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **All Other Systems** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 51-Week Dermal Study of 2,3-Dibromo-1-propanol: 188 mg/kg**

| Animal Number | 0 1 | 0 2 | 0 3 | 0 4 | 0 5 | 0 6 | 0 7 | 0 8 | 0 9 | 1 0 | 1 1 | 1 2 | 1 3 | 1 4 | 1 5 | 1 6 | 1 7 | 1 8 | 1 9 | 2 0 | 2 1 | 2 2 | 2 3 | 2 4 | 2 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Weeks on Study** | 0 5 0 | 0 5 0 | 0 5 0 | 0 5 0 | 0 5 0 | 0 4 5 | 0 5 0 | 0 5 0 | 0 5 0 | 0 4 2 | 0 4 8 | 0 4 8 | 0 4 8 | 0 4 8 | 0 4 8 | 0 5 1 | 0 4 1 | 0 5 1 | 0 4 1 | 0 5 1 | 0 4 8 | 0 4 1 | 0 5 0 | 0 5 0 | 0 5 0 | 0 5 0 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | X | | | | | | | | | | | X | | | | | | | | | | |
| Squamous cell carcinoma | | X | | | | | | | | | | | | X | | | | X | | | | | | X | |
| Basal cell tumor | | | | | | X | X | | | | | | X | | X | | | | X | X | | | X | | |
| Sebaceous adenoma | | X | | | | | | X | | | | | | | | | | | | | | | | | |
| Keratoacanthoma | | | | X | | | | | | | | | | | | X | | X | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Nasal cavity | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenocarcinoma, NOS | | | | | | | | | | | | | | | X | | | | | | | | | | |
| Adenoma, NOS | m | m | X | m | X | m | m | m | m | m | m | m | m | X | m | m | m | m | m | m | m | m | m | m | m |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph nodes | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Circulatory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Digestive System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Oral cavity | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Squamous cell papilloma | m | X | m | m | X | X | m | m | X | | X | X | | | X | X | m | m | m | X | X | X | X | X | X |
| Squamous cell carcinoma | | | | | | X | | | X | X | | | | | | | X | | | X | | X | | | |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Neoplastic nodule | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | X | X | | | | | X | X | | | | | | | | | | X | | | | X | | | X |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | X | |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 51-Week Dermal Study of 2,3-Dibromo-1-propanol: 188 mg/kg** (continued)

| Animal Number | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Weeks on Study | 049 | 049 | 049 | 049 | 044 | 046 | 051 | 051 | 051 | 051 | 048 | 048 | 048 | 048 | 048 | 049 | 049 | 049 | 049 | 049 | 047 | 046 | 051 | 051 | 051 | Total Tissues/ Tumors |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Squamous cell papilloma | m | | | | | | | | | | | | | | | | | | | | | | | | | 3 |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | X | | | | | | | 5 |
| Basal cell tumor | X | | | X | | | | X | | | | X | | X | | X | | | | | | | | | | 13 |
| Sebaceous adenoma | | | | | | | | | | | X | X | | | | | | | X | | | | | | | 5 |
| Keratoacanthoma | | | | | | | | | | | X | | | | | | | | | | | | | | | 4 |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Nasal cavity | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Adenocarcinoma, NOS | | | | | | | | | | | | | | | | | X | | | | | | | | | 2 |
| Adenoma, NOS | m | m | m | m | m | m | m | m | m | m | m | m | | m | m | m | | m | m | m | m | X | m | m | m | 48 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Circulatory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Digestive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Oral cavity | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| Squamous cell papilloma | X | | m | X | | X | m | m | | | X | X | X | X | X | | | X | X | X | X | | X | X | X | 40 |
| Squamous cell carcinoma | | X | | | X | X | | X | X | X | | | | | | | X | X | | | | X | X | | | 16 |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Neoplastic nodule | | X | | | | | | | | | | | | | | | | X | | | | | X | | | 3 |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | | | | X | | | | | | 1 |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | X | X | | | | X | X | X | | | X | X | | | | | | | X | X | | X | | X | X | 19 |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 51-Week Dermal Study of 2,3-Dibromo-1-propanol: 188 mg/kg** (continued)

| **Animal Number** | 0 1 | 0 2 | 0 3 | 0 4 | 0 5 | 0 6 | 0 7 | 0 8 | 0 9 | 1 0 | 1 1 | 1 2 | 1 3 | 1 4 | 1 5 | 1 6 | 1 7 | 1 8 | 1 9 | 2 0 | 2 1 | 2 2 | 2 3 | 2 4 | 2 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Weeks on Study** | 0 5 0 | 0 5 0 | 0 5 0 | 0 5 0 | 0 5 0 | 0 4 5 | 0 5 0 | 0 5 0 | 0 5 0 | 0 4 2 | 0 4 8 | 0 4 8 | 0 4 8 | 0 4 8 | 0 4 8 | 0 5 1 | 0 4 1 | 0 5 1 | 0 5 1 | 0 5 8 | 0 4 1 | 0 5 0 | 0 5 0 | 0 5 0 | 0 5 0 |
| **Digestive System** (continued) | | | | | | | | | | | | | | | | | | | | | | | | | |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenocarcinoma, NOS | X | | | | | | | | | | | | | X | | | | | | | | | | | |
| Adenomatous polyp, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenocarcinoma, NOS | | | | | | | | | | | | | | | X | | | | | | | | | | |
| Adenomatous polyp, NOS | | X | | | X | | X | | X | | | | | | | | | | X | | X | X | | X | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Reproductive System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Testis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Interstitial-cell tumor | | | | X | X | | X | X | | | X | X | X | X | X | | | | | | | | X | | |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Preputial gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Adenoma, NOS | | | | X | X | | | | | | X | X | | | | | | | X | | | | | | |
| Tunica vaginalis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Mesothelioma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Astrocytoma | | | | | | | | | | | | | | | | | | | | | | | | | X |
| **Special Sense Organs** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | N | N | N | N | N | N | N | + | N | N | N | N | N | + | N | N | N | N | + | N | + | N | + | N | N |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Zymbal's gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Adenocarcinoma, NOS | | | | | | | | X | | | | | | X | | | | | X | | X | | X | | |
| Adenoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 51-Week Dermal Study of 2,3-Dibromo-1-propanol: 188 mg/kg** (continued)

| Animal Number | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Weeks on Study | 00 44 99 | 00 44 99 | 00 44 99 | 00 44 99 | 00 44 04 | 00 44 06 | 00 45 11 | 00 45 11 | 00 45 11 | 00 45 11 | 00 44 18 | 00 44 18 | 00 44 18 | 00 44 18 | 00 44 18 | 00 44 19 | 00 44 19 | 00 44 19 | 00 44 19 | 00 44 19 | 00 44 19 | 00 44 19 | 00 45 11 | 00 45 11 | 00 45 11 | Total Tissues/ Tumors |
| **Digestive System** (continued) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenocarcinoma, NOS | X | | X | | | | X | | X | | | | | | | | | | | | X | | | | X | 8 |
| Adenomatous polyp, NOS | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenocarcinoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Adenomatous polyp, NOS | | | | | | X | | | | X | | | | | | | | | X | | | | | X | X | 13 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma, NOS | | | | | | | | | | | | | | | X | | | | | | | | | | | 1 |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | 48 |
| **Reproductive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Testis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Interstitial-cell tumor | | | X | | | X | | | X | | | | | X | | | | | | X | | | | X | X | 17 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Preputial gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| Adenoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | X | | 6 |
| Tunica vaginalis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Mesothelioma, NOS | | | | | | | | | | | | | | | | | | | X | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Astrocytoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Special Sense Organs** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | + | N | N | N | N | N | N | + | N | N | N | N | N | N | + | + | N | N | N | N | N | N | + | + | + | 50[a] |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | X | | 1 |
| Zymbal's gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| Adenocarcinoma, NOS | | | | | | | | X | | | | | | | | | | | | | | | X | | X | 8 |
| Adenoma, NOS | | | | | | | | | | | | | | | X | | | | | | | | | | | 1 |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 51-Week Dermal Study of 2,3-Dibromo-1-propanol: 188 mg/kg** (continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Animal Number** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 |
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 |
| **Number of Weeks on Study** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 5 | 5 | 5 | 5 | 5 | 4 | 5 | 5 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 5 | 4 | 5 | 5 | 4 | 4 | 5 | 5 | 5 | 5 |
| | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 2 | 8 | 8 | 8 | 8 | 8 | 1 | 1 | 1 | 1 | 8 | 1 | 0 | 0 | 0 | 0 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **All Other Systems** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 51-Week Dermal Study of 2,3-Dibromo-1-propanol: 188 mg/kg** (continued)

| Animal Number | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Weeks on Study | 049 | 049 | 049 | 049 | 044 | 046 | 051 | 051 | 051 | 051 | 048 | 048 | 048 | 048 | 048 | 049 | 049 | 049 | 049 | 049 | 047 | 046 | 051 | 051 | 051 | Total Tissues/ Tumors |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **All Other Systems** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 51-Week Dermal Study of 2,3-Dibromo-1-propanol: 375 mg/kg**

| Animal Number | 0 1 | 0 2 | 0 3 | 0 4 | 0 5 | 0 6 | 0 7 | 0 8 | 0 9 | 1 0 | 1 1 | 1 2 | 1 3 | 1 4 | 1 5 | 1 6 | 1 7 | 1 8 | 1 9 | 2 0 | 2 1 | 2 2 | 2 3 | 2 4 | 2 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Weeks on Study** | 0 4 4 | 0 4 6 | 0 4 8 | 0 4 2 | 0 4 3 | 0 3 5 | 0 4 8 | 0 4 8 | 0 4 7 | 0 4 8 | 0 2 5 | 0 3 1 | 0 4 4 | 0 4 9 | 0 4 9 | 0 4 9 | 0 4 9 | 0 4 4 | 0 4 8 | 0 3 4 | 0 4 2 | 0 2 3 | 0 3 7 | 0 3 9 | 0 5 0 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell carcinoma | | X | X | X | X | | | | | | | | | | | | | | | | | | | | |
| Basal cell tumor | | | X | | X | X | | | | X | | | | X | X | X | X | X | X | | X | | | | X |
| Sebaceous adenoma | | | | | | | | X | | | | | | | | | | | | | | | | X | |
| Keratoacanthoma | X | | | X | | | | | X | | | | X | | | X | | | | | | | | | X |
| Mammary gland | N | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma, NOS, metastatic | | | | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Lung, adenocarcinoma, metastatic, colon | | | | | | | | | X | | | | | | | | | | | | | | | | |
| Trachea | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Nasal cavity | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenocarcinoma, NOS | | | | | X | | | | | | | | | | | | | | | | | | | | |
| Adenoma, NOS | m | m | m | m | | m | m | m | m | X | | m | m | m | m | m | m | m | m | m | m | m | m | m | m |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangioma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Circulatory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Digestive System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Oral cavity | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Squamous cell papilloma | X | X | X | | X | | X | X | X | m | | | X | m | X | m | | X | X | | X | | X | X | X |
| Squamous cell carcinoma | m | | X | | | X | | m | | | | X | | | m | | X | X | | X | | X | | X | |
| Keratoacanthoma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Odontoma, NOS | | | | | | | | | X | | | | | | | | | | | | | | | | |
| Salivary gland | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Neoplastic nodule | | | | | | | | | X | | | | X | | | | | | | | | | | | |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Hemangiosarcoma, metastatic | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 51-Week Dermal Study of 2,3-Dibromo-1-propanol: 375 mg/kg** (continued)

| Animal Number | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Weeks on Study | 042 | 446 | 055 | 043 | 050 | 043 | 035 | 050 | 041 | 041 | 051 | 051 | 033 | 036 | 047 | 046 | 047 | 038 | 045 | 052 | 046 | 041 | 056 | 053 | 049 | Total Tissues/ Tumors |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Squamous cell carcinoma | | | X | | | | | X | | | | | | | | X | | | | | X | | | | | 8 |
| Basal cell tumor | | | | X | X | | | X | | | X | X | | | | | | | | X | X | X | | | X | 21 |
| Sebaceous adenoma | | | | | | | | | | | | X | | | X | | | | | | | | X | | | 5 |
| Keratoacanthoma | | | X | | | | | | | | X | X | | | X | | X | | | | | X | | | | 12 |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | 50[a] |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Carcinoma, NOS, metastatic | | | | | | | | | | | | | | | | | | | | | | | | | X | 1 |
| Alveolar/bronchiolar adenoma | X | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Lung, adenocarcinoma, metastatic, colon | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Nasal cavity | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Adenocarcinoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Adenoma, NOS | m | m | m | m | m | m | m | m | m | m | m | m | m | m | m | m | m | m | m | m | m | m | m | m | m | 48 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hemangioma | | | | | X | | | | | | | | | | | | | | | | | X | | | | 3 |
| Hemangiosarcoma | | X | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | + | – | + | + | + | + | + | + | – | + | + | + | + | – | + | + | + | + | – | + | + | 45 |
| **Circulatory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Digestive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Oral cavity | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| Squamous cell papilloma | X | | m | | | X | X | | | X | m | X | X | | X | m | X | X | X | | | m | X | | | 33 |
| Squamous cell carcinoma | | X | | X | X | | | X | X | X | | X | | X | | | | | | m | X | X | X | X | X | 25 |
| Keratoacanthoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Odontoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Neoplastic nodule | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Hepatocellular carcinoma | | | | | | X | | | | | | | | | | X | | | | | | | | | | 3 |
| Hemangiosarcoma, metastatic | | X | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 51-Week Dermal Study of 2,3-Dibromo-1-propanol: 375 mg/kg** (continued)

| Animal Number | 0 1 | 0 2 | 0 3 | 0 4 | 0 5 | 0 6 | 0 7 | 0 8 | 0 9 | 1 0 | 1 1 | 1 2 | 1 3 | 1 4 | 1 5 | 1 6 | 1 7 | 1 8 | 1 9 | 2 0 | 2 1 | 2 2 | 2 3 | 2 4 | 2 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Weeks on Study | 0 4 4 | 0 4 6 | 0 4 8 | 0 4 2 | 0 4 3 | 0 3 5 | 0 4 8 | 0 4 8 | 0 4 7 | 0 4 8 | 0 2 5 | 0 3 1 | 0 4 4 | 0 4 9 | 0 4 9 | 0 4 9 | 0 4 9 | 0 4 4 | 0 4 8 | 0 3 4 | 0 4 2 | 0 2 3 | 0 3 7 | 0 3 9 | 0 5 0 |
| **Digestive System** (continued) | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | X | X | X | X | | X | X | | X | | | X | X | X | X | X | X | | | X | | | | X |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | X | X | X | | | X | | X | | | | X | X | | X | X | | | | | | X | | |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenocarcinoma, NOS | | | | | | | | | | | X | | | | | X | | | | | | | | | X |
| Adenomatous polyp, NOS | | | | | | | | | | | | | | | | X | | | | | | | X | | |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenocarcinoma, NOS | | | | | | | | | X | | | | | | | | | | | | | | | | |
| Adenomatous polyp, NOS | X | X | X | X | X | | X | X | m | X | | | X | X | | X | X | X | | | | | X | X | X |
| Rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenomatous polyp, NOS | | | | | | | | | | | | | | | X | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tubular-cell adenoma | | X | X | | | | | | X | | | | | | | | | | | | | | | | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C-cell adenoma | | | | | | | | | | | | X | | | | | | | | | | | | | |
| Parathyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Reproductive System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Testis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Interstitial-cell tumor | X | | | | | | | | | | | | | X | | | | | | | | | | | |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Preputial gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Adenoma, NOS | | | | | X | | | | | | | | | | | | | | | | | | | | |
| Tunica vaginalis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Mesothelioma, NOS | | | | | | | | | X | | | | X | | | | | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Astrocytoma | | | | X | | | | | | | | | | | | | | | | | | | | | |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 51-Week Dermal Study of 2,3-Dibromo-1-propanol: 375 mg/kg** (continued)

| Animal Number | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Weeks on Study** | 042 | 446 | 505 | 403 | 505 | 403 | 355 | 050 | 401 | 411 | 511 | 513 | 338 | 336 | 407 | 416 | 437 | 338 | 445 | 522 | 426 | 451 | 416 | 435 | 409 | **Total Tissues/ Tumors** |
| **Digestive System** (continued) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | X | X | X | X | X | | | X | X | | X | X | | | X | X | X | | X | X | X | X | X | | X | 33 |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | | X | | | X | | | | | X | | X | | | | | X | | | | | X | | | X | 17 |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenocarcinoma, NOS | X | X | | | | | | X | | | X | X | | | X | | | X | X | | | | | | | 11 |
| Adenomatous polyp, NOS | | X | | | | | | | | | | | | | | | | | | | | | | | | 3 |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenocarcinoma, NOS | | | | X | | | | | | | | | | | | | | | | | | | | | | 2 |
| Adenomatous polyp, NOS | X | | | | X | X | | | | X | | X | | | X | X | | | | X | X | X | X | | | 28 |
| Rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Adenomatous polyp, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Tubular-cell adenoma | | | X | | | | | | | | | | | | | | | | | | | | | | | 4 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | 48 |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pheochromocytoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| C-cell adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Parathyroid | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | 48 |
| **Reproductive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Testis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Interstitial-cell tumor | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Preputial gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| Adenoma, NOS | | | | | X | | | | | | | | | | | X | | | | | | | | | | 3 |
| Tunica vaginalis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Mesothelioma, NOS | | | | | | | | X | | | | | | | | X | | | | | | | | | | 4 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Astrocytoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 51-Week Dermal Study of 2,3-Dibromo-1-propanol: 375 mg/kg** (continued)

| **Animal Number** | 0 1 | 0 2 | 0 3 | 0 4 | 0 5 | 0 6 | 0 7 | 0 8 | 0 9 | 1 0 | 1 1 | 1 2 | 1 3 | 1 4 | 1 5 | 1 6 | 1 7 | 1 8 | 1 9 | 2 0 | 2 1 | 2 2 | 2 3 | 2 4 | 2 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Weeks on Study** | 0 4 4 | 0 4 6 | 0 4 8 | 0 4 2 | 0 4 3 | 0 3 5 | 0 4 8 | 0 4 8 | 0 4 7 | 0 4 8 | 0 2 5 | 0 3 1 | 0 4 4 | 0 4 9 | 0 4 9 | 0 4 9 | 0 4 9 | 0 4 4 | 0 4 8 | 0 3 4 | 0 4 2 | 0 2 3 | 0 3 7 | 0 3 9 | 0 5 0 |
| **Special Sense Organs** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + |
| Zymbal's gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Adenoma, NOS | | | | | | | | | | | | | X | X | | | | | m | | | | | | |
| Adenocarcinoma, NOS | X | X | | X | X | | X | X | | X | | | | X | X | X | X | X | | | X | | X | X | X |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **All Other Systems** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Leukemia, mononuclear cell | | | | | | | | | | | | | | | | X | | | | | | | | | |

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the 51-Week Dermal Study of 2,3-Dibromo-1-propanol: 375 mg/kg** (continued)

| Animal Number | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Weeks on Study | 42 | 46 | 50 | 43 | 50 | 43 | 35 | 50 | 41 | 41 | 51 | 51 | 38 | 36 | 47 | 46 | 47 | 38 | 45 | 44 | 46 | 51 | 46 | 35 | 49 | Total Tissues/ Tumors |
| **Special Sense Organs** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | + | + | + | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Zymbal's gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| Adenoma, NOS | | | | X | | X | | | | | | | | | | | | | | X | X | | | | | 7 |
| Adenocarcinoma, NOS | X | X | X | | X | | X | | X | X | | | | | X | X | X | | X | | | X | | | X | 29 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **All Other Systems** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| Leukemia, mononuclear cell | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

[a] Number of animals necropsied

TABLE A3
**Historical Incidence of Neoplasms in Untreated Male F344/N Rats for Studies Lasting 8 to 13 Months**

| Study | Study Length | Study Laboratory |
|---|---|---|
| Diglycidyl resorcinol ether | 58 weeks | EG&G Mason Research Institute |
| 1,2-Dichloropropane | 40 weeks | EG&G Mason Research Institute |
| Butyl benzyl phthalate | 35 weeks | EG&G Mason Research Institute |
| Benzyl acetate | 48 weeks | Southern Research Institute |
| Geranyl acetate | 45 weeks | Southern Research Institute |

**Incidence of Neoplasms**[a]

| | |
|---|---|
| Skin | |
| Epithelial neoplasms (all types) | 0/250 |
| Liver | |
| Neoplastic nodule, hepatocellular adenoma, or hepatocellular carcinoma | 0/249 |
| Small intestine | |
| Adenomatous polyp, adenoma, or adenocarcinoma | 0/250 |
| Large intestine | |
| Adenoma, adenomatous polyp, or adenocarcinoma | 0/250 |
| Esophagus | |
| Squamous cell papilloma or carcinoma | 0/250 |
| Forestomach | |
| Squamous cell papilloma or carcinoma | 0/250 |
| Kidney | |
| Tubule cell adenoma or carcinoma | 0/250 |
| Oral mucosa | |
| Squamous cell papilloma or carcinoma | 0/250 |
| Nose | |
| Adenoma or carcinoma | 0/250 |
| Zymbal's gland | |
| Adenoma or carcinoma | 0/250 |
| Spleen | |
| Hemangioma or hemangiosarcoma | 0/250 |
| Mesothelioma | 0/250 |

[a] Combined data for EG&G Mason Research Institute and Southern Research Institute

TABLE A4
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 51-Week Dermal Study of 2,3-Dibromo-1-propanol**

| | Vehicle Control | 188 mg/kg | 375 mg/kg |
|---|---|---|---|
| **Disposition Summary** | | | |
| Animals initially in study | 50 | 50 | 50 |
| Early deaths | | | |
| Natural deaths | | 2 | 4 |
| Moribund | | 7 | 30 |
| Survivors | | | |
| Terminal sacrifice | 50 | 41 | 16 |
| Animals necropsied | 50 | 50 | 50 |
| Animals examined histopathologically | 50 | 50 | 50 |
| **Integumentary System** | | | |
| Skin[a] | (50) | (50) | (50) |
| Epidermal inclusion cyst | 1 (2%) | 3 (6%) | 1 (2%) |
| Dermal inclusion cyst | | 1 (2%) | |
| Inflammation, NOS[b] | | 1 (2%) | |
| Inflammation, focal | | | 1 (2%) |
| Hyperkeratosis | | 1 (2%) | 23 (46%) |
| Acanthosis | | | 1 (2%) |
| Sebaceous cyst | | 2 (4%) | |
| **Respiratory System** | | | |
| Lung[c] | (50) | (50) | (50) |
| Pneumonia, aspiration | | 1 (2%) | |
| Inflammation, acute | | 1 (2%) | 3 (6%) |
| Inflammation, chronic | | | 1 (2%) |
| Pneumonia, interstitial chronic | | 1 (2%) | |
| Fibrosis | | | 1 (2%) |
| Perivascular cuffing | 2 (4%) | | 1 (2%) |
| Hyperplasia, adenomatous | | | 1 (2%) |
| Nasal cavity[a] | (50) | (50) | (50) |
| Inflammation, chronic | 9 (18%) | 2 (4%) | 5 (10%) |
| Granulation tissue | | | 1 (2%) |
| Hyperkeratosis | | | 2 (4%) |
| Dysplasia, epithelial | | 33 (66%) | 49 (98%) |
| Hyperplasia, epithelial | | 1 (2%) | |
| **Hematopoietic System** | | | |
| Spleen[c] | (50) | (50) | (50) |
| Hemorrhage | | | 1 (2%) |
| Fibrosis, focal | | 1 (2%) | 1 (2%) |
| Hemosiderosis | | 2 (4%) | 5 (10%) |
| Splenic red pulp[c] | (50) | (50) | (50) |
| Hyperplasia, NOS | | 1 (2%) | |
| Lymph node[c] | (50) | (49) | (50) |
| Inflammation, NOS | | 1 (2%) | |
| Angiectasis | | | 1 (2%) |

TABLE A4
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 51-Week Dermal Study of 2,3-Dibromo-1-propanol** (continued)

| | Vehicle Control | 188 mg/kg | 375 mg/kg |
|---|---|---|---|
| **Circulatory System** | | | |
| Myocardium[c] | (50) | (50) | (50) |
| Degeneration, NOS | 1 (2%) | 1 (2%) | 3 (6%) |
| Mitral valve[c] | (50) | (50) | (50) |
| Fibrosis | | 1 (2%) | |
| Artery[a] | (50) | (50) | (50) |
| Periarteritis | | 1 (2%) | 4 (8%) |
| **Digestive System** | | | |
| Tongue[a] | (50) | (50) | (50) |
| Hyperkeratosis | | 1 (2%) | |
| Salivary gland[c] | (50) | (48) | (49) |
| Inflammation, NOS | | 1 (2%) | 2 (4%) |
| Liver[c] | (49) | (50) | (50) |
| Inflammation, focal | 1 (2%) | 2 (4%) | 2 (4%) |
| Inflammation, chronic | | | 1 (2%) |
| Fibrosis | | 1 (2%) | 1 (2%) |
| Necrosis, NOS | | 1 (2%) | 2 (4%) |
| Cytoplasmic vacuolization | | | 1 (2%) |
| Basophilic cyto change | 2 (4%) | 28 (56%) | 16 (32%) |
| Clear-cell change | 2 (4%) | 15 (30%) | 5 (10%) |
| Pleomorphism | | | 37 (74%) |
| Angiectasis | 2 (4%) | 26 (52%) | 46 (92%) |
| Eosinophilic cyto change | | 2 (4%) | 4 (8%) |
| Periportal bile duct[c] | (49) | (50) | (50) |
| Hyperplasia, NOS | 20 (40%) | 13 (26%) | 10 (20%) |
| Liver/centrilobular[c] | (49) | (50) | (50) |
| Inflammation, NOS | | | 1 (2%) |
| Degeneration, NOS | | | 2 (4%) |
| Pancreas[c] | (50) | (50) | (50) |
| Inflammation, chronic | 1 (2%) | | |
| Atrophy, NOS | 4 (8%) | 3 (6%) | |
| Pancreatic duct[c] | (50) | (50) | (50) |
| Dilatation, NOS | | 1 (2%) | |
| Pharynx[a] | (50) | (50) | (50) |
| Hyperkeratosis | | | 1 (2%) |
| Esophagus[c] | (50) | (50) | (50) |
| Hyperkeratosis | | 18 (36%) | 48 (96%) |
| Forestomach[c] | (50) | (50) | (50) |
| Inflammation, NOS | | 1 (2%) | 3 (6%) |
| Ulcer, NOS | | 3 (6%) | 5 (10%) |
| Hyperkeratosis | 2 (4%) | 6 (12%) | 32 (64%) |
| Acanthosis | | 1 (2%) | 6 (12%) |
| Dysplasia, epithelial | | 6 (12%) | 1 (2%) |
| Jejunum[c] | (50) | (50) | (50) |
| Inflammation, chronic | | 1 (2%) | |
| Ileum[c] | (50) | (50) | (50) |
| Inflammation, chronic | | | 1 (2%) |

TABLE A4
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 51-Week Dermal Study of 2,3-Dibromo-1-propanol** (continued)

| | Vehicle Control | 188 mg/kg | 375 mg/kg |
|---|---|---|---|
| **Digestive System** (continued) | | | |
| Ileocecal valve[c] | (50) | (50) | (50) |
| Inflammation, chronic | 1 (2%) | | |
| Colon[c] | (50) | (50) | (50) |
| Inflammation, NOS | | 1 (2%) | |
| Ulcer, NOS | | | 1 (2%) |
| Rectum[a] | (50) | (50) | (50) |
| Inflammation, NOS | | | 1 (2%) |
| **Urinary System** | | | |
| Kidney[c] | (50) | (50) | (50) |
| Nephropathy | 48 (96%) | 45 (90%) | 48 (96%) |
| Hyperplasia, tubular cell | | 1 (2%) | 5 (10%) |
| Kidney/tubule[c] | (50) | (50) | (50) |
| Nuclear enlargement | | | 41 (82%) |
| **Endocrine System** | | | |
| Pituitary[c] | (50) | (50) | (48) |
| Congenital malformation, NOS | 1 (2%) | 4 (8%) | |
| Anterior pituitary[c] | (50) | (50) | (48) |
| Colloid cyst | | | 1 (2%) |
| Hyperplasia, focal | 10 (20%) | 8 (16%) | 8 (17%) |
| Angiectasis | 1 (2%) | | |
| Adrenal cortex[c] | (50) | (50) | (50) |
| Hyperplasia, focal | | 1 (2%) | 2 (4%) |
| Adrenal medulla[c] | (50) | (50) | (50) |
| Hyperplasia, focal | 1 (2%) | | 1 (2%) |
| Thyroid[c] | (50) | (50) | (50) |
| Inflammation, NOS | | 1 (2%) | |
| Hyperplasia, C-cell | 2 (4%) | | |
| Pancreatic islets[c] | (50) | (50) | (50) |
| Hyperplasia, NOS | 1 (2%) | | |
| **Reproductive System** | | | |
| Preputial gland[a] | (50) | (50) | (50) |
| Cyst, NOS | | | 2 (4%) |
| Inflammation, NOS | 1 (2%) | | |
| Atrophy, NOS | | | 1 (2%) |
| Hyperplasia, focal | | | 1 (2%) |
| Prostate[c] | (50) | (50) | (50) |
| Inflammation, chronic | 1 (2%) | | |
| Testis[c] | (50) | (50) | (50) |
| Multinucleate giant-cell | | | 1 (2%) |
| Atrophy, NOS | | 2 (4%) | |
| Hyperplasia, interstitial cell | 40 (80%) | 28 (56%) | 12 (24%) |
| **Nervous System** | | | |
| None | | | |

TABLE A4
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 51-Week Dermal Study of 2,3-Dibromo-1-propanol** (continued)

| | Vehicle Control | 188 mg/kg | 375 mg/kg |
|---|---|---|---|
| **Special Sense Organs** | | | |
| Eye/retina[a] | (50) | (50) | (50) |
| Degeneration, NOS | 1 (2%) | | |
| Eye/crystalline lens[a] | (50) | (50) | (50) |
| Degeneration, NOS | 1 (2%) | | |
| Zymbal's gland[a] | (50) | (50) | (50) |
| Dilatation, NOS | | 1 (2%) | |
| Cyst, NOS | | | 2 (4%) |
| Hyperplasia, NOS | | 1 (2%) | 1 (2%) |
| **Musculoskeletal System** | | | |
| None | | | |
| **Body Cavities** | | | |
| Peritoneal cavity[a] | (50) | (50) | (50) |
| Inflammation, NOS | | 1 (2%) | |
| **All Other Systems** | | | |
| Adipose tissue | | | |
| Necrosis, fat | | 2 | |
| **Special Morphology Summary** | | | |
| None | | | |

[a] Number of animals necropsied
[b] NOS=not specified
[c] Number of animals with tissue examined microscopically

# APPENDIX B
# SUMMARY OF LESIONS IN FEMALE RATS IN THE 55-WEEK DERMAL STUDY OF 2,3-DIBROMO-1-PROPANOL


| | | |
|---|---|---|
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TABLE B1
**Summary of the Incidence of Neoplasms in Female Rats in the 55-Week Dermal Study of 2,3-Dibromo-1-propanol**

| | Vehicle Control | 188 mg/kg | 375 mg/kg |
|---|---|---|---|
| **Disposition Summary** | | | |
| Animals initially in study | 50 | 50 | 50 |
| Early deaths | | | |
| Natural deaths | | 1 | 2 |
| Moribund | 2 | 11 | 24 |
| Survivors | | | |
| Died during terminal sacrifice period | | | 3 |
| Terminal sacrifice | 48 | 38 | 21 |
| Animals necropsied | 50 | 50 | 50 |
| Animals examined histopathologically | 50 | 50 | 50 |
| **Integumentary System** | | | |
| Skin[a] | (50) | (50) | (50) |
| Squamous cell papilloma | | | 2 (4%) |
| Squamous cell carcinoma | | | 1 (2%) |
| Basal cell tumor | | 3 (6%) | 12 (24%) |
| Sebaceous adenoma | | | 2 (4%) |
| Keratoacanthoma | | | 5 (10%) |
| Mammary gland[a] | (50) | (50) | (50) |
| Adenocarcinoma, NOS[b] | | | 5 (10%) |
| Fibroadenoma | 1 (2%) | 1 (2%) | |
| **Respiratory System** | | | |
| Lung[c] | (50) | (50) | (50) |
| Alveolar/bronchiolar adenoma | | 1 (2%) | |
| Nasal cavity[a] | (50) | (50) | (50) |
| Squamous cell carcinoma | | | 1 (2%) |
| Adenoma NOS | | 44 (88%) | 49 (98%) |
| **Hematopoietic System** | | | |
| Spleen[c] | (50) | (50) | (49) |
| Hemangioma | | | 2 (4%) |
| **Circulatory System** | | | |
| None | | | |
| **Digestive System** | | | |
| Oral cavity, NOS[a] | (50) | (50) | (50) |
| Squamous cell papilloma | | 1 (2%) | |
| Palate[a] | (50) | (50) | (50) |
| Squamous cell papilloma | | 1 (2%) | 4 (8%) |
| Lip[a] | (50) | (50) | (50) |
| Squamous cell papilloma | | | 1 (2%) |
| Tongue[a] | (50) | (50) | (50) |
| Squamous cell papilloma | | 24 (48%) | 34 (68%) |
| Squamous cell carcinoma | | 15 (30%) | 24 (48%) |

TABLE B1
**Summary of the Incidence of Neoplasms in Female Rats in the 55-Week Dermal Study of 2,3-Dibromo-1-propanol** (continued)

| | Vehicle Control | 188 mg/kg | 375 mg/kg |
|---|---|---|---|
| **Digestive System** (continued) | | | |
| Liver[c] | (50) | (50) | (50) |
| Neoplastic nodule | | 10 (20%) | 11 (22%) |
| Hepatocellular carcinoma | | 2 (4%) | 6 (12%) |
| Hemangiosarcoma | | | 1 (2%) |
| Pharynx[a] | (50) | (50) | (50) |
| Squamous cell papilloma | | 8 (16%) | 17 (34%) |
| Squamous cell carcinoma | | | 5 (10%) |
| Esophagus[c] | (50) | (50) | (50) |
| Squamous cell papilloma | | 9 (18%) | 38 (76%) |
| Squamous cell carcinoma | | | 1 (2%) |
| Forestomach[c] | (50) | (50) | (50) |
| Squamous cell papilloma | 1 (2%) | 3 (6%) | 23 (46%) |
| Squamous cell carcinoma | | | 1 (2%) |
| Duodenum[c] | (50) | (50) | (49) |
| Adenocarcinoma, NOS | | 1 (2%) | |
| Jejunum[c] | (50) | (50) | (49) |
| Adenocarcinoma, NOS | | 1 (2%) | 4 (8%) |
| Adenomatous polyp, NOS | | 1 (2%) | |
| Ileum[c] | (50) | (50) | (49) |
| Adenocarcinoma, NOS | | 1 (2%) | |
| Colon[c] | (50) | (50) | (50) |
| Adenomatous polyp, NOS | | 12 (24%) | 35 (70%) |
| Rectum[a] | (50) | (50) | (50) |
| Adenomatous polyp, NOS | | | 8 (16%) |
| **Urinary System** | | | |
| Kidney[c] | (50) | (50) | (50) |
| Tubular-cell adenoma | | 1 (2%) | 4 (8%) |
| **Endocrine System** | | | |
| Anterior pituitary[c] | (50) | (50) | (50) |
| Adenoma, NOS | 2 (4%) | 2 (4%) | 3 (6%) |
| Thyroid[c] | (50) | (50) | (49) |
| Squamous cell carcinoma | | | 1 (2%) |
| C-cell adenoma | 1 (2%) | | 1 (2%) |
| **Reproductive System** | | | |
| Clitoral gland[a] | (50) | (50) | (50) |
| Adenoma, NOS | | 1 (2%) | 3 (6%) |
| Adenocarcinoma, NOS | | | 3 (6%) |
| Uterus[c] | (50) | (50) | (48) |
| Endometrial stromal polyp | 7 (14%) | 3 (6%) | 9 (19%) |
| Endometrial stromal sarcoma | | | 1 (2%) |
| Ovary[c] | (50) | (50) | (48) |
| Granulosa cell tumor, benign | | | 1 (2%) |
| Thecoma | | | 1 (2%) |

TABLE B1
**Summary of the Incidence of Neoplasms in Female Rats in the 55-Week Dermal Study of 2,3-Dibromo-1-propanol** (continued)

| | Vehicle Control | 188 mg/kg | 375 mg/kg |
|---|---|---|---|
| **Nervous System** | | | |
| Brain[c] | (50) | (50) | (49) |
| Adenocarcinoma, NOS, invasive | | 1 (2%) | |
| **Special Sense Organs** | | | |
| Ear canal[a] | (50) | (50) | (50) |
| Squamous cell papilloma | | 2 (4%) | |
| Zymbal's gland[a] | (50) | (50) | (50) |
| Adenoma, NOS | | 7 (14%) | 3 (6%) |
| Adenocarcinoma, NOS | 1 (2%) | 2 (4%) | 19 (38%) |
| **Musculoskeletal System** | | | |
| None | | | |
| **All Other Systems** | | | |
| Multiple organs[a] | (50) | (50) | (50) |
| Leukemia, mononuclear cell | | | 2 (4%) |
| **Neoplasm Summary** | | | |
| Total animals with primary neoplasms[d] | 13 | 50 | 50 |
| Total primary neoplasms | 13 | 159 | 347 |
| Total animals with benign neoplasms | 12 | 35 | 48 |
| Total benign neoplasms | 12 | 81 | 209 |
| Total animals with malignant neoplasms | 1 | 49 | 50 |
| Total malignant neoplasms | 1 | 68 | 125 |
| Total animals with metastatic neoplasms | | 1 | |
| Total metastatic neoplasms | | 1 | |
| Total animals with neoplasms uncertain-benign or malignant | | 10 | 13 |
| Total uncertain neoplasms | | 10 | 13 |

[a] Number of animals necropsied
[b] NOS=not specified
[c] Number of animals with tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
**Individual Animal Tumor Pathology of Female Rats in the 55-Week Dermal Study of 2,3-Dibromo-1-propanol: Vehicle Control**

| Animal Number | 01 | 02 | 03 | 04 | 05 | 06 | 07 | 08 | 09 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Weeks on Study | 055 | 055 | 055 | 055 | 055 | 055 | 055 | 055 | 055 | 055 | 055 | 055 | 055 | 055 | 055 | 055 | 055 | 055 | 055 | 055 | 055 | 055 | 055 | 055 | 055 |
| | 222 | 222 | 222 | 222 | 225 | 255 | 255 | 255 | 255 | 253 | 333 | 333 | 333 | 333 | 355 | 555 | 555 | 555 | 555 | 222 | 222 | 222 | 222 | 222 | 222 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibroadenoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Nasal cavity | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Circulatory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Digestive System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Oral cavity | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

+: Tissue examined microscopically
–: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
m: Multiple occurrences of morphology
NOS: Not specified
Blank: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE B2
**Individual Animal Tumor Pathology of Female Rats in the 55-Week Dermal Study of 2,3-Dibromo-1-propanol: Vehicle Control** (continued)

| Animal Number | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Weeks on Study** | 038 | 255 | 252 | 252 | 255 | 252 | 252 | 252 | 252 | 252 | 255 | 255 | 255 | 255 | 255 | 254 | 254 | 254 | 254 | 254 | 254 | 254 | 254 | 254 | 255 | **Total Tissues/ Tumors** |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Fibroadenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Nasal cavity | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Circulatory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Digestive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Oral cavity | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | | | | | | | | X | | | | | | | | | | | | | | | | | | 1 |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 55-Week Dermal Study of 2,3-Dibromo-1-propanol: Vehicle Control** (continued)

| Animal Number | 01 | 02 | 03 | 04 | 05 | 06 | 07 | 08 | 09 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Weeks on Study | 52 | 52 | 52 | 52 | 52 | 55 | 55 | 55 | 55 | 55 | 53 | 53 | 53 | 53 | 53 | 55 | 55 | 55 | 55 | 55 | 52 | 52 | 52 | 52 | 52 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma, NOS | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C-cell adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Parathyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + |
| **Reproductive System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Endometrial stromal polyp | X | | X | | X | | | | X | | | | | | | | | | | | | | | | |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Sense Organs** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Zymbal's gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Adenocarcinoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **All Other Systems** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

TABLE B2
**Individual Animal Tumor Pathology of Female Rats in the 55-Week Dermal Study of 2,3-Dibromo-1-propanol: Vehicle Control** (continued)

| Animal Number | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Weeks on Study | 038 | 052 | 052 | 052 | 052 | 052 | 052 | 052 | 052 | 052 | 055 | 055 | 055 | 055 | 055 | 054 | 054 | 054 | 054 | 054 | 054 | 054 | 052 | 052 | 054 | Total Tissues/ Tumors |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma, NOS | | | | | | | | | | | | X | | | | | | | | | | | | | | 2 |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| C-cell adenoma | | | | | | | X | | | | | | | | | | | | | | | | | | | 1 |
| Parathyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | 48 |
| **Reproductive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Endometrial stromal polyp | | | | | | X | | | | | | | | | | | X | | | | | | | X | | 7 |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Sense Organs** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| Zymbal's gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| Adenocarcinoma, NOS | X | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **All Other Systems** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |

TABLE B2
**Individual Animal Tumor Pathology of Female Rats in the 55-Week Dermal Study of 2,3-Dibromo-1-propanol: 188 mg/kg**

| Animal Number | 0 1 | 0 2 | 0 3 | 0 4 | 0 5 | 0 6 | 0 7 | 0 8 | 0 9 | 1 0 | 1 1 | 1 2 | 1 3 | 1 4 | 1 5 | 1 6 | 1 7 | 1 8 | 1 9 | 2 0 | 2 1 | 2 2 | 2 3 | 2 4 | 2 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Weeks on Study** | 0 5 1 | 0 4 5 | 0 5 2 | 0 5 2 | 0 5 2 | 0 5 2 | 0 5 2 | 0 5 2 | 0 5 2 | 0 5 2 | 0 5 5 | 0 5 5 | 0 5 0 | 0 5 5 | 0 5 5 | 0 4 6 | 0 5 1 | 0 5 3 | 0 5 1 | 0 5 3 | 0 5 2 | 0 5 2 | 0 5 2 | 0 5 2 | 0 3 1 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Basal cell tumor | X | | | | | | | | | | | X | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibroadenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Nasal cavity | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma, NOS | m | m | | m | m | m | m | m | m | m | m | m | m | m | m | m | m | X | m | m | m | m | m | m | |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Circulatory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Digestive System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Oral cavity | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Squamous cell papilloma | X | | | X | | | m | X | | X | X | X | | | m | X | | X | | X | | X | m | X | |
| Squamous cell carcinoma | | | X | | | | | | | | | | X | | | X | X | | X | X | | | | | X |
| Salivary gland | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Neoplastic nodule | | | X | | | X | | | | | X | | | | | | | | | | | | | | |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | X | | | | | | | | |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | X | | X | | | | X | | X | | | | | | | | | |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | X | | | | | |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenocarcinoma, NOS | | | | | | | | | | | X | | X | | | | | | | | | | | | |
| Adenomatous polyp | | | | | | | | | | | | | | | | | | | | | | | | | |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenomatous polyp, NOS | | | X | | | | X | X | | X | | X | | X | X | X | | X | | X | | | | | |

TABLE B2
**Individual Animal Tumor Pathology of Female Rats in the 55-Week Dermal Study of 2,3-Dibromo-1-propanol: 188 mg/kg** (continued)

| Animal Number | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Weeks on Study | 054 | 054 | 054 | 042 | 054 | 055 | 051 | 054 | 039 | 047 | 054 | 054 | 054 | 054 | 054 | 055 | 032 | 055 | 055 | 055 | 052 | 052 | 052 | 052 | 052 | Total Tissues/ Tumors |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Basal cell tumor | | | | | | | X | | | | | | | | | | | | | | | | | | | 3 |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Fibroadenoma | | | | | | | | | | | | | X | | | | | | | | | | | | | 1 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Nasal cavity | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Adenoma, NOS | m | m | | X | m | m | | m | m | m | m | m | m | m | m | m | m | | m | m | m | | m | m | m | m | 44 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | 50 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Circulatory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Digestive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Oral cavity | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| Squamous cell papilloma | m | | m | | X | | | X | | | | X | X | | X | X | | | X | X | X | X | m | | | 27 |
| Squamous cell carcinoma | | | | X | | X | X | | X | | | | | | | X | X | X | | | | | | | X | 15 |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Neoplastic nodule | X | | X | | | | | | | | | X | X | | | | | | X | X | | | | | X | 10 |
| Hepatocellular carcinoma | X | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | X | | X | | | | X | | | | | | | X | | | | | | | X | | | | | 9 |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | | | | | | | | | | | | X | | | X | | | | | | | | | | | 3 |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenocarcinoma, NOS | | | | | | | | | | | | | | | | | | | | | | X | | | | 3 |
| Adenomatous polyp | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenomatous polyp, NOS | | | | | | | | | | | | | | | | | | | X | | X | | | | | 12 |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 55-Week Dermal Study of 2,3-Dibromo-1-propanol: 188 mg/kg** (continued)

| Animal Number | 01 | 02 | 03 | 04 | 05 | 06 | 07 | 08 | 09 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Weeks on Study | 05 | 04 | 05 | 05 | 05 | 05 | 05 | 05 | 05 | 05 | 05 | 05 | 05 | 05 | 05 | 04 | 05 | 05 | 05 | 05 | 05 | 05 | 05 | 05 | 03 |
| | 51 | 52 | 22 | 22 | 22 | 22 | 22 | 22 | 22 | 25 | 50 | 50 | 05 | 55 | 56 | 61 | 31 | 13 | 32 | 22 | 22 | 22 | 22 | 21 | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tubular-cell adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma, NOS | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + |
| **Reproductive System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Adenoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Endometrial stromal polyp | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenocarcinoma, NOS, invasive | | X | | | | | | | | | | | | | | | | | | | | | | | |
| **Special Sense Organs** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | N | + | N | N | N | N | N | N | N | N | N | N | N | + | + | N | N | N | N | N | N | + | N | N | N |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Zymbal's gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Adenoma, NOS | | | | | | | | | | | | | | X | X | | | | | | | | | | |
| Adenocarcinoma, NOS | | X | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **All Other Systems** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

TABLE B2
**Individual Animal Tumor Pathology of Female Rats in the 55-Week Dermal Study of 2,3-Dibromo-1-propanol: 188 mg/kg** (continued)

| Animal Number | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Weeks on Study | 05 | 05 | 05 | 04 | 05 | 05 | 05 | 05 | 03 | 04 | 05 | 05 | 05 | 05 | 05 | 05 | 03 | 05 | 05 | 05 | 05 | 05 | 05 | 05 | 05 | Total Tissues/ Tumors |
| | 44 | 44 | 44 | 42 | 44 | 45 | 41 | 44 | 49 | 47 | 44 | 44 | 44 | 44 | 44 | 45 | 42 | 45 | 45 | 45 | 42 | 42 | 42 | 42 | 42 | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Tubular-cell adenoma | | | | | | | | | | | | | | | | | | | | X | | | | | | 1 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma, NOS | | | | | | | | | | | | | | | | | | | | X | | | | | | 2 |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid | + | + | + | + | + | – | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| **Reproductive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| Adenoma, NOS | | | | | | | | | | | | | | | | | | | | X | | | | | | 1 |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Endometrial stromal polyp | | | | | | X | | X | | | | | | | | | | | X | | | | | | | 3 |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenocarcinoma, NOS, invasive | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Special Sense Organs** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | N | + | N | N | N | + | N | + | N | + | + | + | N | N | N | N | N | N | + | + | N | N | + | N | N | 50[a] |
| Squamous cell papilloma | | | | | | X | | | | | | | | | | | | | X | | | | | | | 2 |
| Zymbal's gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| Adenoma, NOS | | X | | | | m | | | | | X | | | | | | | | | X | | | X | | | 7 |
| Adenocarcinoma, NOS | | | | | | | | | | X | | | | | | | | | | | | | | | | 2 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **All Other Systems** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |

TABLE B2
**Individual Animal Tumor Pathology of Female Rats in the 55-Week Dermal Study of 2,3-Dibromo-1-propanol: 375 mg/kg**

| Animal Number | 0 1 | 0 2 | 0 3 | 0 4 | 0 5 | 0 6 | 0 7 | 0 8 | 0 9 | 1 0 | 1 1 | 1 2 | 1 3 | 1 4 | 1 5 | 1 6 | 1 7 | 1 8 | 1 9 | 2 0 | 2 1 | 2 2 | 2 3 | 2 4 | 2 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Weeks on Study** | 0 5 3 | 0 5 2 | 0 5 4 | 0 4 3 | 0 5 4 | 0 5 1 | 0 5 3 | 0 5 3 | 0 5 3 | 0 4 1 | 0 5 0 | 0 5 0 | 0 5 5 | 0 3 1 | 0 5 2 | 0 4 4 | 0 5 4 | 0 4 8 | 0 3 6 | 0 4 2 | 0 5 3 | 0 3 4 | 0 5 3 | 0 5 2 | 0 5 0 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Squamous cell carcinoma | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Basal cell tumor | | X | | | | | | | X | | X | | X | | | | X | | | | X | | X | | |
| Sebaceous adenoma | | | | | | | | | | | | | | | | | | | | | | | | X | X |
| Keratoacanthoma | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenocarcinoma, NOS | | | | | | | X | | | | | | | | | | | | | X | | | | X | X |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Nasal cavity | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell carcinoma | | | | | | | | | | | | | | | X | | | | | | | | | | |
| Adenoma, NOS | m | X | m | m | m | m | m | m | m | m | m | m | m | m | m | m | m | m | | m | m | m | m | m | m |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph nodes | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Circulatory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Digestive System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Oral cavity | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Squamous cell papilloma | X | | m | | X | X | X | X | X | | m | m | m | | m | X | | X | | X | m | X | X | m | X |
| Squamous cell carcinoma | | X | | X | | | X | | | X | | | X | X | X | | | X | X | | | | | X | |
| Salivary gland | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Neoplastic nodule | | | | | | | | | | | | X | X | | | | | | | | X | | | X | |
| Hepatocellular carcinoma | | | | | | | | | | X | | | X | | | | | X | | | | | | X | X |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pancreas [a] | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | X | X | X | X | X | X | X | X | | X | X | | X | | X | X | X | X | | | X | | X | X | X |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 55-Week Dermal Study of 2,3-Dibromo-1-propanol: 375 mg/kg** (continued)

| Animal Number | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Weeks on Study | 053 | 043 | 038 | 053 | 049 | 053 | 053 | 053 | 050 | 055 | 049 | 053 | 053 | 055 | 046 | 053 | 053 | 049 | 038 | 041 | 052 | 055 | 045 | 055 | 050 | Total Tissues/ Tumors |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Squamous cell papilloma | | | | | | | | | | | | | X | | | | | | | | | | | | | 2 |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Basal cell tumor | X | | | | | | | X | | | | | X | | | X | X | | | | | | | | | 12 |
| Sebaceous adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Keratoacanthoma | | | | | | | X | | | | | | X | | | | | | | | X | X | | | | 5 |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | 50[a] |
| Adenocarcinoma, NOS | | | | | | | | | | | | | | | | | | | | | X | | | | | 5 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Nasal cavity | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Adenoma, NOS | m | m | m | m | m | m | m | m | m | m | m | m | m | m | m | m | m | m | m | m | X | m | m | m | m | 49 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Hemangioma | | | | | | | | | | | | | X | | | | | X | | | | | | | | 2 |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Thymus | + | + | + | + | – | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| **Circulatory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **Digestive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Oral cavity | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| Squamous cell papilloma | X | X | X | | X | X | X | X | X | X | m | | X | X | X | m | m | X | | m | m | X | X | m | m | 41 |
| Squamous cell carcinoma | X | | | X | X | X | X | X | | X | X | m | | X | X | | X | X | X | | | | m | X | X | 27 |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Neoplastic nodule | | | | | | X | X | X | | | | | | | X | X | X | | | | | X | | | | 11 |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | X | | | | | | | | | 6 |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | X | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | X | X | | X | | 38 |
| Squamous cell carcinoma | | X | | | | | | | | | | | | | | | | | | | | | | | | 1 |

TABLE B2
**Individual Animal Tumor Pathology of Female Rats in the 55-Week Dermal Study of 2,3-Dibromo-1-propanol: 375 mg/kg** (continued)

| **Animal Number** | 01 | 02 | 03 | 04 | 05 | 06 | 07 | 08 | 09 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Weeks on Study** | 053 | 055 | 054 | 043 | 054 | 051 | 053 | 053 | 053 | 041 | 045 | 050 | 055 | 053 | 051 | 052 | 054 | 054 | 048 | 036 | 042 | 053 | 043 | 053 | 052 | 050 |
| **Digestive System** (continued) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | X | X | | | | | | | X | | X | X | X | | X | X | | | X | X | X | |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Small intestine | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenocarcinoma, NOS | | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenomatous polyp, NOS | X | X | X | X | X | X | X | X | X | | X | X | X | | X | X | X | X | | | X | | X | X | X | |
| Rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenomatous polyp, NOS | X | X | | | X | | | | | | | | | | | X | | | | | | | | X | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tubular-cell adenoma | | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Urinary bladder | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma, NOS | | | | | | | | | | | X | X | | | | | | | | | | | | | | |
| Adrenal | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thyroid | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | X |
| C-cell adenoma | | | | | | | | | | | | | | | | | X | | | | | | | | | |
| Parathyroid | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Reproductive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Adenoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adenocarcinoma, NOS | | | | | | | | | | | X | | | | | | X | | | | | | | | | |
| Uterus | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Endometrial stromal polyp | | | | | | | X | | X | | | | X | | | | | | | X | | X | | | | |
| Endometrial stromal sarcoma | | | | | | | | | | | | | | | | | | | | | | X | | | | |
| Ovary | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thecoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Granulosa cell tumor, benign | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

TABLE B2
**Individual Animal Tumor Pathology of Female Rats in the 55-Week Dermal Study of 2,3-Dibromo-1-propanol: 375 mg/kg** (continued)

| Animal Number | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Weeks on Study | 05 | 43 | 38 | 35 | 49 | 33 | 33 | 30 | 00 | 09 | 33 | 30 | 66 | 33 | 98 | 12 | 05 | 50 | 55 | 40 | 50 | 55 | 43 | 55 | 50 | Total Tissues/ Tumors |
| **Digestive System** (continued) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | | | | | X | X | | X | | X | | X | | X | X | X | X | X | | | | | | X | X | 23 |
| Squamous cell carcinoma | | | | | | X | | | | | | | | | | | | | | | | | | | | 1 |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Adenocarcinoma, NOS | | | | | | | | | | | | | | | | X | | | | | X | | | X | | 4 |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenomatous polyp, NOS | | | | X | X | X | X | X | | X | | X | X | X | | X | X | X | | | X | | X | X | | 35 |
| Rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Adenomatous polyp, NOS | | | | X | | | | | X | | | | | | | | | | | | | X | | | | 8 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Tubular-cell adenoma | | | | X | | | | | | X | | | | | | | | | | | | | | X | | 4 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma, NOS | | | | | | | | | | | | | | | | X | | | | | | | | | | 3 |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| C-cell adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Parathyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **Reproductive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| Adenoma, NOS | | | | | | | | | X | X | | | | | | | | | | | X | | | | | 3 |
| Adenocarcinoma, NOS | | | | X | | | | | | | | | | | | | | | | | | | | | | 3 |
| Uterus | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Endometrial stromal polyp | X | | | | X | | | X | | | | | | | | X | | | | | | | | | | 9 |
| Endometrial stromal sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Ovary | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Thecoma | | | | | | | | | | | | | | | | | | | | | | X | | | | 1 |
| Granulosa cell tumor, benign | | | | | | | X | | | | | | | | | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |

TABLE B2
**Individual Animal Tumor Pathology of Female Rats in the 55-Week Dermal Study of 2,3-Dibromo-1-propanol: 375 mg/kg** (continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Animal Number** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 |
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 |
| **Number of Weeks on Study** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 5 | 5 | 5 | 4 | 5 | 5 | 5 | 5 | 5 | 4 | 5 | 5 | 5 | 3 | 5 | 4 | 5 | 4 | 3 | 4 | 5 | 3 | 5 | 5 | 5 |
| | 3 | 2 | 4 | 3 | 4 | 1 | 3 | 3 | 3 | 1 | 0 | 0 | 5 | 1 | 2 | 4 | 4 | 8 | 6 | 2 | 3 | 4 | 3 | 2 | 0 |
| **Special Sense Organs** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Zymbal's gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Adenoma, NOS | | | | | | | | | | | | | | | X | | | | | | | | | X | |
| Adenocarcinoma, NOS | X | X | | X | | X | X | X | | | | X | X | | | | | X | | | | | X | | X |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **All Other Systems** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Leukemia, mononuclear cell | | | | | | | X | | | | | | | | | | | | | | | | | | |

TABLE B2
**Individual Animal Tumor Pathology of Female Rats in the 55-Week Dermal Study of 2,3-Dibromo-1-propanol: 375 mg/kg** (continued)

| Animal Number | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Weeks on Study | 053 | 043 | 038 | 053 | 049 | 053 | 053 | 053 | 050 | 050 | 049 | 053 | 053 | 050 | 046 | 053 | 053 | 049 | 038 | 041 | 045 | 040 | 045 | 055 | 050 | Total Tissues/ Tumors |
| **Special Sense Organs** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Zymbal's gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| Adenoma, NOS | | | | | | | | | | | | | | | | | | | | | | | X | | | 3 |
| Adenocarcinoma, NOS | | | X | | X | | X | | | | | X | | X | | | | | | X | | X | | | X | 19 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **All Other Systems** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| Leukemia, mononuclear cell | | | | | | | | | X | | | | | | | | | | | | | | | | | 2 |

[a] Number of animals necropsied

TABLE B3
**Historical Incidence of Neoplasms in Untreated Female F344/N Rats for Studies Lasting 8 to 13 Months**

| Study | Study Length | Study Laboratory |
|---|---|---|
| Diglycidyl resorcinol ether | 59 weeks | EG&G Mason Research Institute |
| 1,2-Dichloropropane | 41 weeks | EG&G Mason Research Institute |
| Benzyl acetate | 48 weeks | Southern Research Institute |
| Geranyl acetate | 46 weeks | Southern Research Institute |
| **Incidence of Neoplasms**[a] | | |
| Skin | | |
| Epithelial neoplasms (all types) | 0/200 | |
| Liver | | |
| Neoplastic nodule, hepatocellular adenoma, or hepatocellular carcinoma | 0/200 | |
| Small intestine | | |
| Adenomatous polyp, adenoma, or adenocarcinoma | 0/200 | |
| Large intestine | | |
| Adenoma, adenomatous polyp, or adenocarcinoma | 0/200 | |
| Esophagus | | |
| Squamous cell papilloma or carcinoma | 0/200 | |
| Forestomach | | |
| Squamous cell papilloma or carcinoma | 0/200 | |
| Kidney | | |
| Tubule cell adenoma or carcinoma | 0/200 | |
| Clitoral gland | | |
| Adenoma or carcinoma | 0/200 | |
| Mammary gland | | |
| Adenocarcinoma | 0/200 | |
| Oral mucosa | | |
| Squamous cell papilloma or carcinoma | 0/200 | |
| Nose | | |
| Adenoma or carcinoma | 0/200 | |
| Zymbal's gland | | |
| Adenoma or carcinoma | 0/200 | |

[a] Combined data for EG&G Mason Research Institute and Southern Research Institute

TABLE B4
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 55-Week Dermal Study of 2,3-Dibromo-1-propanol**

| | Vehicle Control | 188 mg/kg | 375 mg/kg |
|---|---|---|---|
| **Disposition Summary** | | | |
| Animals initially in study | 50 | 50 | 50 |
| Early deaths | | | |
| Natural deaths | | 1 | 2 |
| Moribund | 2 | 11 | 24 |
| Survivors | | | |
| Died during terminal sacrifice period | | | 3 |
| Terminal sacrifice | 48 | 38 | 21 |
| Animals necropsied | 50 | 50 | 50 |
| Animals examined histopathologically | 50 | 50 | 50 |
| **Integumentary System** | | | |
| Skin[a] | (50) | (50) | (50) |
| Hyperkeratosis | | | 24 (48%) |
| Subcutaneous tissue[a] | (50) | (50) | (50) |
| Inflammation, NOS[b] | | | 1 (2%) |
| **Respiratory System** | | | |
| Lung[c] | (50) | (50) | (50) |
| Inflammation, acute | | | 3 (6%) |
| Inflammation, chronic | 1 (2%) | | |
| Pneumonia, interstitial chronic | | | 1 (2%) |
| Perivascular cuffing | 1 (2%) | | 2 (4%) |
| Nasal cavity[a] | (50) | (50) | (50) |
| Inflammation, chronic | 5 (10%) | 1 (2%) | 2 (4%) |
| Inflammation, chronic focal | | | 1 (2%) |
| Hyperkeratosis | | 1 (2%) | 1 (2%) |
| Dysplasia, epithelial | 1 (2%) | 49 (98%) | 50 (100%) |
| **Hematopoietic System** | | | |
| Spleen[c] | (50) | (50) | (49) |
| Hemosiderosis | 1 (2%) | 16 (32%) | 7 (14%) |
| Angiectasis | | 1 (2%) | |
| Splenic red pulp[c] | (50) | (50) | (49) |
| Hyperplasia, NOS | | 2 (4%) | 2 (4%) |
| Thymus[c] | (50) | (50) | (47) |
| Hemorrhage | 1 (2%) | | |
| **Circulatory System** | | | |
| Heart[c] | (50) | (50) | (49) |
| Inflammation, chronic | 1 (2%) | | |
| Myocardium[c] | (50) | (50) | (49) |
| Degeneration, NOS | 1 (2%) | 2 (4%) | |

TABLE B4
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 55-Week Dermal Study of 2,3-Dibromo-1-propanol** (continued)

| | Vehicle Control | 188 mg/kg | 375 mg/kg |
|---|---|---|---|
| **Digestive System** | | | |
| Palate[a] | (50) | (50) | (50) |
| Inflammation, NOS | | | 1 (2%) |
| Hyperkeratosis | | 1 (2%) | |
| Acanthosis | | | 1 (2%) |
| Tongue[a] | (50) | (50) | (50) |
| Hyperkeratosis | | 4 (8%) | |
| Acanthosis | | | 1 (2%) |
| Inflammation, chronic | 1 (2%) | | |
| Hyperplasia, epithelial | | 4 (8%) | |
| Liver[c] | (50) | (50) | (50) |
| Cyst, NOS | | | 1 (2%) |
| Degeneration, NOS | | | 1 (2%) |
| Pigmentation, NOS | | 2 (4%) | |
| Nuclear alteration | | | 1 (2%) |
| Basophilic cytoplasm change | 5 (10%) | 27 (54%) | 19 (38%) |
| Clear-cell change | 1 (2%) | 8 (16%) | 7 (14%) |
| Pleomorphism | | | 44 (88%) |
| Atrophy, NOS | | 1 (2%) | |
| Hyperplasia, focal | | 2 (4%) | |
| Hyperplasia, lymphoid | | 1 (2%) | |
| Angiectasis | | 1 (2%) | 3 (6%) |
| Eosinophilic cyto change | | 1 (2%) | 3 (6%) |
| Periportal bile duct[c] | (50) | (50) | (50) |
| Hyperplasia, NOS | 1 (2%) | 6 (12%) | 37 (74%) |
| Liver/centrilobular[c] | (50) | (50) | (50) |
| Lipoidosis | | 2 (4%) | |
| Liver/periportal[c] | (50) | (50) | (50) |
| Inflammation, NOS | | 1 (2%) | |
| Liver/hepatocytes[c] | (50) | (50) | (50) |
| Necrosis, NOS | | 2 (4%) | |
| Pancreas[c] | (50) | (50) | (50) |
| Inflammation, chronic | 1 (2%) | 1 (2%) | |
| Atrophy, NOS | | 1 (2%) | 4 (8%) |
| Atrophy, focal | 2 (4%) | | |
| Pharynx[a] | (50) | (50) | (50) |
| Ulcer, NOS | | | 1 (2%) |
| Acanthosis | | | 1 (2%) |
| Esophagus[c] | (50) | (50) | (50) |
| Hyperkeratosis | 1 (2%) | 20 (40%) | 49 (98%) |
| Glandular stomach[c] | (50) | (50) | (50) |
| Erosion | | | 1 (2%) |
| Forestomach[c] | (50) | (50) | (50) |
| Ulcer, NOS | | | 2 (4%) |
| Hyperkeratosis | | 6 (12%) | 30 (60%) |
| Acanthosis | | | 1 (2%) |
| Dysplasia, epithelial | | 1 (2%) | 8 (16%) |
| Hyperplasia | | 2 (4%) | 4 (8%) |
| Rectum | | | |
| Hyperplasia, adenomatous | | 1 (2%) | |

TABLE B4
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 55-Week Dermal Study of 2,3-Dibromo-1-propanol** (continued)

| | Vehicle Control | 188 mg/kg | 375 mg/kg |
|---|---|---|---|
| **Urinary System** | | | |
| Kidney[c] | (50) | (50) | (50) |
| Hemorrhage | 1 (2%) | | |
| Nephropathy | 30 (60%) | 37 (74%) | 43 (86%) |
| Hyperplasia, tubular cell | | 1 (2%) | 2 (4%) |
| Kidney/tubule[c] | (50) | (50) | (50) |
| Nuclear enlargement | | 6 (12%) | 47 (94%) |
| **Endocrine System** | | | |
| Pituitary intermedia[c] | (50) | (50) | (50) |
| Colloid cyst | | 2 (4%) | |
| Angiectasis | 1 (2%) | | |
| Anterior pituitary[c] | (50) | (50) | (50) |
| Congenital malformation, NOS | | 1 (2%) | |
| Colloid cyst | 4 (8%) | 21 (42%) | 2 (4%) |
| Hemorrhage | | | 1 (2%) |
| Hyperplasia, focal | 6 (12%) | 9 (18%) | 1 (2%) |
| Angiectasis | 3 (6%) | 2 (4%) | |
| Adrenal[c] | (50) | (50) | (49) |
| Hematopoiesis | | | 1 (2%) |
| Adrenal cortex[c] | (50) | (50) | (49) |
| Hyperplasia, focal | | 1 (2%) | 1 (2%) |
| Angiectasis | 1 (2%) | | |
| Adrenal medulla[c] | (50) | (50) | (49) |
| Hyperplasia, focal | | 1 (2%) | |
| Thyroid[c] | (50) | (50) | (49) |
| Congenital malformation, NOS | | 1 (2%) | |
| Hyperplasia, C-cell | 1 (2%) | | |
| **Reproductive System** | | | |
| Clitoral gland[a] | (50) | (50) | (50) |
| Inflammation, NOS | | | 1 (2%) |
| Uterus[c] | (50) | (50) | (48) |
| Cyst, NOS | | | 3 (6%) |
| Inflammation, NOS | 1 (2%) | | |
| Dysplasia, epithelial | | | 1 (2%) |
| Ovary[c] | (50) | (50) | (48) |
| Cyst, NOS | | 1 (2%) | |
| **Nervous System** | | | |
| Brain[c] | (50) | (50) | (49) |
| Epidermal inclusion cyst | | | 1 (2%) |

TABLE B4
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 55-Week Dermal Study of 2,3-Dibromo-1-propanol** (continued)

| | Vehicle Control | 188 mg/kg | 375 mg/kg |
|---|---|---|---|
| **Special Sense Organs** | | | |
| Eye[a] | (50) | (50) | (50) |
| Degeneration, NOS | 1 (2%) | | |
| Eye/retina[a] | (50) | (50) | (50) |
| Degeneration, NOS | 1 (2%) | | |
| Harderian gland[a] | (50) | (50) | (50) |
| Inflammation, chronic | 1 (2%) | | |
| Ear[a] | (50) | (50) | (50) |
| Inflammation, granulomatous | | | 1 (2%) |
| Zymbal's gland[a] | (50) | (50) | (50) |
| Cyst, NOS | | 2 (4%) | |
| **Musculoskeletal System** | | | |
| Vertebra[a] | (50) | (50) | (50) |
| Callus | | 1 (2%) | |
| Skeletal muscle[a] | (50) | (50) | (50) |
| Degeneration, Zenker's | 1 (2%) | | |
| **All Other Systems** | | | |
| Adipose tissue | | | |
| Necrosis, fat | | 6 | 2 |
| Tail | | | |
| Congenital malformation, NOS | | 1 | |
| Inflammation, necrotizing | | 1 | |
| **Special Morphology Summary** | | | |
| No lesion reported | 18 | | |

[a] Number of animals necropsied
[b] NOS=not specified
[c] Number of animals with tissue examined microscopically

# APPENDIX C
# SUMMARY OF LESIONS IN MALE MICE IN THE 39-WEEK DERMAL STUDY OF 2,3-DIBROMO-1-PROPANOL


| | | |
|---|---|---|
| TABLE C1 | Summary of the Incidence of Neoplasms in Male Mice in the 39-Week Dermal Study of 2,3-Dibromo-1-propanol | 126 |
| TABLE C2 | Individual Animal Tumor Pathology of Male Mice in the 39-Week Dermal Study of 2,3-Dibromo-1-propanol | 128 |
| TABLE C3 | Historical Incidence of Neoplasms in Untreated Male B6C3F$_1$ Mice for Studies Lasting 9 to 14 Months | 140 |
| TABLE C4 | Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 39-Week Dermal Study of 2,3-Dibromo-1-propanol | 141 |

TABLE C1
**Summary of the Incidence of Neoplasms in Male Mice in the 39-Week Dermal Study of 2,3-Dibromo-1-propanol**

| | Vehicle Control | 88 mg/kg | 177 mg/kg |
|---|---|---|---|
| **Disposition Summary** | | | |
| Animals initially in study | 50 | 50 | 50 |
| Survivors | | | |
| Died during terminal sacrifice period | | 1 | |
| Terminal sacrifice | 50 | 49 | 50 |
| Animals necropsied | 50 | 50 | 50 |
| Animals examined histopathologically | 50 | 50 | 50 |
| **Integumentary System** | | | |
| Skin[a] | (50) | (50) | (50) |
| Squamous cell papilloma | | 3 (6%) | 9 (18%) |
| Squamous cell carcinoma | | | 2 (4%) |
| Sebaceous adenoma | | 1 (2%) | 8 (16%)[b] |
| Subcutaneous tissue[a] | (50) | (50) | (50) |
| Sarcoma, NOS[c] | | 1 (2%) | |
| **Respiratory System** | | | |
| Lung[d] | (50) | (50) | (50) |
| Alveolar/bronchiolar adenoma | 1 (2%) | 1 (2%) | 6 (12%) |
| **Hematopoietic System** | | | |
| None | | | |
| **Circulatory System** | | | |
| None | | | |
| **Digestive System** | | | |
| Liver[d] | (50) | (50) | (50) |
| Hepatocellular adenoma | 1 (2%) | 2 (4%) | 9 (18%) |
| Hepatocellular carcinoma | | | 3 (6%) |
| Glandular stomach[d] | (50) | (50) | (49) |
| Squamous cell carcinoma, invasive | | | 1 (2%) |
| Forestomach[d] | (50) | (50) | (49) |
| Squamous cell papilloma | | 12 (24%) | 20 (41%) |
| Squamous cell carcinoma | | 2 (4%) | 1 (2%) |
| **Urinary System** | | | |
| None | | | |
| **Endocrine System** | | | |
| Adrenal medulla[d] | (50) | (49) | (50) |
| Pheochromocytoma | 1 (2%) | | |

TABLE C1
**Summary of the Incidence of Neoplasms in Male Mice in the 39-Week Dermal Study of 2,3-Dibromo-1-propanol**
(continued)

| | Vehicle Control | 88 mg/kg | 177 mg/kg |
|---|---|---|---|
| **Reproductive System** | | | |
| None | | | |
| **Nervous System** | | | |
| None | | | |
| **Special Sense Organs** | | | |
| None | | | |
| **Musculoskeletal System** | | | |
| None | | | |
| **All Other Systems** | | | |
| None | | | |
| **Neoplasm Summary** | | | |
| Total animals with primary neoplasms[e] | 3 | 20 | 33 |
| Total primary neoplasms | 3 | 22 | 59 |
| Total animals with benign neoplasms | 3 | 17 | 30 |
| Total benign neoplasms | 3 | 19 | 53 |
| Total animals with malignant neoplasms | | 3 | 6 |
| Total malignant neoplasms | | 3 | 6 |
| Total animals with metastatic neoplasms | | | 1 |
| Total metastatic neoplasms | | | 1 |

[a] Number of animals necropsied
[b] Multiple occurrence of morphology in the same organ tissue is counted only once.
[c] NOS=not specified
[d] Number of animals with tissue examined microscopically
[e] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 39-Week Dermal Study of 2,3-Dibromo-1-propanol: Vehicle Control**

| Animal Number | 0 1 | 0 2 | 0 3 | 0 4 | 0 5 | 0 6 | 0 7 | 0 8 | 0 9 | 1 0 | 1 1 | 1 2 | 1 3 | 1 4 | 1 5 | 1 6 | 1 7 | 1 8 | 1 9 | 2 0 | 2 1 | 2 2 | 2 3 | 2 4 | 2 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Weeks on Study** | 0 3 6 | 0 3 6 | 0 3 6 | 0 3 6 | 0 3 6 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 8 | 0 3 8 | 0 3 8 | 0 3 8 | 0 3 8 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Subcutaneous tissue | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Mammary gland | N | N | N | N | N | N | N | N | N | N | + | N | N | N | N | N | N | N | N | N | N | + | N | N | N |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Circulatory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Digestive System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular adenoma | | | | | | | | | | X | | | | | | | | | | | | | | | |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder & common bile duct | + | + | + | + | + | + | + | + | + | + | N | N | + | N | + | N | + | + | + | + | + | + | + | + | + |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

+: Tissue examined microscopically
–: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
m: Multiple occurrences of morphology
NOS: Not specified
Blank: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 39-Week Dermal Study of 2,3-Dibromo-1-propanol: Vehicle Control** (continued)

| Animal Number | 2 6 | 2 7 | 2 8 | 2 9 | 3 0 | 3 1 | 3 2 | 3 3 | 3 4 | 3 5 | 3 6 | 3 7 | 3 8 | 3 9 | 4 0 | 4 1 | 4 2 | 4 3 | 4 4 | 4 5 | 4 6 | 4 7 | 4 8 | 4 9 | 5 0 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Weeks on Study** | 0 3 8 | 0 3 8 | 0 3 8 | 0 3 8 | 0 3 8 | 0 3 8 | 0 3 8 | 0 3 8 | 0 3 8 | 0 3 8 | 0 3 9 | 0 3 9 | 0 3 9 | 0 3 9 | 0 3 9 | 0 3 9 | 0 3 9 | 0 3 9 | 0 3 9 | 0 3 9 | 0 3 9 | 0 3 9 | 0 3 9 | 0 3 9 | 0 3 9 | **Total Tissues/ Tumors** |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Subcutaneous tissue | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Mammary gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Circulatory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Digestive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder & common bile duct | + | N | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 39-Week Dermal Study of 2,3-Dibromo-1-propanol: Vehicle Control** (continued)

| Animal Number | 0 1 | 0 2 | 0 3 | 0 4 | 0 5 | 0 6 | 0 7 | 0 8 | 0 9 | 1 0 | 1 1 | 1 2 | 1 3 | 1 4 | 1 5 | 1 6 | 1 7 | 1 8 | 1 9 | 2 0 | 2 1 | 2 2 | 2 3 | 2 4 | 2 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Weeks on Study** | 0 3 6 | 0 3 6 | 0 3 6 | 0 3 6 | 0 3 6 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 8 | 0 3 8 | 0 3 8 | 0 3 8 | 0 3 8 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – |
| **Reproductive System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Testis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Sense Organs** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **All Other Systems** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 39-Week Dermal Study of 2,3-Dibromo-1-propanol: Vehicle Control** (continued)

| Animal Number | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Weeks on Study | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 039 | 039 | 039 | 039 | 039 | 039 | 039 | 039 | 039 | 039 | 039 | 039 | 039 | 039 | 039 | Total Tissues/ Tumors |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pheochromocytoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| **Reproductive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Testis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Sense Organs** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **All Other Systems** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 39-Week Dermal Study of 2,3-Dibromo-1-propanol: 88 mg/kg**

| Animal Number | 0 1 | 0 2 | 0 3 | 0 4 | 0 5 | 0 6 | 0 7 | 0 8 | 0 9 | 1 0 | 1 1 | 1 2 | 1 3 | 1 4 | 1 5 | 1 6 | 1 7 | 1 8 | 1 9 | 2 0 | 2 1 | 2 2 | 2 3 | 2 4 | 2 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Weeks on Study** | 0 3 6 | 0 3 6 | 0 3 6 | 0 3 6 | 0 3 6 | 0 3 6 | 0 3 6 | 0 3 6 | 0 3 6 | 0 3 6 | 0 3 6 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Sebaceous adenoma | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Sarcoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | N | + | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | X | | | | | | | | | | | | | |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + |
| **Circulatory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Digestive System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular adenoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder & common bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | X | | | | | | | | | | | | | | X | | X | |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 39-Week Dermal Study of 2,3-Dibromo-1-propanol: 88 mg/kg** (continued)

| Animal Number | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Weeks on Study | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 039 | 069 | 099 | 099 | 099 | 099 | 099 | 099 | 099 | Total Tissues/ Tumors |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Squamous cell papilloma | | | | | | | X | | | | | | | | | X | | | | | | | | | | 3 |
| Sebaceous adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Sarcoma, NOS | | | | | | | | | | | | | | | | | X | | | | | | | | | 1 |
| Mammary gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| **Circulatory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Digestive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | | | | | | | | | X | 2 |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder & common bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | X | | | X | X | X | | | X | | X | | | | | X | | | X | | | X | | | | 12 |
| Squamous cell carcinoma | | | | | | | | X | | | | | | X | | | | | | | | | | | | 2 |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 39-Week Dermal Study of 2,3-Dibromo-1-propanol: 88 mg/kg** (continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Animal Number** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 |
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 |
| **Number of Weeks on Study** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | – |
| **Reproductive System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Testis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Sense Organs** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **All Other Systems** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 39-Week Dermal Study of 2,3-Dibromo-1-propanol: 88 mg/kg** (continued)

| Animal Number | 2 2 2 2 3 3 3 3 3 3 3 3 3 3 4 4 4 4 4 4 4 4 4 5<br>6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 | |
|---|---|---|
| Number of Weeks on Study | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0<br>3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3<br>8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 9 6 9 9 9 9 9 9 9 | Total Tissues/ Tumors |
| **Endocrine System** | | |
| Pituitary | + + + + + + – + + + + + + + + + + + + + + + + + + | 49 |
| Adrenal | + + + + + + + + + + + + + + + + + + + + + + + + + | 49 |
| Thyroid | + + + + + + + + + + + + + + + + + + + + + + + + + | 50 |
| Parathyroid | + + + + + + + + + + + + + + + + + + + + + + + + + | 47 |
| **Reproductive System** | | |
| Testis | + + + + + + + + + + + + + + + + + + + + + + + + + | 50 |
| Prostate | + + + + + + + + + + + + + + + + + + + + + + + + + | 50 |
| **Nervous System** | | |
| Brain | + + + + + + + + + + + + + + + + + + + + + + + + + | 50 |
| **Special Sense Organs** | | |
| None | | |
| **Musculoskeletal System** | | |
| None | | |
| **All Other Systems** | | |
| None | | |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 39-Week Dermal Study of 2,3-Dibromo-1-propanol: 177 mg/kg**

| Animal Number | 0 1 | 0 2 | 0 3 | 0 4 | 0 5 | 0 6 | 0 7 | 0 8 | 0 9 | 1 0 | 1 1 | 1 2 | 1 3 | 1 4 | 1 5 | 1 6 | 1 7 | 1 8 | 1 9 | 2 0 | 2 1 | 2 2 | 2 3 | 2 4 | 2 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Weeks on Study** | 0 3 6 | 0 3 6 | 0 3 6 | 0 3 6 | 0 3 6 | 0 3 6 | 0 3 6 | 0 3 6 | 0 3 6 | 0 3 6 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 | 0 3 7 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | X | | | | | | | | | | | | | |
| Squamous cell carcinoma | | | | | X | | | | | | | | | | | X | | | | | | | | | |
| Sebaceous adenoma | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | + |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | X | | | | | X | | | | | | | | | | X | | | | | | |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + |
| **Circulatory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Digestive System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular adenoma | | | | X | | | | X | X | | | | | | | | | X | | | | | | | |
| Hepatocellular carcinoma | | | | | | | | | | | X | | | | | | | | | | | | | | |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder & common bile duct | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + | N | N | + | + | + |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | X | | X | X | | | | X | X | | | X | | | | | | | | | | | X | | |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Squamous cell carcinoma, invasive | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 39-Week Dermal Study of 2,3-Dibromo-1-propanol: 177 mg/kg** (continued)

| Animal Number | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Weeks on Study | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 039 | 039 | 039 | 039 | 039 | 039 | 039 | 039 | 039 | Total Tissues/ Tumors |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Squamous cell papilloma | X | | X | | X | | X | X | | | X | | | | | | | | | | X | | | X | | 9 |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Sebaceous adenoma | | | | X | | m | | | X | X | | | | | | X | | | | | | | | X | X | 8 |
| Mammary gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | | | X | | | | | | | | X | | | X | | | | | | | | | | | | 6 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **Circulatory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Digestive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hepatocellular adenoma | | | X | | X | | | | | | | | | | | | | | X | | | X | X | | | 9 |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | | | X | X | | | | | | 3 |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder & common bile duct | + | N | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Esophagus | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Squamous cell papilloma | | | | X | X | X | | | X | X | X | | | X | X | X | X | | | | X | X | | X | | 20 |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Squamous cell carcinoma, invasive | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 39-Week Dermal Study of 2,3-Dibromo-1-propanol: 177 mg/kg** (continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Animal Number** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 |
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 |
| **Number of Weeks on Study** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | – |
| **Reproductive System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Testis | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Sense Organs** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **All Other Systems** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |

TABLE C2
**Individual Animal Tumor Pathology of Male Mice in the 39-Week Dermal Study of 2,3-Dibromo-1-propanol: 177 mg/kg** (continued)

| Animal Number | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Weeks on Study | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 038 | 039 | 039 | 039 | 039 | 039 | 039 | 039 | 039 | 039 | 039 | Total Tissues/ Tumors |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | 46 |
| **Reproductive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Testis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Sense Organs** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **All Other Systems** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |

[a] Number of animals necrospied

TABLE C3
**Historical Incidence of Neoplasms in Untreated Male B6C3F$_1$ Mice in Studies Lasting 9 to 14 Months**

| Study | Study Length | Study Laboratory |
|---|---|---|
| Diglycidyl resorcinol ether | 62 weeks | EG&G Mason Research Institute |
| 1,2-Dichloropropane | 41 weeks | EG&G Mason Research Institute |
| Benzyl acetate | 62 weeks | Southern Research Institute |
| Geranyl acetate | 44 weeks | Southern Research Institute |
| **Incidence of Neoplasms**[a] | | |
| Skin | | |
| Epithelial neoplasms (all types) | 0/200 | |
| Lung | | |
| Alveolar/bronchiolar adenoma or carcinoma | 7/199 | |
| Liver | | |
| Hepatocellular adenoma or carcinoma | 6/200 | |
| Forestomach | | |
| Squamous cell papilloma or carcinoma | 0/199 | |

[a] Combined data for EG&G Mason Research Institute and Southern Research Institute

TABLE C4
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 39-Week Dermal Study of 2,3-Dibromo-1-propanol**

| | Vehicle Control | 88 mg/kg | 177 mg/kg |
|---|---|---|---|
| **Disposition Summary** | | | |
| Animals initially in study | 50 | 50 | 50 |
| Survivors | | | |
| Died during terminal sacrifice period | | 1 | |
| Terminal sacrifice | 50 | 49 | 50 |
| Animals necropsied | 50 | 50 | 50 |
| Animals examined histopathologically | 50 | 50 | 50 |
| **Integumentary System** | | | |
| Skin[a] | (50) | (50) | (50) |
| Epidermal inclusion cyst | | | 1 (2%) |
| Inflammation, NOS[b] | 1 (2%) | 3 (6%) | |
| Inflammation, focal | | 4 (8%) | 2 (4%) |
| Fibrosis, diffuse | | | 1 (2%) |
| Calcification, dystrophic | | 1 (2%) | |
| Hyperplasia, NOS | | 1 (2%) | 9 (18%) |
| Hyperplasia, epithelial | | 6 (12%) | 3 (6%) |
| Hyperplasia, focal | | | 1 (2%) |
| Subcutaneous tissue[a] | (50) | (50) | (50) |
| Mastocytosis | | | 1 (2%) |
| **Respiratory System** | | | |
| Lung/bronchiole[c] | (50) | (50) | (50) |
| Pleomorphism | | 50 (100%) | 50 (100%) |
| Lung[c] | (50) | (50) | (50) |
| Hyperplasia, focal | | 1 (2%) | 6 (12%) |
| Histiocytosis | | | 1 (2%) |
| **Hematopoietic System** | | | |
| Splenic red pulp[c] | (50) | (50) | (50) |
| Hyperplasia, NOS | | 1 (2%) | |
| Lymph node[c] | (50) | (50) | (50) |
| Hyperplasia, NOS | | 1 (2%) | |
| **Circulatory System** | | | |
| None | | | |
| **Digestive System** | | | |
| Liver[c] | (50) | (50) | (50) |
| Necrosis, coagulative | | | 1 (2%) |
| Basophilic cyto change | | 1 (2%) | 2 (4%) |
| Eosinophilic cyto change | | | 11 (22%) |

TABLE C4
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 39-Week Dermal Study of 2,3-Dibromo-1-propanol** (continued)

| | Vehicle Control | 88 mg/kg | 177 mg/kg |
|---|---|---|---|
| **Digestive System** (continued) | | | |
| Liver/hepatocytes[c] | (50) | (50) | (50) |
| Inclusion, nuclear | | | 1 (2%) |
| Pancreas[c] | (50) | (50) | (50) |
| Necrosis, focal | | | 1 (2%) |
| Atrophy, NOS | 2 (4%) | | 1 (2%) |
| Glandular stomach[c] | (50) | (50) | (49) |
| Inflammation, NOS | | | 1 (2%) |
| Forestomach[c] | (50) | (50) | (49) |
| Hyperplasia, epithelial | | 2 (4%) | |
| Dysplasia, epithelial | | 14 (28%) | 33 (67%) |
| **Urinary System** | | | |
| Kidney[c] | (50) | (50) | (50) |
| Cyst, NOS | 1 (2%) | | |
| **Endocrine System** | | | |
| Parathyroid[c] | (48) | (47) | (46) |
| Cyst, NOS | | 1 (2%) | |
| **Reproductive System** | | | |
| Seminal vesicle[a] | (50) | (50) | (50) |
| Inflammation, NOS | | 1 (2%) | |
| Testis[c] | (50) | (50) | (49) |
| Aspermatogenesis | | | 1 (2%) |
| Epididymis[a] | (50) | (50) | (50) |
| Granuloma, spermatic | | 1 (2%) | 2 (4%) |
| **Nervous System** | | | |
| None | | | |
| **Special Sense Organs** | | | |
| None | | | |
| **Musculoskeletal System** | | | |
| Skeletal muscle[a] | (50) | (50) | (50) |
| Degeneration, NOS | | 1 (2%) | |
| Degeneration, Zenker's | | 1 (2%) | |
| Regeneration, NOS | 1 (2%) | | 1 (2%) |

TABLE C4
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 39-Week Dermal Study of 2,3-Dibromo-1-propanol** (continued)

| | Vehicle Control | 88 mg/kg | 177 mg/kg |
|---|---|---|---|
| **All Other Systems** | | | |
| Multiple organs[a] | (50) | (50) | (50) |
| Atypia, NOS | | | 2 (4%) |
| Hyperplasia, lymphoid | | | 1 (2%) |
| **Special Morphology Summary** | | | |
| No lesion reported | 43 | | |

[a] Number of animals necropsied
[b] NOS=not specified
[c] Number of animals with tissue examined microscopically

# APPENDIX D
# SUMMARY OF LESIONS IN FEMALE MICE IN THE 42-WEEK DERMAL STUDY OF 2,3-DIBROMO-1-PROPANOL


| | | |
|---|---|---|
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TABLE D1
**Summary of the Incidence of Neoplasms in Female Mice in the 42-Week Dermal Study of 2,3-Dibromo-1-propanol**

| | Vehicle Control | 88 mg/kg | 177 mg/kg |
|---|---|---|---|
| **Disposition Summary** | | | |
| Animals initially in study | 50 | 50 | 50 |
| Early deaths | | | |
| Natural deaths | | 2 | |
| Survivors | | | |
| Terminal sacrifice | 50 | 48 | 50 |
| Animals necropsied | 50 | 50 | 50 |
| Animals examined histopathologically | 50 | 50 | 50 |
| **Integumentary System** | | | |
| Skin[a] | (50) | (50) | (50) |
| Squamous cell papilloma | | 1 (2%) | 5 (10%) |
| Squamous cell carcinoma | | | 1 (2%) |
| Sebaceous adenoma | | 3 (6%) | 2 (4%) |
| Keratoacanthoma | | | 1 (2%) |
| Mammary gland[a] | (50) | (50) | (50) |
| Adenocarcinoma, NOS[b] | 1 (2%) | | |
| **Respiratory System** | | | |
| Lung[c] | (50) | (50) | (50) |
| Alveolar/bronchiolar adenoma | | 3 (6%) | 4 (8%) |
| Alveolar/bronchiolar carcinoma | 1 (2%) | | |
| **Hematopoietic System** | | | |
| None | | | |
| **Circulatory System** | | | |
| None | | | |
| **Digestive System** | | | |
| Liver[c] | (50) | (50) | (50) |
| Hepatocellular adenoma | | | 1 (2%) |
| Hepatocellular carcinoma | 1 (2%) | | |
| Esophagus[c] | (50) | (50) | (50) |
| Squamous cell papilloma | | 1 (2%) | |
| Forestomach[c] | (50) | (49) | (50) |
| Squamous cell papilloma | | 12 (24%) | 17 (34%) |
| Squamous cell carcinoma | | 7 (14%) | 6 (12%) |
| **Urinary System** | | | |
| None | | | |

TABLE D1
**Summary of the Incidence of Neoplasms in Female Mice in the 42-Week Dermal Study of 2,3-Dibromo-1-propanol**
(continued)

| | Vehicle Control | 88 mg/kg | 177 mg/kg |
|---|---|---|---|
| **Endocrine System** | | | |
| None | | | |
| **Reproductive System** | | | |
| Uterus[c] | (50) | (50) | (50) |
| Endometrial stromal polyp | 2 (4%) | 5 (10%) | 7 (14%) |
| **Nervous System** | | | |
| None | | | |
| **Special Sense Organs** | | | |
| None | | | |
| **Musculoskeletal System** | | | |
| None | | | |
| **All Other Systems** | | | |
| Multiple organs[a] | (50) | (50) | (50) |
| Malignant lymphoma, mixed type | 1 (2%) | | |
| **Neoplasm Summary** | | | |
| Total animals with primary neoplasms[d] | 5 | 26 | 28 |
| Total primary neoplasms | 6 | 32 | 44 |
| Total animals with benign neoplasms | 2 | 21 | 27 |
| Total benign neoplasms | 2 | 25 | 37 |
| Total animals with malignant neoplasms | 4 | 7 | 7 |
| Total malignant neoplasms | 4 | 7 | 7 |

[a] Number of animals necropsied
[b] NOS=not specified
[c] Number of animals with tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 42-Week Dermal Study of 2,3-Dibromo-1-propanol: Vehicle Control**

| Animal Number | 0 1 | 0 2 | 0 3 | 0 4 | 0 5 | 0 6 | 0 7 | 0 8 | 0 9 | 1 0 | 1 1 | 1 2 | 1 3 | 1 4 | 1 5 | 1 6 | 1 7 | 1 8 | 1 9 | 2 0 | 2 1 | 2 2 | 2 3 | 2 4 | 2 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Weeks on Study** | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 1 4 1 | 1 4 1 | 1 4 1 | 1 4 1 | 1 4 1 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenocarcinoma, NOS | X | | | | | | | | | | | | | | | | | | | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | X | | | | | | | | | | | | | | |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Circulatory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Digestive System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder & common bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

+: Tissue examined microscopically
–: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
NOS: Not specified
Blank: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 42-Week Dermal Study of 2,3-Dibromo-1-propanol: Vehicle Control** (continued)

| Animal Number | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Weeks on Study | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | Total Tissues/ Tumors |
| | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Adenocarcinoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Circulatory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Digestive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | | | | X | | | | | | 1 |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder & common bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 42-Week Dermal Study of 2,3-Dibromo-1-propanol: Vehicle Control** (continued)

| Animal Number | 0 1 | 0 2 | 0 3 | 0 4 | 0 5 | 0 6 | 0 7 | 0 8 | 0 9 | 1 0 | 1 1 | 1 2 | 1 3 | 1 4 | 1 5 | 1 6 | 1 7 | 1 8 | 1 9 | 2 0 | 2 1 | 2 2 | 2 3 | 2 4 | 2 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Weeks on Study** | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 1 | 0 4 1 | 0 4 1 | 0 4 1 | 0 4 1 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Reproductive System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Endometrial stromal polyp | X | | | | | | | | | | | | | | | | | | X | | | | | | |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Sense Organs** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **All Other Systems** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Malignant lymphoma, mixed type | | | | | | | | | | | | | | X | | | | | | | | | | | |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 42-Week Dermal Study of 2,3-Dibromo-1-propanol: Vehicle Control** (continued)

| Animal Number | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Weeks on Study | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | Total Tissues/ Tumors |
| | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Reproductive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Endometrial stromal polyp | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Sense Organs** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **All Other Systems** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |
| Malignant lymphoma, mixed type | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 42-Week Dermal Study of 2,3-Dibromo-1-propanol: 88 mg/kg**

| Animal Number | 0 1 | 0 2 | 0 3 | 0 4 | 0 5 | 0 6 | 0 7 | 0 8 | 0 9 | 1 0 | 1 1 | 1 2 | 1 3 | 1 4 | 1 5 | 1 6 | 1 7 | 1 8 | 1 9 | 2 0 | 2 1 | 2 2 | 2 3 | 2 4 | 2 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Weeks on Study** | 0 3 9 | 0 3 9 | 0 3 9 | 0 3 9 | 0 3 9 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 3 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 1 | 0 4 1 | 0 4 1 | 0 4 1 | 0 4 1 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Sebaceous adenoma | | | | | | | | | | | X | | | | | | | | | | | | | | X |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | X | X | | | | | | | | | | | | | | | | | | | | | | | |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Circulatory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Digestive System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder & common bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | X | | X | | X | X | | | X | | | | | | | | X | X | X | |
| Squamous cell carcinoma | | | | X | | | | | | | | | | | | | | | X | X | | | X | | |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 42-Week Dermal Study of 2,3-Dibromo-1-propanol: 88 mg/kg** (continued)

| Animal Number | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Weeks on Study | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 02 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | 04 | Total Tissues/ Tumors |
| | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 10 | 11 | 11 | 11 | 11 | 11 | 11 | 12 | 22 | 22 | 22 | 22 | 22 | 22 | 22 | 22 | 22 | |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Sebaceous adenoma | | | | | | | | | | | X | | | | | | | | | | | | | | | 3 |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | X | | 3 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **Circulatory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Digestive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | | 49 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | 50 |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | 50 |
| Gallbladder & common bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | 50[a] |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | 50 |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | 50 |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | X | | | | | | | | | 1 |
| Stomach | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | 49 |
| Squamous cell papilloma | | | | | | | X | X | | | | | | | | | X | | | | | | | X | | 12 |
| Squamous cell carcinoma | | | | X | | | | | | | | | | | | | | | X | X | | | | | | 7 |
| Small intestine | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | 49 |
| Large intestine | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | 49 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | 49 |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 42-Week Dermal Study of 2,3-Dibromo-1-propanol: 88 mg/kg** (continued)

| Animal Number | 0 1 | 0 2 | 0 3 | 0 4 | 0 5 | 0 6 | 0 7 | 0 8 | 0 9 | 1 0 | 1 1 | 1 2 | 1 3 | 1 4 | 1 5 | 1 6 | 1 7 | 1 8 | 1 9 | 2 0 | 2 1 | 2 2 | 2 3 | 2 4 | 2 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Weeks on Study** | 0 3 9 | 0 3 9 | 0 3 9 | 0 3 9 | 0 3 9 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 3 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 1 | 0 4 1 | 0 4 1 | 0 4 1 | 0 4 1 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + |
| **Reproductive System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Endometrial stromal polyp | | | | | | | | | X | | | | | | | | | | | | | | | | |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Sense Organs** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **All Other Systems** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 42-Week Dermal Study of 2,3-Dibromo-1-propanol: 88 mg/kg** (continued)

| Animal Number | 22 26 | 22 27 | 22 28 | 22 29 | 23 30 | 23 31 | 23 32 | 23 33 | 23 34 | 23 35 | 23 36 | 23 37 | 23 38 | 23 39 | 24 40 | 24 41 | 24 42 | 24 43 | 24 44 | 24 45 | 24 46 | 24 47 | 24 48 | 24 49 | 25 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Weeks on Study** | 04 41 | 04 41 | 04 41 | 04 41 | 04 41 | 04 41 | 04 41 | 04 41 | 02 10 | 04 41 | 04 41 | 04 41 | 04 41 | 04 41 | 04 41 | 04 41 | 04 42 | 04 42 | 04 42 | 04 42 | 04 42 | 04 42 | 04 42 | 04 42 | 04 42 | **Total Tissues/ Tumors** |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| **Reproductive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Endometrial stromal polyp | | | | | | | | | | | | X | | X | | | | X | | | | | | | X | 5 |
| Ovary | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Sense Organs** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **All Other Systems** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 42-Week Dermal Study of 2,3-Dibromo-1-propanol: 177 mg/kg**

| Animal Number | 0 1 | 0 2 | 0 3 | 0 4 | 0 5 | 0 6 | 0 7 | 0 8 | 0 9 | 1 0 | 1 1 | 1 2 | 1 3 | 1 4 | 1 5 | 1 6 | 1 7 | 1 8 | 1 9 | 2 0 | 2 1 | 2 2 | 2 3 | 2 4 | 2 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Weeks on Study** | 0 3 9 | 0 3 9 | 0 3 9 | 0 3 9 | 0 3 9 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 0 | 0 4 1 | 0 4 1 | 0 4 1 | 0 4 1 | 0 4 1 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | X | | | | | | | | | | | | | | | | X | | | | | | | |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Sebaceous adenoma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Keratoacanthoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | X | | | | | | | | | | | | | | | | | | X | X | | | | | |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Circulatory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Digestive System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder & common bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | X | | X | X | | | X | | X | X | | | | X | X | |
| Squamous cell carcinoma | | | | | | X | | | | | | X | | | | | | | | | | | X | | |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 42-Week Dermal Study of 2,3-Dibromo-1-propanol: 177 mg/kg** (continued)

| Animal Number | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Weeks on Study** | 041 | 041 | 041 | 041 | 041 | 041 | 041 | 041 | 041 | 041 | 041 | 041 | 041 | 041 | 041 | 041 | 042 | 042 | 042 | 042 | 042 | 042 | 042 | 042 | 042 | **Total Tissues/ Tumors** |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Squamous cell papilloma | | | | | | | X | | | | | | | X | | | | | | X | | | | | | 5 |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | X | | | | | 1 |
| Sebaceous adenoma | | | | | | | | | | | | | | | | | | | | | | | | | X | 2 |
| Keratoacanthoma | X | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | X | | | | | | | | | | | | 4 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Circulatory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Digestive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | X | | | | | | | | | 1 |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder & common bile duct | + | + | N | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50[a] |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | | X | | | | | X | | X | X | | | X | X | | | X | X | | | X | | | | | 17 |
| Squamous cell carcinoma | | X | | | | | | | | | | | | | | | | X | X | | | | | | | 6 |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 42-Week Dermal Study of 2,3-Dibromo-1-propanol: 177 mg/kg** (continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Animal Number** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | | |
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | |
| **Number of Weeks on Study** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| | 9 | 9 | 9 | 9 | 9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Parathyroid | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | – | + | + | + | + | + | + | + | + | |
| **Reproductive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Endometrial stromal polyp | | X | | | | X | | | | | | | | X | | X | X | | | | | | | | | |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| **Special Sense Organs** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **All Other Systems** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | |

TABLE D2
**Individual Animal Tumor Pathology of Female Mice in the 42-Week Dermal Study of 2,3-Dibromo-1-propanol: 177 mg/kg** (continued)

| Animal Number | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Weeks on Study** | 041 | 041 | 041 | 041 | 041 | 041 | 041 | 041 | 041 | 041 | 041 | 041 | 041 | 041 | 041 | 042 | 042 | 042 | 042 | 042 | 042 | 042 | 042 | 042 | 042 | **Total Tissues/ Tumors** |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| **Reproductive System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Endometrial stromal polyp | | | | | | | | | | | | X | | X | | | | | | | | | | | | 7 |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Sense Organs** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **All Other Systems** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50[a] |

[a] Number of animals necropsied

TABLE D3
**Historical Incidence of Neoplasms in Untreated Female B6C3F$_1$ Mice in Studies Lasting 9 to 14 Months**

| Study | Study Length | Study Laboratory |
|---|---|---|
| Diglycidyl resorcinol ether | 62 weeks | EG&G Mason Research Institute |
| 1,2-Dichloropropane | 41 weeks | EG&G Mason Research Institute |
| Benzyl acetate | 62 weeks | Southern Research Institute |
| Geranyl acetate | 45 weeks | Southern Research Institute |
| **Incidence of Neoplasms**[a] | | |
| Skin | | |
| Epithelial neoplasms (all types) | 0/200 | |
| Lung | | |
| Alveolar/bronchiolar adenoma or carcinoma | 3/199 | |
| Liver | | |
| Hepatocellular adenoma or carcinoma | 3/198 | |
| Forestomach | | |
| Squamous cell papilloma or carcinoma | 0/198 | |

[a] Combined data for EG&G Mason Research Institute and Southern Research Institute

TABLE D4
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 42-Week Dermal Study of 2,3-Dibromo-1-propanol**

| | Vehicle Control | 88 mg/kg | 177 mg/kg |
|---|---|---|---|
| **Disposition Summary** | | | |
| Animals initially in study | 50 | 50 | 50 |
| Early deaths | | | |
| Natural deaths | | 2 | |
| Survivors | | | |
| Terminal sacrifice | 50 | 48 | 50 |
| Animals necropsied | 50 | 50 | 50 |
| Animals examined histopathologically | 50 | 50 | 50 |
| **Integumentary System** | | | |
| Skin[a] | (50) | (50) | (50) |
| Folliculitis | | | 1 (2%) |
| Inflammation, chronic focal | 1 (2%) | | |
| Hyperplasia, NOS[b] | | 5 (10%) | 3 (6%) |
| Hyperplasia, epithelial | | 3 (6%) | 2 (4%)[c] |
| Mammary gland[a] | (50) | (50) | (50) |
| Hyperplasia, NOS | | 1 (2%) | |
| **Respiratory System** | | | |
| Nose[a] | (50) | (50) | (50) |
| Hyperplasia, epithelial | | | 1 (2%) |
| Lung/bronchiole[d] | (50) | (50) | (50) |
| Pleomorphism | | 46 (92%) | 50 (100%) |
| Lung[d] | (50) | (50) | (50) |
| Inflammation, chronic | | | 1 (2%) |
| Hyperplasia, focal | | 6 (12%) | 5 (10%) |
| **Hematopoietic System** | | | |
| Thymus[d] | (50) | (49) | (50) |
| Necrosis, NOS | | 1 (2%) | |
| **Circulatory System** | | | |
| Heart[d] | (50) | (50) | (50) |
| Inflammation, chronic | | 1 (2%) | |
| Artery[a] | (50) | (50) | (50) |
| Periarteritis | 2 (4%) | 1 (2%) | |
| **Digestive System** | | | |
| Liver[d] | (50) | (50) | (50) |
| Inflammation, focal | 1 (2%) | 3 (6%) | 2 (4%) |
| Inflammation, active chronic | | | 2 (4%) |
| Basophilic cyto change | 1 (2%) | | |
| Eosinophilic cyto change | | | 2 (4%) |
| Hypertrophy, focal | | | 2 (4%) |
| Liver/hepatocytes[d] | (50) | (50) | (50) |
| Inclusion, nuclear | | 1 (2%) | |

TABLE D4
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 42-Week Dermal Study of 2,3-Dibromo-1-propanol** (continued)

| | Vehicle Control | 88 mg/kg | 177 mg/kg |
|---|---|---|---|
| **Digestive System** (continued) | | | |
| Forestomach[d] | (50) | (49) | (50) |
| Ulcer, NOS | | | 2 (4%) |
| Hyperplasia, epithelial | | 9 (18%) | |
| Dysplasia, epithelial | | 16 (33%) | 41 (82%) |
| **Urinary System** | | | |
| Kidney[d] | (50) | (50) | (50) |
| Hydronephrosis | 1 (2%) | | |
| Congestion, NOS | | 1 (2%) | |
| Kidney/glomerulus[d] | (50) | (50) | (50) |
| Amyloidosis | | 1 (2%) | |
| Urinary bladder[d] | (50) | (49) | (49) |
| Hemorrhage | | 1 (2%) | |
| **Endocrine System** | | | |
| Anterior pituitary[d] | (50) | (50) | (50) |
| Hyperplasia, focal | | 1 (2%) | |
| Adrenal medulla[d] | (50) | (50) | (50) |
| Angiectasis | 1 (2%) | | |
| **Reproductive System** | | | |
| Uterus[d] | (50) | (50) | (50) |
| Inflammation, NOS | 1 (2%) | | 1 (2%) |
| Degeneration, lipoid | 1 (2%) | | |
| Cervix uteri[d] | (50) | (50) | (50) |
| Inflammation, NOS | | 8 (16%) | |
| Uterus/endometrium[d] | (50) | (50) | (50) |
| Hyperplasia, cystic | 26 (52%) | 28 (56%) | 25 (50%) |
| Dysplasia, epithelial | | | 2 (4%) |
| Ovary[d] | (50) | (49) | (50) |
| Cyst, NOS | 3 (6%) | | 1 (2%) |
| Pigmentation, NOS | | 1 (2%) | |
| **Nervous System** | | | |
| Brain[d] | (50) | (50) | (50) |
| Epidermal inclusion cyst | 2 (4%) | | |
| **Special Sense Organs** | | | |
| None | | | |
| **Musculoskeletal System** | | | |
| Skeletal muscle[a] | (50) | (50) | (50) |
| Inflammation, NOS | 1 (2%) | | |

TABLE D4
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 42-Week Dermal Study of 2,3-Dibromo-1-propanol** (continued)

| | Vehicle Control | 88 mg/kg | 177 mg/kg |
|---|---|---|---|
| **All Other Systems** | | | |
| Adipose tissue | | | |
| Inflammation, chronic | | | 1 |
| Multiple organs[a] | (50) | (50) | (50) |
| Hyperplasia, lymphoid | 1 (2%) | 1 (2%) | 1 (2%) |
| **Special Morphology Summary** | | | |
| No lesion reported | 15 | | |

[a] Number of animals necropsied
[b] NOS=not specified
[c] Multiple occurrence of morphology in the same organ tissue is counted once only.
[d] Number of animals with tissue examined microscopically

# APPENDIX E
# GENETIC TOXICOLOGY

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# GENETIC TOXICOLOGY

## *SALMONELLA TYPHIMURIUM* MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Haworth *et al.* (1983). 2,3-Dibromo-1-propanol was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains (TA100, TA1535, TA1537, and TA98) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with *l*-histidine and *d*-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of 2,3-dibromo-1-propanol. The high dose was limited by toxicity. All positive trials were repeated under the conditions that elicited the positive response. If no positive responses were seen, all negative trials were repeated.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants which is not dose related, not reproducible, or is of insufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There was no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

## MOUSE LYMPHOMA MUTAGENICITY TEST PROTOCOL

The experimental protocol is presented in detail by Myhr *et al.* (1985). 2,3-Dibromo-1-propanol was supplied as a coded aliquot by Radian Corporation. Mouse lymphoma L5178Y cells were maintained at 37° C as suspension cultures in Fischer's medium supplemented with *l*-glutamine, sodium pyruvate, pluronic F68, antibiotics, and heat-inactivated horse serum; normal cycling time was approximately 10 hours. To reduce the number of spontaneously occurring trifluorothymidine-resistant cells, subcultures were exposed to medium containing THMG (thymidine, hypoxanthine, methotrexate, and glycine) for 1 day, to THG for 1 day, and to normal medium for 3 to 5 days. For cloning, horse serum content was increased and Noble agar was added.

All treatment levels within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained $6 \times 10^6$ cells in 10 mL of medium. Incubation with 2,3-dibromo-1-propanol continued for 4 hours, at which time the medium plus 2,3-dibromo-1-propanol was removed and the cells were resuspended in fresh medium and incubated for an additional 2 days to express the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, $3 \times 10^6$ cells were plated in medium and soft agar supplemented with trifluorothymidine (TFT) for selection of TFT-resistant ($TK^{-/-}$) cells; 600 cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37° C in 5% $CO_2$ for 10 to 12 days. S9 was not used because a positive response was seen without S9.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented in Caspary *et al.* (1988). All data were evaluated statistically for trend and peak responses. Both responses had to be significant ($P \leq 0.05$) for 2,3-dibromo-1-propanol to be considered positive, *i.e.*, capable of inducing TFT resistance. A single significant response led to a "questionable" conclusion, and the absence of both a trend and a peak response resulted in a "negative" call.

## CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). 2,3-Dibromo-1-propanol was sent to the laboratory as a coded aliquot from Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of 2,3-dibromo-1-propanol; the high dose was limited by toxicity.

***Sister Chromatid Exchange Test:*** In the SCE test without S9, CHO cells were incubated for 26 hours with 2,3-dibromo-1-propanol in McCoy's 5A medium supplemented with fetal bovine serum, *l*-glutamine, and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing 2,3-dibromo-1-propanol was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for approximately 2 to 3 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with 2,3-dibromo-1-propanol, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no 2,3-dibromo-1-propanol and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 to 3 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level; however, fewer cells were scored if a high frequency of SCEs was seen.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P \leq 0.05$) in the absence of any responses reaching 20% above background led to a call of equivocal.

***Chromosomal Aberrations Test:*** In the Abs test without S9, cells were incubated in McCoy's 5A medium with 2,3-dibromo-1-propanol for 18 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with 2,3-dibromo-1-propanol and S9 for 2 hours, after which the treatment medium was removed and the cells incubated for 10 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test: if cell cycle delay was anticipated, the incubation period was extended.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype ($21 \pm 2$ chromosomes). All slides were scored blind and those from a single test were read by the same person. Up to 200 first-division metaphase cells were scored at each dose level. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) are considered weak evidence for a positive response; significant differences for two or more doses indicate the trial is positive. A positive trend test in the absence of a statistically significant increase at any one dose results in an equivocal call (Galloway *et al.*, 1987). Ultimately the trial calls were

based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

## *DROSOPHILA MELANOGASTER* PROTOCOLS

The assays for induction of sex-linked recessive lethal (SLRL) mutations and chromosomal translocations were performed with adult flies as described in Yoon *et al.* (1985). 2,3-Dibromo-1-propanol was supplied as a coded aliquot from Radian Corporation and was assayed in the SLRL test by feeding for 3 days to adult Canton-S wild-type males no more than 24 hours old at the beginning of treatment. Because a positive result was obtained in the SLRL test, 2,3-dibromo-1-propanol was assayed for induction of reciprocal translocations (RTs) using the same route of exposure.

Toxicity tests were performed to set concentrations of 2,3-dibromo-1-propanol at a level that would induce 30% mortality after 72 hours of feeding while keeping induced sterility at an acceptable level. For the SLRL test, oral exposure was achieved by allowing Canton-S males to feed for 72 hours on a solution of 2,3-dibromo-1-propanol in 5% sucrose. Treated males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three matings of 3, 2, and 2 days (in each case, sample sperm from successive matings were treated at successively earlier post-meiotic stages). $F_1$ heterozygous females were mated with their siblings and then placed in individual vials. $F_1$ daughters from the same parental male were kept together to identify clusters. (A cluster occurs when a number of mutants from a given male result from a single spontaneous premeiotic mutation event, and is identified when the number of mutants from that male exceeds the number predicted by a Poisson distribution.) If a cluster was identified, all data from the male in question were discarded. Presumptive lethal mutations were identified as vials containing fewer than 5% of the expected number of wild-type males after 17 days; these were retested to confirm the response.

SLRL data were analyzed by simultaneous comparison with the concurrent and historical controls, using a normal approximation to the binomial test (Margolin *et al.*, 1983). A test result is considered to be positive if the P value is less than 0.01 and the mutation frequency in the tested group is greater than 0.10%, or if the P value is less than 0.05 and the frequency in the treatment group is greater than 0.15%. A test is considered to be inconclusive if (a) the P value is between 0.05 and 0.01 but the frequency in the treatment group is between 0.10% and 0.15% or (b) the P value is between 0.10 and 0.05 but the frequency in the treatment group is greater than 0.10%. A test is considered to be negative if the P value is greater than 0.10 or if the frequency in the treatment group is less than 0.10%.

***Reciprocal Translocation Test:*** The treatment regimen was essentially the same as that for the SLRL test except that Canton-S males were mated en masse to marker (*bw;st* or *bw;e*) females. The females were transferred to fresh medium every 3 to 4 days for a period of about 3 weeks to produce a total of 6 broods. The results of the SLRL test were used to determine the germ cell stage most likely to be affected by 2,3-dibromo-1-propanol. $F_1$ heterozygous males were backcrossed individually to *bw;st* females and the $F_2$ progeny were screened for pseudolinkage, which results from the induction of a translocation in a germ cell of the parental male. Flies suspected of carrying reciprocal translocations were retested to confirm the findings. The translocation data were analyzed according to the conditional binomial response of Kastenbaum and Bowman (1970).

## MOUSE BONE MARROW MICRONUCLEUS TEST PROTOCOL

Preliminary range-finding studies were performed. Factors affecting dose selection included toxicity, solubility, and the extent of cell cycle delay induced by chemical exposure. In this study, toxicity was the limiting factor. Male mice were injected intraperitoneally three times at 24-hour intervals with 2,3-dibromo-1-propanol dissolved in phosphate-buffered saline (PBS); the dosing volume was 0.4 mL. Solvent control animals were injected with 0.4 mL PBS only; the positive control mice received injections

of mitomycin-C. The mice were killed by cervical dislocation 24 hours after the third injection, and smears were prepared from bone marrow cells obtained from the femurs. Air-dried smears were fixed and stained; 2,000 polychromatic erythrocytes (PCEs) were scored for the frequency of micronucleated cells in each of five animals per dose group. In addition, the percentage of PCEs among the total erythrocyte population in the bone marrow was scored for each dose group as a measure of toxicity. The results were tabulated as the mean of the pooled results from all animals within a treatment group plus or minus the standard error of the mean.

## RESULTS

2,3-Dibromo-1-propanol was mutagenic in all but one of the short-term tests conducted by the NTP. It induced gene mutations in three strains of *Salmonella typhimurium* (TA100, TA1535, and TA98) when tested in a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9; no clearly positive response was observed in strain TA1537 (Table E1; Haworth *et al.*, 1983). 2,3-Dibromo-1-propanol produced a positive response in the absence of S9 activation in the mouse lymphoma assay for induction of trifluorothymidine resistance in L5178Y cells; it was not tested with S9 (Table E2). Increases in SCEs and Abs were induced in CHO cells both with and without Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Tables E3 and E4). 2,3-Dibromo-1-propanol induced significant increases in SLRL mutations and RTs in male germ cells of *Drosophila melanogaster* (Tables E5 and E6; Yoon *et al.*, 1985). Intraperitoneal injection (25-100 mg/kg) of 2,3-dibromo-1-propanol, administered three times at 24-hour intervals, did not increase the frequency of micronucleated PCEs in the bone marrow of male B6C3$F_1$ mice sampled 24 hours after the third injection. Also, the percentages of PCEs among the total erythrocyte population were not affected by 2,3-dibromo-1-propanol administration, indicating no toxicity in the bone marrow.

TABLE E1
**Mutagenicity of 2,3-Dibromo-1-propanol in *Salmonella typhimurium*[a]**

| Strain | Dose (μg/plate) | Revertants/plate[b] -S9 Trial 1 | -S9 Trial 2 | +10% hamster S9 Trial 1 | +10% hamster S9 Trial 2 | +10% rat S9 Trial 1 | +10% rat S9 Trial 2 |
|---|---|---|---|---|---|---|---|
| **TA100** | 0.0 | 119 ± 0.9 | 102 ± 1.7 | 152 ± 2.6 | 101 ± 9.7 | 110 ± 10.2 | 90 ± 7.5 |
| | 3.3 | | 113 ± 4.7 | | 258 ± 12.4 | | 145 ± 5.8 |
| | 33.0 | 191 ± 9.7 | 101 ± 11.3 | 1,078 ± 28.9 | 824 ± 36.1 | 266 ± 29.1 | 220 ± 9.8 |
| | 100.0 | 317 ± 7.1 | 159 ± 4.7 | 2,170 ± 111.5 | 2,100 ± 60.8 | 681 ± 30.7 | 417 ± 4.2 |
| | 333.0 | 914 ± 40.6 | 396 ± 38.1 | 3,411 ± 34.5 | 3,438 ± 41.0 | 1,414 ± 77.2[c] | 1,226 ± 42.7 |
| | 1,000.0 | 1,418 ± 33.2[c] | 1,946 ± 84.7 | 2,803 ± 37.0[c] | 3,699 ± 210.4 | 3,264 ± 113.6[c] | 2,485 ± 285.9 |
| | 2,000.0 | 899 ± 48.1[c] | | 470 ± 182.5[c] | | 667 ± 73.0[c] | |
| Trial summary | | Positive | Positive | Positive | Positive | Positive | Positive |
| Positive control[d] | | 2,322 ± 87.3 | 1,748 ± 28.3 | 1,440 ± 51.2 | 1,031 ± 137.2 | 1,311 ± 56.4 | 509 ± 35.5 |
| **TA1535** | 0.0 | 18 ± 3.1 | 18 ± 0.7 | 14 ± 3.3 | 16 ± 2.0 | 9 ± 0.3 | 13 ± 1.2 |
| | 3.3 | | 17 ± 3.5 | | 64 ± 5.5 | | 26 ± 2.0 |
| | 33.0 | 26 ± 5.2 | 21 ± 1.7 | 278 ± 16.3 | 206 ± 28.6 | 43 ± 4.3 | 42 ± 3.8 |
| | 100.0 | 66 ± 6.7 | 27 ± 4.0 | 628 ± 32.5 | 702 ± 149.4 | 156 ± 18.3 | 142 ± 1.2 |
| | 333.0 | 216 ± 42.4 | 68 ± 2.0 | 1,245 ± 30.7 | 1,225 ± 96.1 | 498 ± 26.7 | 434 ± 57.5 |
| | 1,000.0 | 518 ± 28.0[c] | 407 ± 4.7 | 1,445 ± 40.8 | 787 ± 111.5 | 1,351 ± 229.5[c] | 733 ± 235.0 |
| | 2,000.0 | 68 ± 12.1[c] | | 94 ± 9.0[c] | | 99 ± 10.2[c] | |
| Trial summary | | Positive | Positive | Positive | Positive | Positive | Positive |
| Positive control | | 1,915 ± 26.7 | 1,146 ± 91.2 | 153 ± 5.5 | 103 ± 27.1 | 73 ± 2.6 | 54 ± 1.7 |
| **TA1537** | 0.0 | 11 ± 1.5 | 7 ± 1.9 | 8 ± 2.6 | 7 ± 2.2 | 7 ± 1.9 | 7 ± 1.3 |
| | 3.3 | | 6 ± 1.2 | | 8 ± 1.2 | | 7 ± 2.2 |
| | 33.0 | 9 ± 1.5 | 6 ± 0.6 | 7 ± 1.8 | 8 ± 2.0 | 11 ± 0.3 | 8 ± 2.7 |
| | 100.0 | 9 ± 0.7[c] | 5 ± 0.9 | 8 ± 1.3 | 11 ± 2.7 | 10 ± 1.7 | 7 ± 1.5 |
| | 333.0 | 9 ± 2.2[c] | 4 ± 1.5 | 10 ± 2.8 | 8 ± 1.5 | 9 ± 1.5 | 10 ± 1.5 |
| | 1,000.0 | 7 ± 0.6[c] | 13 ± 1.7 | 17 ± 1.9[c] | 19 ± 6.8 | 27 ± 3.3[c] | 23 ± 1.2 |
| | 2,000.0 | Toxic | | Toxic | | 8 ± 0.9[c] | |
| Trial summary | | Negative | Negative | Negative | Negative | Equivocal | Equivocal |
| Positive control | | 504 ± 85.6 | 518 ± 74.0 | 144 ± 8.5 | 127 ± 4.2 | 86 ± 7.1 | 56 ± 2.0 |
| **TA98** | 0.0 | 17 ± 3.9 | 15 ± 0.7 | 29 ± 1.5 | 23 ± 2.7 | 30 ± 0.7 | 23 ± 3.8 |
| | 3.3 | | 20 ± 1.5 | | 28 ± 1.0 | | 20 ± 1.3 |
| | 33.0 | 22 ± 1.2 | 13 ± 1.5 | 37 ± 2.6 | 28 ± 5.9 | 35 ± 9.7 | 22 ± 2.1 |
| | 100.0 | 24 ± 2.3 | 18 ± 2.6 | 58 ± 2.7 | 40 ± 6.7 | 37 ± 4.7 | 32 ± 2.3 |
| | 333.0 | 43 ± 1.5[c] | 24 ± 1.9 | 110 ± 4.8 | 82 ± 20.7 | 58 ± 3.4 | 55 ± 3.0 |
| | 1,000.0 | 68 ± 3.5[c] | 34 ± 20.2[c] | 162 ± 2.7[c] | 136 ± 18.3 | 154 ± 12.5 | 80 ± 31.4 |
| | 2,000.0 | Toxic | | 76 ± 12.5[c] | | 106 ± 20.5[c] | |
| Trial summary | | Positive | Equivocal | Positive | Positive | Positive | Positive |
| Positive control | | 1,759 ± 43.4 | 1,186 ± 21.8 | 1,262 ± 60.4 | 1,266 ± 43.3 | 1,146 ± 66.9 | 675 ± 27.4 |

[a] Study performed at EG&G Mason Research Institute. The detailed protocol and these data are presented in Haworth *et al.* (1983). High dose was limited by toxicity.
[b] Revertants are presented as mean ± standard error from three plates.
[c] Slight toxicity
[d] The positive controls in the absence of metabolic activation were sodium azide (TA1535 and TA100), 9-aminoacridine (TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE E2
**Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by 2,3-Dibromo-1-propanol[a]**

| Compound | Concentration (μg/mL) | Cloning Efficiency (%) | Relative Total Growth (%) | Mutant Count | Mutant Fraction[b] | Average Mutant Fraction |
|---|---|---|---|---|---|---|
| **-S9** | | | | | | |
| **Trial 1** | | | | | | |
| Ethanol | | 108 | 125 | 116 | 36 | |
| | | 91 | 99 | 116 | 43 | |
| | | 92 | 90 | 133 | 48 | |
| | | 91 | 86 | 120 | 44 | 43 |
| Methyl methanesulfonate | | | | | | |
| | 5 | 50 | 25 | 543 | 361 | |
| | | 62 | 48 | 548 | 294 | |
| | | 76 | 50 | 539 | 236 | 297* |
| 2,3-Dibromo-1-propanol | | | | | | |
| | 0.0625 | 108 | 89 | 137 | 42 | |
| | | 103 | 83 | 159 | 52 | |
| | | 106 | 81 | 179 | 56 | 50 |
| | 0.125 | 108 | 84 | 234 | 72 | |
| | | 120 | 74 | 232 | 65 | 69* |
| | 0.25 | 92 | 44 | 365 | 133 | |
| | | 109 | 53 | 329 | 101 | |
| | | 104 | 45 | 405 | 129 | 121* |
| | 0.375 | 81 | 20 | 493 | 202 | |
| | | 79 | 29 | 529 | 222 | |
| | | 96 | 24 | 634 | 220 | 215* |
| | 0.5 | 99 | 32 | 503 | 170 | |
| | | 70 | 9 | 628 | 300 | 235* |
| | 0.75 | Lethal | | | | |
| | | Lethal | | | | |
| | | Lethal | | | | |

TABLE E2
**Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by 2,3-Dibromo-1-propanol** (continued)

| Compound | Concentration (μg/mL) | Cloning Efficiency (%) | Relative Total Growth (%) | Mutant Count | Mutant Fraction | Average Mutant Fraction |
|---|---|---|---|---|---|---|
| **Trial 2** | | | | | | |
| Ethanol | | 86 | 131 | 81 | 31 | |
| | | 59 | 88 | 65 | 37 | |
| | | 74 | 91 | 93 | 42 | |
| | | 64 | 90 | 91 | 47 | 39 |
| Methyl methanesulfonate | | | | | | |
| | 5 | 61 | 56 | 541 | 294 | |
| | | 53 | 58 | 559 | 354 | |
| | | 72 | 64 | 564 | 262 | 303* |
| 2,3-Dibromo-1-propanol | | | | | | |
| | 0.0625 | 65 | 45 | 284 | 145 | |
| | | 89 | 96 | 144 | 54 | |
| | | 74 | 87 | 142 | 64 | 88* |
| | 0.125 | 81 | 68 | 300 | 124 | |
| | | 82 | 82 | 254 | 103 | |
| | | 74 | 59 | 268 | 120 | 116* |
| | 0.25 | 85 | 59 | 428 | 169 | |
| | | 79 | 47 | 558 | 236 | |
| | | 85 | 62 | 498 | 195 | 200* |
| | 0.375 | 55 | 16 | 780 | 476 | |
| | | 60 | 17 | 753 | 417 | |
| | | 60 | 26 | 710 | 392 | 428* |
| | 0.5 | 42 | 5 | 669 | 527 | |
| | | 41 | 6 | 681 | 556 | |
| | | 47 | 13 | 687 | 492 | 525* |
| | 0.75 | Lethal | | | | |
| | | Lethal | | | | |

* Significant positive response ($P \leq 0.05$)
[a] Study performed at Litton Bionetics, Inc. The experimental protocol is presented in detail by Myhr *et al.* (1985). The highest dose of 2,3-dibromo-1-propanol was determined by toxicity. All doses are tested in triplicate; the average of the three tests is presented in the table.
[b] Mutant fraction (frequency) is a ratio of the mutant count to the cloning efficiency, divided by 3 (to arrive at MF/1 × $10^6$ cells treated).

TABLE E3
**Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by 2,3-Dibromo-1-propanol[a]**

| Compound | Dose (μg/mL) | Total Cells | No. of Chromosomes | No. of SCEs | SCEs/ Chromosome | SCEs/ Cell | Hrs in BrdU | Relative SCEs/ Chromosome (%)[b] |
|---|---|---|---|---|---|---|---|---|
| **-S9** | | | | | | | | |
| **Trial 1** | | | | | | | | |
| Summary: Positive | | | | | | | | |
| Dimethylsulfoxide | | 50 | 1,049 | 449 | 0.42 | 9.0 | 25.6 | |
| Mitomycin-C | 0.001 | 50 | 1,045 | 558 | 0.53 | 11.2 | 25.6 | 24.75* |
| | 0.010 | 5 | 104 | 197 | 1.89 | 39.4 | 25.6 | 342.56* |
| 2,3-Dibromo-1-propanol | 50.9 | 50 | 1,047 | 727 | 0.69 | 14.5 | 25.6 | 62.23* |
| | 169.6 | 10 | 210 | 352 | 1.67 | 35.2 | 25.6 | 291.61* |
| | 508.8 | 10 | 209 | 394 | 1.88 | 39.4 | 31.4[c] | 340.44* |
| | 1,700.0 | 0 | | | | | | |
| | | | | | | | | P<0.001[d] |
| **Trial 2** | | | | | | | | |
| Summary: Positive | | | | | | | | |
| Dimethylsulfoxide | | 25 | 526 | 245 | 0.46 | 9.8 | 25.9 | |
| Mitomycin-C | 0.001 | 25 | 520 | 249 | 0.47 | 10.0 | 25.9 | 2.81 |
| | 0.010 | 5 | 107 | 176 | 1.64 | 35.2 | 25.9 | 253.15* |
| 2,3-Dibromo-1-propanol | 110.7 | 25 | 529 | 696 | 1.31 | 27.8 | 25.9 | 182.47* |
| | 169.9 | 10 | 205 | 374 | 1.82 | 37.4 | 25.9 | 291.69* |
| | 253.6 | 5 | 105 | 230 | 2.19 | 46.0 | 25.9 | 370.29* |
| | 507.1 | 0 | | | | | | |
| | | | | | | | | P<0.001 |
| **+S9** | | | | | | | | |
| **Trial 1** | | | | | | | | |
| Summary: Positive | | | | | | | | |
| Dimethylsulfoxide | | 50 | 1,048 | 412 | 0.39 | 8.2 | 25.6 | |
| Cyclophosphamide | 0.4 | 50 | 1,049 | 465 | 0.44 | 9.3 | 25.6 | 12.76 |
| | 2.0 | 5 | 104 | 109 | 1.04 | 21.8 | 25.6 | 166.60 |
| 2,3-Dibromo-1-propanol | 50.9 | 50 | 1,047 | 521 | 0.49 | 10.4 | 25.6 | 26.58* |
| | 169.6 | 50 | 1,049 | 784 | 0.74 | 15.7 | 25.6 | 90.11* |
| | 508.8 | 50 | 1,050 | 1,154 | 1.09 | 23.1 | 25.6 | 179.57* |
| | 1,700.0 | 0 | | | | | | |
| | | | | | | | | P<0.001 |

* Positive (≥20% increase over solvent control)
[a] Study performed at Litton Bionetics, Inc. SCE=sister chromatid exchange; BrdU=bromodeoxyuridine.
[b] SCEs/chromosome of culture exposed to 2,3-dibromo-1-propanol relative to those of culture exposed to solvent.
[c] Because 2,3-dibromo-1-propanol induced a delay in the cell division cycle, harvest time was extended to maximize the proportion of second division cells available for analysis.
[d] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose

TABLE E4
**Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by 2,3-Dibromo-1-propanol[a]**

| -S9 | | | | | +S9 | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Dose (μg/mL) | Total Cells | No. of Abs | Abs/ Cell | Percent Cells w/Abs | Dose (μg/mL) | Total Cells | No. of Abs | Abs/ Cell | Percent Cells w/Abs |
| **Trial 1** - Harvest time: 20.2 hours[b] Summary: Positive | | | | | **Trial 1** - Harvest time: 12.0 hours Summary: Positive | | | | |
| Dimethylsulfoxide | | | | | Dimethylsulfoxide | | | | |
| | 200 | 1 | 0.01 | 0.5 | | 200 | 3 | 0.02 | 1.0 |
| Mitomycin-C | | | | | Cyclophosphamide | | | | |
| 0.05 | 200 | 119 | 0.60 | 37.0 | 7.5 | 200 | 29 | 0.15 | 13.5 |
| 0.08 | 25 | 35 | 1.40 | 56.0 | 37.5 | 25 | 20 | 0.80 | 40.0 |
| 2,3-Dibromo-1-propanol | | | | | 2,3-Dibromo-1-propanol | | | | |
| 626.4 | 200 | 36 | 0.18 | 16.5* | 626.4 | 200 | 45 | 0.23 | 12.5* |
| 1,252.8 | 50 | 23 | 0.46 | 36.0* | 1,252.8 | 50 | 22 | 0.44 | 34.0* |
| 1,869.8 | 10 | 22 | 2.20 | 80.0* | 1,869.8 | 25 | 17 | 0.68 | 48.0* |
| 2,493.1 | 0 | | | | 2,493.1 | 0 | | | |
| | | | | P<0.001[c] | | | | | P<0.001 |
| **Trial 2** - Harvest time: 20 hours[b] Summary: Positive | | | | | | | | | |
| Dimethylsulfoxide | | | | | | | | | |
| | 100 | 4 | 0.04 | 4.0 | | | | | |
| Mitomycin-C | | | | | | | | | |
| 0.05 | 100 | 20 | 0.20 | 17.0 | | | | | |
| 0.08 | 25 | 20 | 0.80 | 60.0 | | | | | |
| 2,3-Dibromo-1-propanol | | | | | | | | | |
| 620.6 | 100 | 16 | 0.16 | 15.0* | | | | | |
| 1,241.1 | 50 | 20 | 0.40 | 32.0* | | | | | |
| 1,880.5 | 10 | 15 | 1.50 | 90.0* | | | | | |
| 2,238.7 | 0 | | | | | | | | |
| | | | | P<0.001 | | | | | |

* Positive (P<0.05)
[a] Study performed at Litton Bionetics, Inc. Abs=aberrations.
[b] Because of chemical-induced cell cycle delay, incubation time prior to addition of Colcemid was lengthened from the normal time of 10 to 12 hours to provide sufficient metaphases at harvest.
[c] Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose

TABLE E5
**Induction of Sex-Linked Recessive Lethal Mutations in *Drosophila melanogaster* by 2,3-Dibromo-1-propanol[a]**

| Route of Exposure | Dose (ppm) | Incidence of Deaths (%) | Incidence of Sterility (%) | No. of Lethals/No. of X Chromosomes Tested | | | |
|---|---|---|---|---|---|---|---|
| | | | | Mating 1 | Mating 2 | Mating 3 | Total[b] |
| Feeding | 500 | 51 | 9 | 8/1,116 | 20/1,244 | 25/950 | 53/3,310 (1.60%)* |
| | 0 | | | 2/2,103 | 1/1,945 | 0/1,850 | 3/5,898 (0.05%) |

* Results were significant ($P<0.0001$) at the 5% level (Margolin *et al.*, 1983).
[a] Study performed at University of Wisconsin, Madison. A detailed protocol of the sex-linked recessive lethal assay and these data are presented in Yoon *et al.* (1985).
[b] Combined total number of lethal mutations/number of X chromosomes tested for three mating trials

TABLE E6
**Induction of Reciprocal Translocations in *Drosophila melanogaster* by 2,3-Dibromo-1-propanol[a]**

| Route of Exposure | Dose (ppm) | Transfers (translocations/total $F_1$ tested) | | | | | | No. of Tests | Total No. of Translocations | Total Translocations (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 | | | |
| Feeding | 400 | 0/1,268 | 9/1,274 | 9/1,190 | 13/880 | 5/379 | 0/0 | 4,991 | 36 | 0.72* |
| Concurrent control | | | | | | | | 32,516 | 1 | 0.00 |
| Historical control | | | | | | | | 116,163 | 2 | 0.00 |

* Results were significant ($P<0.01$) at the 5% level (Kastenbaum and Bowman, 1970).
[a] Study performed at University of Wisconsin, Madison. A detailed protocol of the reciprocal translocation assay and these data are presented in Yoon *et al.* (1985).

TABLE E7
**Frequency of Micronucleated Erythrocytes in Bone Marrow Cells of Male Mice Treated with 2,3-Dibromo-1-propanol[a]**

| Compound | Dose (mg/kg) | Micronucleated Cells/1,000 Cells | PCEs (%) |
|---|---|---|---|
| 2,3-Dibromo-1-propanol | 0 | 3.9 ± 0.60 | 38.9 ± 6.28 |
| | 25 | 4.1 ± 0.31 | 35.2 ± 3.07 |
| | 50 | 3.0 ± 0.39 | 26.0 ± 6.12 |
| | 100 | 3.5 ± 0.50 | 37.4 ± 5.47 |
| | | Trend test: P=0.763 | ANOVA: P=0.363 |
| Mitomycin-C[b] | | 6.7 ± 1.17 | 16.8 ± 1.67 |

[a] 2,3-Dibromo-1-propanol, dissolved in phosphate-buffered saline, was administered by intraperitoneal injection three times at 24-hour intervals to male B6C3F$_1$ mice. Injection volume was 0.4 mL. Bone marrow sampling was performed 24 hours after the third injection.
[b] Positive control

# APPENDIX F
# LIVER WEIGHTS
# AND LIVER-WEIGHT-TO-BODY-WEIGHT RATIOS

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TABLE F1
**Liver Weights and Liver-Weight-to-Body-Weight Ratios for Rats in the 13-Week Dermal Study of 2,3-Dibromo-1-propanol[a]**

| | Vehicle Control | 44 mg/kg | 88 mg/kg | 177 mg/kg | 375 mg/kg | 750 mg/kg |
|---|---|---|---|---|---|---|
| **Male** | | | | | | |
| n | 10 | 10 | 10 | 10 | 10 | 10 |
| Final body wt | 310 | 299 | 310 | 307 | 301 | 292 |
| Liver wt | | | | | | |
| Absolute | 15.50 | 14.15 | 13.90 | 15.38 | 17.11 | 18.47 |
| Relative | 5.0 | 4.7 | 4.5 | 5.0 | 5.7 | 6.3 |
| **Female** | | | | | | |
| n | 10 | 10 | 10 | 10 | 10 | 10 |
| Final body wt | 181 | 181 | 179 | 184 | 174 | 170 |
| Liver wt | | | | | | |
| Absolute | 7.21 | 7.75 | 7.21 | 7.91 | 7.64 | 12.34 |
| Relative | 4.0 | 4.3 | 4.0 | 4.3 | 4.4 | 7.3 |

[a] Liver weights and body weights are given in grams; liver-weight-to-body-weight ratios are percentages.

TABLE F2
**Liver Weights and Liver-Weight-to-Body-Weight Ratios for Mice in the 13-Week Dermal Study of 2,3-Dibromo-1-propanol[a]**

| | Vehicle Control | 44 mg/kg | 88 mg/kg | 177 mg/kg | 375 mg/kg | 750 mg/kg |
|---|---|---|---|---|---|---|
| **Male** | | | | | | |
| n | 10 | 10 | 10 | 10 | 10 | 2 |
| Final body wt | 27.6 | 28.1 | 27.6 | 27.0 | 27.9 | 27.9 |
| Liver wt | | | | | | |
| Absolute | 1.38 | 1.52 | 1.59 | 1.33 | 1.84 | 2.23 |
| Relative | 5.0 | 5.4 | 5.8 | 4.9 | 6.6 | 8.0 |
| **Female** | | | | | | |
| n | 10 | 10 | 10 | 10 | 10 | 10 |
| Final body wt | 24.5 | 24.5 | 25.0 | 23.6 | 23.1 | 24.1 |
| Liver wt | | | | | | |
| Absolute | 1.23 | 1.35 | 1.46 | 1.25 | 1.28 | 1.71 |
| Relative | 5.0 | 5.5 | 5.8 | 5.3 | 5.5 | 7.1 |

[a] Liver weights and body weights are given in grams; liver-weight-to-body-weight ratios are percentages.

# APPENDIX G
# CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES


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# CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

## PROCUREMENT AND CHARACTERIZATION OF 2,3-DIBROMO-1-PROPANOL

2,3-Dibromo-1-propanol was obtained from Great Lakes Chemical Corporation (Bayport, TX) in two lots. Lot 4-44-726 was used during the 16-day, 13-week, and long-term studies, and lot H1P was used throughout the remainder of the long-term studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses conducted in support of the 2,3-dibromo-1-propanol studies are on file at the National Institute of Environmental Health Sciences.

Both lots of the bulk chemical, a clear, colorless, viscous liquid, were identified as 2,3-dibromo-1-propanol by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with those expected for the structure and with the literature spectra (*Sadtler Standard Spectra*) of 2,3-dibromo-1-propanol (Figures G1 and G2).

The purity of the bulk chemical was determined by elemental analyses, Karl Fischer water analysis, titration of acidic components with sodium hydroxide, thin-layer chromatography (TLC), and gas chromatography. Titration of acidic components was performed in methanol with 0.05N sodium hydroxide as the titrant. Titration was monitored potentiometrically with a combination pH/mV electrode. TLC was performed on Silica Gel 60 F-254 plates with two solvent systems: 1) 100% methylene chloride and 2) hexane:acetone (70:30). Visualization was accomplished with ultraviolet (254 nm) light and with a spray of 5% potassium permanganate in 1N sodium hydroxide. Gas chromatography was performed with a flame ionization detector and a nitrogen carrier gas, with two systems:

A) 20% SP-2100/0.1% Carbowax 1500 on 100/120 mesh Supelcoport, with a carrier gas flow rate of 70 mL/minute for lot 4-44-726 and 65 mL/minute for lot H1P, and with an oven temperature program of 50° C for 5 minutes, then 50° to 170° C at 10° C/minute, and
B) 10% Carbowax 20M-TPA on 80/100 mesh Chromasorb W(AW), with a carrier gas flow rate of 70 mL/minute for lot 4-44-726 and 100 mL/minute for lot H1P, and with an oven temperature program of 50° C for 5 minutes, then 50° to 200° C at 10° C/minute (lot 4-44-726), or 60° C for 6 minutes, then 60° to 200° C at 10° C/minute (lot H1P).

For lot 4-44-726, the elemental analyses for carbon, hydrogen, and bromine were in agreement with the theoretical values. Karl Fischer water analysis indicated 0.066 ± 0.004% water. Titration for acidic components indicated less than 25 ppm acid (hydrogen bromide). TLC indicated only a major spot using system 1 and a major spot and one slight trace impurity using system 2. Gas chromatography using system A indicated a major peak and five impurities with a combined area of approximately 1% of the major peak area and seven additional impurities with areas less than 1%; six impurities eluted before the major peak, and six eluted after. Gas chromatography using system B indicated a major peak and 10 impurities, all eluting before the major peak, with a combined area of 1.4% of the major peak area. The purity of lot 4-44-726 was determined to be approximately 98%.

The homogeneity of lot H1P was verified by determining the relative purity of two samples, each taken from a different container of the bulk chemical, using gas chromatography with system B. The two samples were found to have identical impurity profiles. The elemental analyses for carbon, hydrogen, and bromine were in agreement with the theoretical values. Karl Fischer water analysis indicated 0.049 ± 0.002% water. Titration for acidic components indicated less than 20 ppm acid (hydrogen bromide). TLC indicated only a major spot using system 1 and a major spot and one trace impurity using system 2. Gas chromatography using system A indicated a major peak and two impurities with a combined area of 0.3% of the major peak area. Gas chromatography using system B indicated a major peak and five

impurities with a combined area of approximately 2% of the major peak area. Both gas chromatography systems identified 11 additional impurities, with areas less than 0.1% relative to the major peak. The overall purity of lot H1P was determined to be approximately 98%. A concomitant gas chromatographic analysis of lot 4-44-726 with lot H1P indicated three impurities with a combined area relative to the major peak of approximately 0.6% using system A and seven impurities with a combined relative area of approximately 3% using system B.

Stability studies were performed using gas chromatography with system B described for the purity analyses, but with a carrier gas flow rate of 70 mL/minute and an oven temperature of 190° C. Docasane was added as an internal standard. The stability studies indicated that 2,3-dibromo-1-propanol is stable as a bulk chemical for 2 weeks at temperatures up to 60° C. The bulk chemical was stored in amber glass bottles at 0° to 6° C throughout the studies. During the long-term studies, the stability of the bulk chemical was monitored by the study laboratory using gas chromatography with systems A and B with varying column systems, and with a 10% OV-101 on 80/100 mesh Supelcoport with an oven temperature program of 50° C for 5 minutes, then 50° to 150° C at 10° C/minute. No degradation of the study material was observed throughout the studies.

## PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared by mixing 2,3-dibromo-1-propanol with ethanol and diluting to the target concentrations (Table G1). Dose formulations were prepared weekly during the 16-day and 13-week studies and for the first 26 weeks of the long-term studies, and every 2 weeks thereafter. Because the rodents were dosed with a constant volume, the formulation concentrations were changed throughout the studies.

Stability analyses of the dose formulations were conducted by the analytical chemistry laboratory. Samples were diluted with methanol, and 2 mL of a 2 mg/mL solution of 2-methoxynaphthalene in methanol was added as an internal standard. Samples were further diluted to 50% with methanol. The samples were then analyzed using gas chromatography with a flame ionization detector, with a 10% SP-2330 on 100/120 mesh Chromasorb W(AW) and a nitrogen carrier gas at a flow rate of 30 mL/minute. The oven temperature was 158° C. Stability of the dose formulations was confirmed for at least 7 days when stored at room temperature. An additional stability study performed by the study laboratory using the same gas chromatographic system indicated that the dose preparations were stable for up to 8 weeks when stored at 0° to 8° C.

Periodic analyses of the dose formulations were conducted by the study laboratory and by the analytical chemistry laboratory using gas chromatography with the same system used in the dose formulation stability analyses, but with an oven temperature of 160° C. Dose formulations were analyzed twice during the 13-week studies and approximately every 4 weeks during the long-term studies. During the 13-week studies, three of four dose formulations were within 10% of the target concentrations (Table G2). During the long-term studies, all samples were within 10% of the target concentrations (Table G3). Results of the periodic referee analyses performed by the analytical chemistry laboratory indicated good agreement with the results obtained by the study laboratory (Table G4).

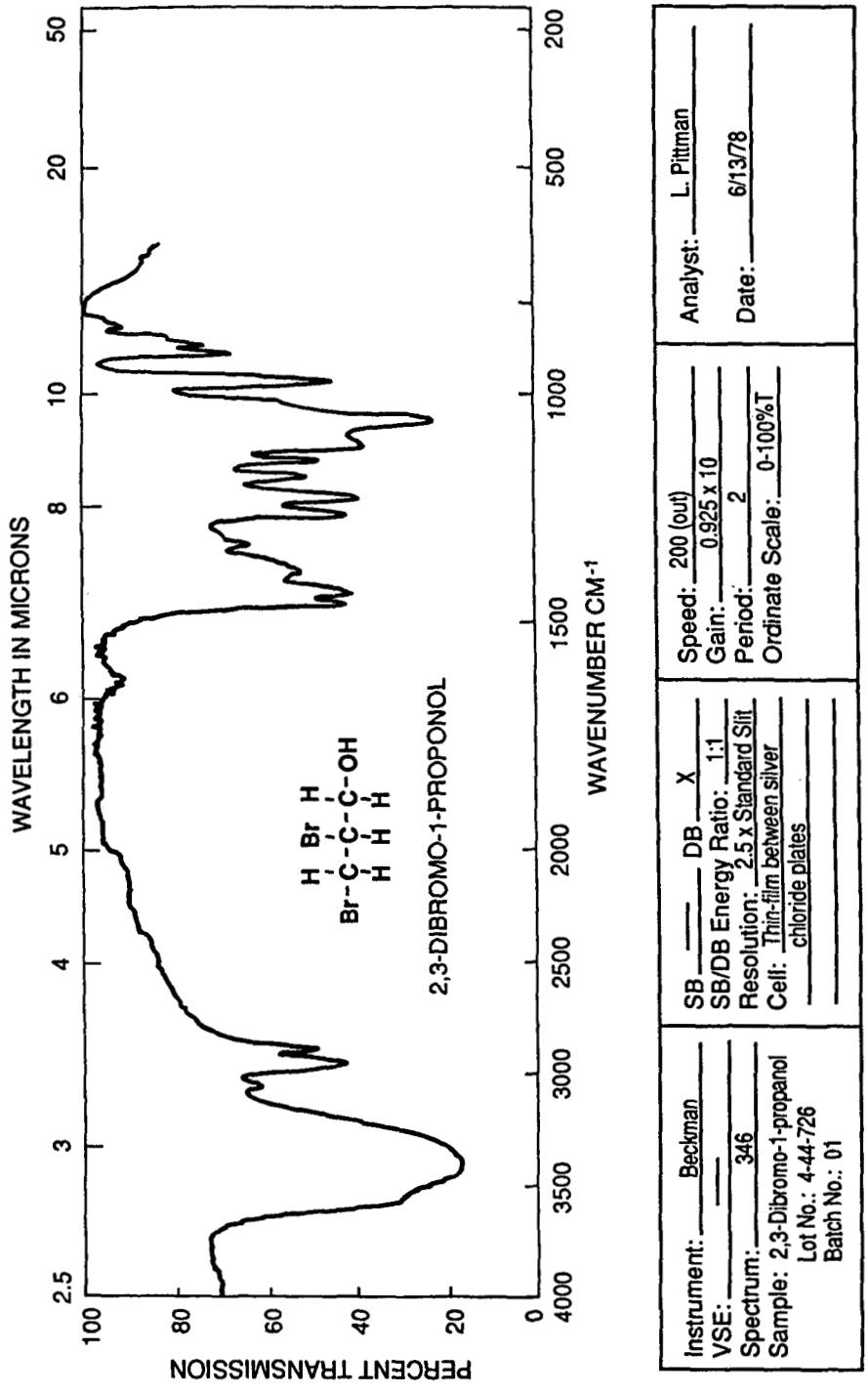


FIGURE G1
Infrared Absorption Spectrum of 2,3-Dibromo-1-propanol

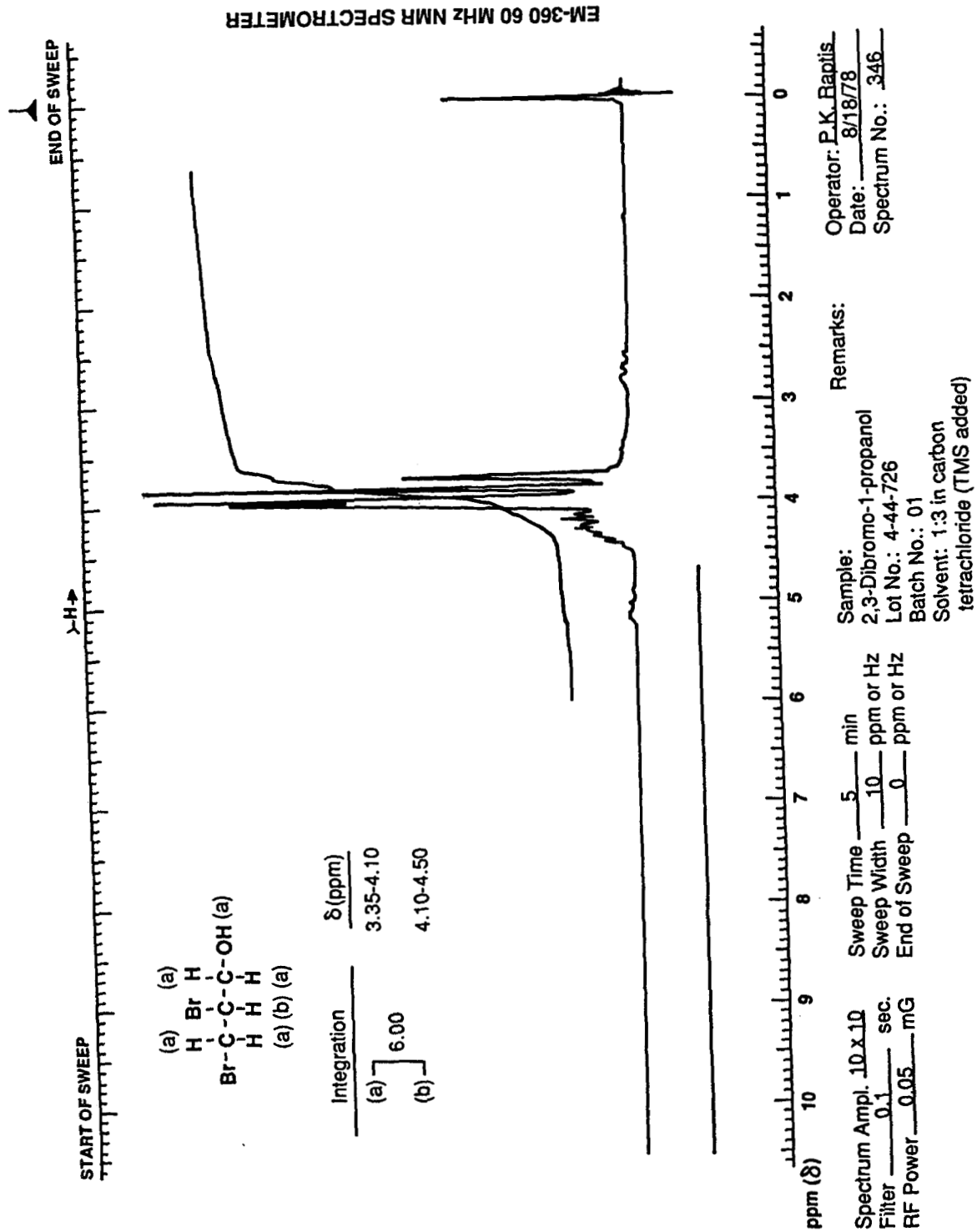


FIGURE G2
Nuclear Magnetic Resonance Spectrum of 2,3-Dibromo-1-propanol

TABLE G1
**Preparation and Storage of Dose Formulations in the Dermal Studies of 2,3-Dibromo-1-propanol**

| 16-Day Studies | 13-Week Studies | Long-Term Studies |
|---|---|---|
| **Preparation** | | |
| 2,3-Dibromo-1-propanol was measured into a mixing cylinder and ethanol was added to obtain the required volume. Dose formulations were prepared weekly. | Same as 16-day studies | Same as 16-day studies. Doses were mixed every 2 weeks after 16 June 1982. |
| **Chemical Lot Number** | | |
| 4-44-726 | 4-44-726 | 4-44-726<br>H1P |
| **Maximum Storage Time** | | |
| 9 days from date of preparation | Same as 16-day studies | 16 days from date of preparation |
| **Storage Conditions** | | |
| 2° to 5° C | Same as 16-day studies | In clear glass vials at 3° to 6° C. Doses were stored in the dark after April 1982. |
| **Study Laboratory** | | |
| Papanicolaou Cancer Research Institute at Miami, Inc., Miami, FL | Same as 16-day studies | Same as 16-day studies |
| **Referee Laboratory** | | |
| Midwest Research Institute, Kansas City, MO | Same as 16-day studies | Same as 16-day studies |

TABLE G2
**Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Dermal Studies of 2,3-Dibromo-1-propanol**

| Date Prepared | Date Analyzed | Target Concentration (wt/vol%) | Determined Concentration[a] (wt/vol%) | Difference from Target (%) |
|---|---|---|---|---|
| 26 September 1980 | 30 September 1980 | 35.09 | 32.13 | –8 |
| | | 20.0 | 19.72 | –1 |
| 7 November 1980 | 9 December 1980 | 17.18 | 18.43 | +7 |
| | | 8.36 | 9.40 | +12 |

[a] Results of duplicate analyses

TABLE G3
**Results of Analysis of Dose Formulations Administered to Rats and Mice in the Long-Term Dermal Studies of 2,3-Dibromo-1-propanol**

| Date Prepared | Date Analyzed | Target Concentration (wt/vol%) | Determined Concentration[a] (wt/vol%) | Difference from Target (%) |
|---|---|---|---|---|
| 10 December 1981 | 16 December 1981 | 19.20 | 18.80 | –2 |
| | | 19.20[b] | 18.83 | –2 |
| | 23 December 1981 | 7.80 | 7.62 | –2 |
| | | 9.70 | 9.51 | –2 |
| | | 15.70 | 15.21 | –3 |
| 7 January 1982 | 8 January 1982 | 10.94 | 11.11 | +2 |
| | | 16.80 | 16.75 | 0 |
| | | 31.92 | 32.31 | +1 |
| 21 January 1982 | 22 January 1982 | 1.53 | 1.49 | –3 |
| | | 2.00 | 1.97 | –2 |
| | | 3.08 | 3.08 | 0 |
| | | 3.99 | 3.91 | –2 |
| 4 February 1982 | 5 February 1982 | 3.57 | 3.57[c] | 0 |
| | | 1.68 | 1.67[c] | –1 |
| | | 11.81 | 11.97[c] | +1 |
| | | 23.63 | 24.04[c] | +2 |
| 4 March 1982 | 5 March 1982 | 2.73 | 2.75 | +1 |
| | | 4.73 | 4.72 | 0 |
| | | 5.46 | 5.44 | 0 |
| | | 22.40 | 22.03 | –2 |
| | | 43.40 | 43.90 | +1 |
| 1 April 1982 | 2 April 1982 | 2.1 | 2.02 | –4 |
| | | 4.2 | 3.93 | –6 |
| | | 12.60 | 12.48 | –1 |
| | | 26.60 | 26.32 | –1 |
| 29 April 1982 | 30 April 1982 | 2.94 | 2.89 | –2 |
| | | 6.30 | 6.17 | –2 |
| | | 23.80 | 23.95 | +1 |
| | | 46.20 | 46.30 | 0 |
| 19 May 1982 | 20 May 1982 | 2.31 | 2.30 | 0 |
| | | 4.62 | 4.61 | 0 |
| | | 14.0 | 13.83 | –1 |
| | | 28.0 | 27.61 | –1 |
| 16 June 1982 | 17-18 June 1982 | 3.36 | 3.27 | –2 |
| | | 6.93 | 6.74 | –3 |
| | | 25.8 | 25.4 | –2 |
| | | 49.8 | 49.8 | 0 |
| 28 July 1982 | 30 July 1982 | 2.52 | 2.53 | 0 |
| | | 5.15 | 5.10 | –1 |
| | | 15.6 | 15.8 | +1 |
| | | 30.0 | 30.3 | +1 |

TABLE G3
**Results of Analysis of Dose Formulations Administered to Rats and Mice in the Long-Term Dermal Studies of 2,3-Dibromo-1-propanol** (continued)

| Date Prepared | Date Analyzed | Target Concentration (wt/vol%) | Determined Concentration[a] (wt/vol%) | Difference from Target (%) |
|---|---|---|---|---|
| 7 October 1982 | 8 October 1982 | 3.92 | 3.68 | -6 |
| | | 7.70 | 7.32 | -5 |
| | | 26.9 | 27.3 | +2 |
| | | 47.2 | 47.6 | +1 |
| | 12 October 1982[b] | 3.92 | 3.86 | -2 |
| | | 7.70 | 7.62 | -1 |
| | | 26.9 | 27.2 | +1 |
| | | 47.2 | 47.7 | +1 |
| 1 December 1982 | 2 December 1982 | 17.9 | 18.2 | +2 |
| | | 30.6 | 30.9 | +1 |
| | 8 December 1982[b] | 17.9 | 17.8 | -1 |
| | | 30.6 | 30.6 | 0 |

[a] Results of duplicate analyses
[b] Animal-room samples
[c] Results of triplicate analyses

TABLE G4
**Results of Referee Analysis of Dose Formulations in the Long-Term Dermal Studies of 2,3-Dibromo-1-propanol**

| Date Prepared | Target Concentration (wt/vol%) | Determined Concentration (wt/vol%) | |
|---|---|---|---|
| | | Study Laboratory[a] | Referee Laboratory[b] |
| 10 December 1981 | 19.20 | 18.80 | 18.8 ± 0.3 |
| 10 December 1981[c] | 19.20 | 18.83 | 19.0 ± 0.3 |
| 16 June 1982 | 49.8 | 49.8 | 50.0 ± 1.7 |
| 1 December 1982 | 17.9 | 18.2 | 18.2 ± 0.0 |

[a] Results of duplicate analysis
[b] Results of triplicate analysis (mean ± standard deviation)
[c] Animal-room sample

# APPENDIX H
# INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH-07 RAT AND MOUSE RATION


| | | |
|---|---|---|
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| TABLE H3 | Nutrient Composition of NIH-07 Rat and Mouse Ration | 191 |
| TABLE H4 | Contaminant Levels in NIH-07 Rat and Mouse Ration | 192 |

TABLE H1
**Ingredients of NIH-07 Rat and Mouse Ration[a]**

| Ingredients[b] | Percent by Weight |
|---|---|
| Ground #2 yellow shelled corn | 24.50 |
| Ground hard winter wheat | 23.00 |
| Soybean meal (49% protein) | 12.00 |
| Fish meal (60% protein) | 10.00 |
| Wheat middlings | 10.00 |
| Dried skim milk | 5.00 |
| Alfalfa meal (dehydrated, 17% protein) | 4.00 |
| Corn gluten meal (60% protein) | 3.00 |
| Soy oil | 2.50 |
| Dried brewer's yeast | 2.00 |
| Dry molasses | 1.50 |
| Dicalcium phosphate | 1.25 |
| Ground limestone | 0.50 |
| Salt | 0.50 |
| Premixes (vitamin and mineral) | 0.25 |

[a] NCI, 1976; NIH, 1978
[b] Ingredients ground to pass through a U.S. Standard Screen No. 16 before being mixed

TABLE H2
**Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]**

| | Amount | Source |
|---|---|---|
| **Vitamins** | | |
| A | 5,500,000 IU | Stabilized vitamin A palmitate or acetate |
| $D_3$ | 4,600,000 IU | D-activated animal sterol |
| $K_3$ | 2.8 g | Menadione |
| *d*-α-Tocopheryl acetate | 20,000 IU | |
| Choline | 560.0 g | Choline chloride |
| Folic acid | 2.2 g | |
| Niacin | 30.0 g | |
| *d*-Pantothenic acid | 18.0 g | *d*-Calcium pantothenate |
| Riboflavin | 3.4 g | |
| Thiamine | 10.0 g | Thiamine mononitrate |
| $B_{12}$ | 4,000 μg | |
| Pyridoxine | 1.7 g | Pyridoxine hydrochloride |
| Biotin | 140.0 mg | *d*-Biotin |
| **Minerals** | | |
| Iron | 120.0 g | Iron sulfate |
| Manganese | 60.0 g | Manganous oxide |
| Zinc | 16.0 g | Zinc oxide |
| Copper | 4.0 g | Copper sulfate |
| Iodine | 1.4 g | Calcium iodate |
| Cobalt | 0.4 g | Cobalt carbonate |

[a] Per ton (2,000 lb) of finished product

TABLE H3
**Nutrient Composition of NIH-07 Rat and Mouse Ration**

| Nutrients | Mean ± Standard Deviation | Range | Number of Samples |
|---|---|---|---|
| Protein (% by weight) | 23.90 ± 0.92 | 22.7 – 26.3 | 14 |
| Crude fat (% by weight) | 5.10 ± 0.51 | 4.2 – 5.7 | 14 |
| Crude fiber (% by weight) | 3.39 ± 0.66 | 2.9 – 5.6 | 14 |
| Ash (% by weight) | 6.22 ± 0.31 | 5.7 – 6.7 | 14 |
| **Amino Acids (% of total diet)** | | | |
| Arginine | 1.308 ± 0.606 | 1.210 – 1.390 | 8 |
| Cystine | 0.306 ± 0.084 | 0.181 – 0.400 | 8 |
| Glycine | 1.150 ± 0.047 | 1.060 – 1.210 | 8 |
| Histidine | 0.576 ± 0.024 | 0.531 – 0.607 | 8 |
| Isoleucine | 0.917 ± 0.029 | 0.881 – 0.944 | 8 |
| Leucine | 1.946 ± 0.055 | 1.850 – 2.040 | 8 |
| Lysine | 1.270 ± 0.058 | 1.200 – 1.370 | 8 |
| Methionine | 0.448 ± 0.128 | 0.306 – 0.699 | 8 |
| Phenylalanine | 0.987 ± 0.140 | 0.665 – 1.110 | 8 |
| Threonine | 0.877 ± 0.042 | 0.824 – 0.940 | 8 |
| Tryptophan | 0.236 ± 0.176 | 0.107 – 0.671 | 8 |
| Tyrosine | 0.676 ± 0.105 | 0.564 – 0.794 | 8 |
| Valine | 1.103 ± 0.040 | 1.050 – 1.170 | 8 |
| **Essential Fatty Acids (% of total diet)** | | | |
| Linoleic | 2.393 ± 0.258 | 1.830 – 2.570 | 7 |
| Linolenic | 0.280 ± 0.040 | 0.210 – 0.320 | 7 |
| **Vitamins** | | | |
| Vitamin A (IU/kg) | 10,114 ± 2,656 | 3,600 – 14,000 | 14 |
| Vitamin D (IU/kg) | 4,450 ± 1,382 | 3,000 – 6,300 | 4 |
| α–Tocopherol (ppm) | 37.95 ± 9.41 | 22.5 – 48.9 | 8 |
| Thiamine (ppm) | 16.57 ± 2.34 | 13.0 – 21.0 | 14 |
| Riboflavin (ppm) | 7.92 ± 0.87 | 6.10 – 9.00 | 8 |
| Niacin (ppm) | 103.4 ± 26.6 | 65.0 – 150.0 | 8 |
| Pantothenic acid (ppm) | 29.54 ± 3.60 | 23.0 – 34.0 | 8 |
| Pyridoxine (ppm) | 9.55 ± 3.48 | 5.60 – 14.0 | 8 |
| Folic acid (ppm) | 2.25 ± 0.73 | 1.80 – 3.70 | 8 |
| Biotin (ppm) | 0.254 ± 0.042 | 0.19 – 0.32 | 8 |
| Vitamin $B_{12}$ (ppb) | 38.45 ± 22.01 | 10.6 – 65.0 | 8 |
| Choline (ppm) | 3,089 ± 329 | 2,400 – 3,430 | 8 |
| **Minerals** | | | |
| Calcium (%) | 1.20 ± 0.08 | 1.11 – 1.36 | 14 |
| Phosphorus (%) | 0.95 ± 0.04 | 0.88 – 1.00 | 14 |
| Potassium (%) | 0.883 ± 0.078 | 0.772 – 0.971 | 6 |
| Chloride (%) | 0.526 ± 0.092 | 0.380 – 0.635 | 8 |
| Sodium (%) | 0.313 ± 0.390 | 0.258 – 0.371 | 8 |
| Magnesium (%) | 0.168 ± 0.010 | 0.151 – 0.181 | 8 |
| Sulfur (%) | 0.280 ± 0.064 | 0.208 – 0.420 | 8 |
| Iron (ppm) | 361 ± 100 | 255.0 – 523.0 | 8 |
| Manganese (ppm) | 92.0 ± 6.0 | 81.70 – 99.40 | 8 |
| Zinc (ppm) | 54.72 ± 5.67 | 46.10 – 64.50 | 8 |
| Copper (ppm) | 11.06 ± 2.50 | 8.090 – 15.39 | 8 |
| Iodine (ppm) | 3.37 ± 0.92 | 1.52 – 4.13 | 6 |
| Chromium (ppm) | 1.79 ± 0.36 | 1.04 – 2.09 | 8 |
| Cobalt (ppm) | 0.68 ± 0.14 | 0.490 – 0.780 | 4 |

TABLE H4
**Contaminant Levels in NIH-07 Rat and Mouse Ration**

| Contaminants | Mean ± Standard Deviation[a] | Range | Number of Samples |
|---|---|---|---|
| Arsenic (ppm) | 0.45 ± 0.09 | 0.29 – 0.56 | 14 |
| Cadmium (ppm) | <0.1 | | 14 |
| Lead (ppm)[b] | 1.0 ± 0.8 | 0.05 – 3.37 | 14 |
| Mercury (ppm) | <0.05 | | 14 |
| Selenium (ppm) | 0.27 ± 0.07 | 0.13 – 0.40 | 14 |
| Aflatoxins (ppb) | <5.0 | | 14 |
| Nitrate nitrogen (ppm)[c] | 9.24 ± 3.44 | 3.80 – 15.0 | 14 |
| Nitrite nitrogen (ppm)[c] | 2.42 ± 1.91 | 0.40 – 6.90 | 14 |
| BHA (ppm) | 6.66 ± 5.74 | <2.00 – 17.0 | 14 |
| BHT (ppm) | 3.68 ± 3.17 | <0.90 – 12.0 | 14 |
| Aerobic plate count (CFU/g)[d] | 31,579 ± 27,944 | 4,900 – 88,000 | 14 |
| Coliform (MPN/g)[e] | 50 ± 121 | <3.00 – 460 | 14 |
| Coliform (MPN/g)[f] | 18.5 ± 26.8 | <3.00 – 93.0 | 13 |
| *E. coli* | 3.00 | | 14 |
| Total nitrosoamines (ppb)[g] | 4.52 ± 3.12 | 1.70 – 9.30 | 14 |
| *N*-Nitrosodimethylamine (ppb)[g] | 3.29 ± 3.06 | 0.80 – 8.30 | 14 |
| *N*-Nitrosopyrrolidine (ppb)[g] | 1.24 ± 0.58 | 0.81 – 2.90 | 14 |
| **Pesticides (ppm)** | | | |
| α-BHC[h] | <0.01 | | 14 |
| β-BHC | <0.02 | | 14 |
| γ-BHC | <0.01 | | 14 |
| δ-BHC | <0.01 | | 14 |
| Heptachlor | <0.01 | | 14 |
| Aldrin | <0.01 | | 14 |
| Heptachlor epoxide | <0.01 | | 14 |
| DDE | <0.01 | | 14 |
| DDD | <0.01 | | 14 |
| DDT | <0.01 | | 14 |
| HCB | <0.01 | | 14 |
| Mirex | <0.01 | | 14 |
| Methoxychlor | <0.05 | | 14 |
| Dieldrin | <0.01 | | 14 |
| Endrin | <0.01 | | 14 |
| Telodrin | <0.01 | | 14 |
| Chlordane | <0.05 | | 14 |
| Toxaphene | <0.1 | | 14 |
| Estimated PCBs | <0.2 | | 14 |
| Ronnel | <0.01 | | 14 |
| Ethion | <0.02 | | 14 |
| Trithion | <0.05 | | 14 |
| Diazinon | <0.1 | | 14 |
| Methyl parathion | <0.02 | | 14 |
| Ethyl parathion | <0.02 | | 14 |
| Malathion[i] | 0.09 ± 0.06 | 0.05 – 0.22 | 14 |
| Endosulfan I | <0.01 | | 14 |
| Endosulfan II | <0.01 | | 14 |
| Endosulfan sulfate | <0.03 | | 14 |

TABLE H4
**Contaminant Levels in NIH-07 Rat and Mouse Ration** (continued)

[a] For values less than the limit of detection, the detection limit is given for the mean.
[b] Mean, standard deviation, and range include one large value of 3.37 ppm.
[c] Sources of contamination: alfalfa, grains, and fish meal
[d] CFU = colony forming unit
[e] MPN = most probable number. Mean, standard deviation, and range include one large value of 460 MPN obtained in the batch milled on 23 September 1982.
[f] Mean, standard deviation, and range exclude one large value of 460 MPN obtained in the batch milled on 23 September 1982.
[g] All values were corrected for percent recovery.
[h] BHC = hexachlorocyclohexane or benzene hexachloride
[i] Seven lots contained more than 0.05 ppm.

# APPENDIX I
# SENTINEL ANIMAL PROGRAM

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TABLE I1 Murine Virus Antibody Determinations for Rats and Mice in the 13-Week and Long-Term Dermal Studies of 2,3-Dibromo-1-propanol ..... 198

# SENTINEL ANIMAL PROGRAM

## METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

### Rats

For the 13-week study, samples for viral screening were collected from three animals of each sex prior to the beginning of the study. The nasopharyngeal area of each animal was cultured for *Mycoplasma*. At the end of the study, samples for viral screening were collected from five control animals of each sex. The blood was allowed to clot, and the serum was separated. The serum was cooled on ice and sent to Microbiological Associates, Incorporated (Bethesda, MD) for determination of antibody titers. The following tests were performed:

| Method of Analysis | Time of Analysis |
|---|---|
| Complement Fixation | |
| RCV (rat coronavirus) | Study termination |
| Hemagglutination Inhibition | |
| H-1 (Toolan's H-1 virus) | Study termination |
| KRV (Kilham rat virus) | Study termination |
| PVM (pneumonia virus of mice) | Preinitiation and study termination |
| Sendai | Study termination |

Prior to the beginning of the long-term study, samples for viral screening were collected from five rats of each sex. The nasopharyngeal area of each animal was cultured for *Mycoplasma*. During the study, 15 rats of each sex were maintained with the study animals to serve as sentinel animals. However, due to the presence of antibodies against lymphocytic choriomeningitis virus (LCM) in three sentinel male mice that were housed in the same room as the rats, blood samples were collected from all animals exhibiting grossly visible tissue masses. The blood was allowed to clot, and the serum was separated. The serum was cooled on ice and sent to Microbiological Associates, Incorporated for determination of antibody titers. The following tests were performed:

| Method of Analysis | Time of Analysis |
|---|---|
| Complement Fixation | |
| LCM (lymphocytic choriomeningitis virus) | Study termination |
| RCV | 6 months |
| Sendai | Preinitiation, 6 months |
| Hemagglutination Inhibition | |
| H-1 | Preinitiation, 6 months |
| KRV | Preinitiation, 6 months |
| PVM | Preinitiation, 6 months |

## Mice

Prior to the beginning of the 13-week study, samples for viral screening were collected from three animals of each sex prior to the beginning of the study. The nasopharyngeal area of each animal was cultured for *Mycoplasma*. At the end of the study, samples for viral screening were collected from five control animals of each sex. The blood was allowed to clot, and the serum was separated. The serum was cooled on ice and sent to Microbiological Associates, Incorporated for determination of antibody titers. The following tests were performed:

| Method of Analysis | Time of Analysis |
|---|---|
| Complement Fixation | |
| MHV (mouse hepatitis virus) | Study termination |
| Hemagglutination Inhibition | |
| PVM | Study termination |
| Sendai | Study termination |

Prior to the beginning of the long-term study, samples for viral screening were collected from five mice of each sex. The nasopharyngeal area of each animal was cultured for *Mycoplasma*. During the study, 15 mice of each sex were maintained with the study animals to serve as sentinel animals. However, due to the presence of antibodies against LCM in three sentinel male mice, blood samples were collected from all animals exhibiting grossly visible tissue masses. The blood was allowed to clot, and the serum was separated. The serum was cooled on ice and sent to Microbiological Associates, Incorporated for determination of antibody titers. The following tests were performed:

| Method of Analysis | Time of Analysis |
|---|---|
| Complement Fixation | |
| LCM | 6 months, study termination |
| Mouse adenoma virus | 6 months |
| MHV | Preinitiation, 6 months |
| Sendai | 6 months |
| Hemagglutination Inhibition | |
| Ectromelia virus (mouse pox) | 6 months |
| GDVII (mouse encephalomyelitis virus) | 6 months |
| MVM (minute virus of mice) | 6 months |
| PVM | Preinitiation, 6 months |
| Polyoma virus | 6 months |
| Reovirus 3 | 6 months |
| Sendai | Preinitiation |
| Immunofluorescent Antibody | |
| LCM | 6 months, study termination |

Serology results for sentinel animals are presented in Table I1.

TABLE I1
**Murine Virus Antibody Determinations for Rats and Mice in the 13-Week and Long-Term Dermal Studies of 2,3-Dibromo-1-propanol[a]**

| Interval | Incidence of Antibody in Sentinel Animals | Positive Serologic Reaction for |
|---|---|---|
| **13-Week Studies** | | |
| Rats | 0/10 | None positive |
| Mice | 0/10 | None positive |
| **Long-Term Studies** | | |
| Rats | | |
| 6 months | 4/11 | RCV |
| Study termination | 0/300 | None positive |
| Mice | | |
| 6 months | 2/10 | LCM |
| Study termination | 43/326 | LCM[b] |

[a] The rat study was terminated at 48 weeks for males and 55 weeks for females; the mouse study was terminated at 36 weeks for males and 42 weeks for females. Data were collected from sentinel and study animals at study termination.
[b] Positive titers were found in 3 sentinel males and 40 study males.

# APPENDIX J
# SINGLE-DOSE GAVAGE AND DERMAL STUDIES

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# SINGLE-DOSE STUDIES

## ACUTE TOXICITY STUDIES

### Materials and Methods

The studies were performed by Papanicolaou Cancer Research Institute at Miami, Incorporated (Miami, FL). Male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries (Indianapolis, IN) and observed for 4 weeks before the studies began. Rats and mice were 10 weeks old at the beginning of the studies. Groups of five rats and five mice of each sex were administered a single dose of 0, 88, 177, 375, 750, or 1,500 mg/kg 2,3-dibromo-1-propanol in corn oil by gavage. Groups of five rats received a single application of 0, 88, 177, 375, 750, or 1,500 mg/kg 2,3-dibromo-1-propanol and groups of five mice received a single application of 0, 177, 375, 750, 1,500, or 3,000 mg/kg 2,3-dibromo-1-propanol in ethanol to the interscapular skin. The studies were terminated 11 days after the day of 2,3-dibromo-1-propanol administration.

Animals were housed five per cage in polycarbonate cages (Lab Products, Inc., Rochelle Park, NJ) with Sani-Chip hardwood bedding (Pinewood Products Co.) on stainless steel racks; cages were changed twice weekly, and racks were changed every 10 days. Water (city of Miami water supply) and feed (Purina Certified Rodent Chow) were available *ad libitum*. The room temperature was maintained between 74° and 76° F; relative humidity was 45% to 55%. Room air was changed 18 to 20 times per hour, and fluorescent light was available on a 12-hour cycle.

### Results

*Rats:* All males and females receiving 1,500 mg/kg 2,3-dibromo-1-propanol by gavage or dermal administration or 750 mg/kg by gavage died on the day of exposure. Three of five males and three of five females that received 375 mg/kg by gavage and one female that received 177 mg/kg by gavage also died by day 2. The surviving rats receiving 375 mg/kg by gavage and all rats exposed to 750 mg/kg by dermal application were sluggish and weak through day 3; all had recovered by day 5.

*Mice:* In mice receiving 2,3-dibromo-1-propanol by gavage, all males and females receiving 1,500 mg/kg, all males and four females receiving 750 mg/kg, three males receiving 375 mg/kg, and one male receiving 177 mg/kg died within 1 day of exposure. Survivors from the 375 and 750 mg/kg groups were weak and atoxic or lethargic and weak through day 3. The remaining female from the 750 mg/kg group and one female from the 375 mg/kg group died on day 4, and the two remaining males from the 375 mg/kg group died on day 5. One male that received 177 mg/kg and two females that received 375 mg/kg died on day 5. Mice in the 88 and 177 mg/kg groups showed no adverse effects.

In mice receiving dermal application of 2,3-dibromo-1-propanol, all males and females receiving 3,000 mg/kg, three males and three females receiving 1,500 mg/kg, and two males receiving 750 mg/kg died within 1 day of exposure. The two remaining males from the 1,500 mg/kg group and one male from the 750 mg/kg group died on day 4; one female from the 1,500 mg/kg group died on day 5. Males from the 1,500 and 750 mg/kg groups that survived through day 3, and one male in the 375 mg/kg group, were atoxic and very weak; survivors recovered by day 4.

## COMPARATIVE GAVAGE AND DERMAL ABSORPTION STUDIES

### Materials and Methods

The studies were performed by Papanicolaou Cancer Research Institute at Miami, Incorporated (Miami, FL). Male F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries and observed for 4 weeks before the studies began. Rats were 6 weeks old and mice were 8 weeks old at the beginning of the studies. Rats were starved overnight and mice for 4 hours before chemical administration; water was available *ad libitum*.

For the dermal administration studies, the backs of 35 rats and 35 mice were shaved. Seven rats and seven mice were maintained as vehicle controls; 28 rats received 500 mg/kg and 28 mice received 177 mg/kg 2,3-dibromo-1-propanol in ethanol, applied to the interscapular skin. For the gavage studies, seven rats and seven mice were maintained as vehicle controls, and 28 rats and 28 mice received 177 mg/kg 2,3-dibromo-1-propanol in corn oil by gavage. The concentration of 2,3-dibromo-1-propanol in blood was measured at 15 and 30 minutes and 1, 2, 4, 12, and 24 hours after dosing. At each interval, blood was withdrawn by cardiac puncture from four exposed animals and one control animal that had been anesthetized with diethyl ether. Blood samples were hemolyzed by shaking with 2 mL saturated salt solution. Solid sodium chloride was added, and the samples were then extracted with 4 mL diethyl ether and centrifuged. The solvent was removed and diluted to 25 mL with isooctane, and then analyzed by gas-liquid partition chromatography to determine whether further dilution was necessary; subsequent dilutions were made with isooctane. Gas chromatography with electron capture detection and a 10% SP-2330 column on 100/120 mesh Chromosorb W(AW), with a nitrogen carrier gas at 30 mL/minute and an oven temperature of 158° C, was used to determine the concentration of 2,3-dibromo-1-propanol in the samples.

### Results

2,3-Dibromo-1-propanol was absorbed through the skin and cleared from the blood rapidly for rats and mice. The absorption efficiency for dermal application relative to gavage administration was 68% for rats and 37% for mice. The highest concentrations of 2,3-dibromo-1-propanol were found 15 minutes after dermal or gavage exposure for rats and 30 minutes after dermal exposure or 2 hours after gavage exposure for mice. Complete clearance of 2,3-dibromo-1-propanol from the blood occurred in less than 4 hours for rats and mice. Fluctuations in the levels of 2,3-dibromo-1-propanol in the blood of rats and mice receiving gavage exposure were not significant by Student's t-test; for animals receiving dermal application of 2,3-dibromo-1-propanol, fluctuations in blood concentrations of rats between 15 minutes and 1 hour and of mice during the first 30 minutes were not significant by the t-test. Results are shown in Tables J1 and J2.

TABLE J1
**Concentration of 2,3-Dibromo-1-propanol in Blood for Rats in the Comparative Gavage and Dermal Studies[a]**

| Time After Dosing | Gavage Study | | Dermal Study | |
|---|---|---|---|---|
| | Vehicle Control[b] | 177 mg/kg[c] | Vehicle Control[b] | 500 mg/kg[c] |
| 15 minutes | 1.0 | 65.6 ± 14.7 | 21.6 | 126.2 ± 29.9 |
| 30 minutes | 2.6 | 47.2 ± 27.4 | 2.6 | 45.3 ± 17.7 |
| 1 hour | 1.9 | 10.3 ± 2.5 | 1.5 | 116.6 ± 37.1 |
| 2 hours | 4.9 | 10.0 ± 2.7 | 4.9 | 8.1 ± 1.3 |
| 4 hours | 2.8 | 6.6 ± 2.2 | 2.4 | 2.0 ± 0.3 |
| 12 hours | 0.9 | 7.5 ± 3.5 | 1.3 | 1.5 ± 0.3 |
| 24 hours | 0.5 | 6.5 ± 2.7[d] | 1.3 | 1.3 ± 0.4 |

[a] Concentrations are given in units of $10^{-7}$ g 2,3-dibromo-1-propanol/mL sample.
[b] Results of triplicate analyses of sample taken from a single vehicle control animal per time period
[c] Mean ± standard error for groups of four animals, unless otherwise specified. Results of triplicate analyses.
[d] n=3

TABLE J2
**Concentration of 2,3-Dibromo-1-propanol in Blood for Mice in the Comparative Gavage and Dermal Studies[a]**

| Time After Dosing | Gavage Study | | Dermal Study | |
|---|---|---|---|---|
| | Vehicle Control[b] | 177 mg/kg[c] | Vehicle Control[b] | 177 mg/kg[c] |
| 15 minutes | 1.7 | 21.3 ± 3.1 | 2.1 | 17.9 ± 2.2 |
| 30 minutes | 1.3 | 35.2 ± 7.3 | 1.6 | 19.1 ± 4.7 |
| 1 hour | 0.7 | 19.4 ± 8.4 | 0.6 | 4.8 ± 1.1 |
| 2 hours | 0.9 | 51.6 ± 15.1 | 1.2 | 1.8 ± 0.4 |
| 4 hours | 1.0 | 19.7 ± 5.5 | 0.9 | 0.9 ± 0.3 |
| 12 hours | 0.5 | 2.2 ± 0.5 | 0.6 | 0.6 ± 0.1 |
| 24 hours | 1.5 | 1.6 ± 0.4 | 2.2 | 1.2 ± 0.3 |

[a] Concentrations are given in units of $10^{-7}$ g 2,3-dibromo-1-propanol/mL sample.
[b] Results of triplicate analyses of sample taken from a single vehicle control animal per time period
[c] Mean ± standard error for groups of four animals. Results of triplicate analyses.

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# PRINTED AS OF DECEMBER 1993

| TR No. | CHEMICAL |
|---|---|
| 201 | 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal) |
| 206 | 1,2-Dibromo-3-chloropropane |
| 207 | Cytembena |
| 208 | FD & C Yellow No. 6 |
| 209 | 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage) |
| 210 | 1,2-Dibromoethane |
| 211 | C.I. Acid Orange 10 |
| 212 | Di(2-ethylhexyl)adipate |
| 213 | Butyl Benzyl Phthalate |
| 214 | Caprolactam |
| 215 | Bisphenol A |
| 216 | 11-Aminoundecanoic Acid |
| 217 | Di(2-Ethylhexyl)phthalate |
| 219 | 2,6-Dichloro-p-phenylenediamine |
| 220 | C.I. Acid Red 14 |
| 221 | Locust Bean Gum |
| 222 | C.I. Disperse Yellow 3 |
| 223 | Eugenol |
| 224 | Tara Gum |
| 225 | D & C Red No. 9 |
| 226 | C.I. Solvent Yellow 14 |
| 227 | Gum Arabic |
| 228 | Vinylidene Chloride |
| 229 | Guar Gum |
| 230 | Agar |
| 231 | Stannous Chloride |
| 232 | Pentachloroethane |
| 233 | 2-Biphenylamine Hydrochloride |
| 234 | Allyl Isothiocyanate |
| 235 | Zearalenone |
| 236 | *D*-Mannitol |
| 237 | 1,1,1,2-Tetrachloroethane |
| 238 | Ziram |
| 239 | Bis(2-chloro-1-Methylethyl)ether |
| 240 | Propyl Gallate |
| 242 | Diallyl Phthalate (Mice) |
| 243 | Trichlorethylene (Rats and Mice) |
| 244 | Polybrominated Biphenyl Mixture |
| 245 | Melamine |
| 246 | Chrysotile Asbestos (Hamsters) |
| 247 | L-Ascorbic Acid |
| 248 | 4,4'-Methylenedianiline Dihydrochloride |
| 249 | Amosite Asbestos (Hamsters) |
| 250 | Benzyl Acetate |
| 251 | 2,4- & 2,6-Toluene Diisocyanate |
| 252 | Geranyl Acetate |
| 253 | Allyl Isovalerate |
| 254 | Dichloromethane (Methylene Chloride) |
| 255 | 1,2-Dichlorobenzene |
| 257 | Diglycidyl Resorcinol Ether |
| 259 | Ethyl Acrylate |
| 261 | Chlorobenzene |
| 263 | 1,2-Dichloropropane |
| 266 | Monuron |
| 267 | 1,2-Propylene Oxide |
| 269 | Telone II® (1,3-Dichloropropene) |
| 271 | HC Blue No. 1 |
| 272 | Propylene |
| 273 | Trichloroethylene (Four Rat Strains) |
| 274 | Tris(2-ethylhexyl)phosphate |
| 275 | 2-Chloroethanol |
| 276 | 8-Hydroxyquinoline |
| 277 | Tremolite |
| 278 | 2,6-Xylidine |
| 279 | Amosite Asbestos |
| 280 | Crocidolite Asbestos |
| 281 | HC Red No. 3 |
| 282 | Chlorodibromomethane |
| 284 | Diallylphthalate (Rats) |
| 285 | C.I. Basic Red 9 Monohydrochloride |
| 287 | Dimethyl Hydrogen Phosphite |
| 288 | 1,3-Butadiene |
| 289 | Benzene |
| 291 | Isophorone |
| 293 | HC Blue No. 2 |
| 294 | Chlorinated Trisodium Phosphate |
| 295 | Chrysotile Asbestos (Rats) |
| 296 | Tetrakis(hydroxymethyl) phosphonium Sulfate & Tetrakis(hydroxymethyl) phosponium Chloride |
| 298 | Dimethyl Morpholinophosphoramidate |
| 299 | C.I. Disperse Blue 1 |
| 300 | 3-Chloro-2-methylpropene |
| 301 | *o*-Phenylphenol |
| 303 | 4-Vinylcyclohexene |
| 304 | Chlorendic Acid |
| 305 | Chlorinated Paraffins ($C_{23}$, 43% chlorine) |
| 306 | Dichloromethane (Methylene Chloride) |
| 307 | Ephedrine Sulfate |
| 308 | Chlorinated Pariffins ($C_{12}$, 60% chlorine) |
| 309 | Decabromodiphenyl Oxide |
| 310 | Marine Diesel Fuel and JP-5 Navy Fuel |
| 311 | Tetrachloroethylene (Inhalation) |
| 312 | *n*-Butyl Chloride |
| 313 | Mirex |
| 314 | Methyl Methacrylate |
| 315 | Oxytetracycline Hydrochloride |
| 316 | 1-Chloro-2-methylpropene |
| 317 | Chlorpheniramine Maleate |
| 318 | Ampicillin Trihydrate |
| 319 | 1,4-Dichlorobenzene |
| 320 | Rotenone |
| 321 | Bromodichloromethane |
| 322 | Phenylephrine Hydrochloride |
| 323 | Dimethyl Methylphosphonate |
| 324 | Boric Acid |
| 325 | Pentachloronitrobenzene |
| 326 | Ethylene Oxide |
| 327 | Xylenes (Mixed) |
| 328 | Methyl Carbamate |
| 329 | 1,2-Epoxybutane |
| 330 | 4-Hexylresorcinol |
| 331 | Malonaldehyde, Sodium Salt |
| 332 | 2-Mercaptobenzothiazole |
| 333 | *N*-Phenyl-2-naphthylamine |
| 334 | 2-Amino-5-nitrophenol |
| 335 | C.I. Acid Orange 3 |

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# NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS PRINTED AS OF DECEMBER 1993 (CONT.)

| TR No. | CHEMICAL |
|---|---|
| 336 | Penicillin VK |
| 337 | Nitrofurazone |
| 338 | Erythromycin Stearate |
| 339 | 2-Amino-4-nitrophenol |
| 340 | Iodinated Glycerol |
| 341 | Nitrofurantoin |
| 342 | Dichlorvos |
| 343 | Benzyl Alcohol |
| 344 | Tetracycline Hydrochloride |
| 345 | Roxarsone |
| 346 | Chloroethane |
| 347 | D-Limonene |
| 348 | α-Methyldopa Sesquihydrate |
| 349 | Pentachlorophenol |
| 350 | Tribromomethane |
| 351 | *p*-Chloroaniline Hydrochloride |
| 352 | N-Methylolacrylamide |
| 353 | 2,4-Dichlorophenol |
| 354 | Dimethoxane |
| 355 | Diphenhydramine Hydrochloride |
| 356 | Furosemide |
| 357 | Hydrochlorothiazide |
| 358 | Ochratoxin A |
| 359 | 8-Methoxypsoralen |
| 360 | N,N-Dimethylaniline |
| 361 | Hexachloroethane |
| 362 | 4-Vinyl-1-Cyclohexene Diepoxide |
| 363 | Bromoethane (Ethyl Bromide) |
| 364 | Rhodamine 6G (C.I. Basic Red 1) |
| 365 | Pentaerythritol Tetranitrate |
| 366 | Hydroquinone |
| 367 | Phenylbutazone |
| 368 | Nalidixic Acid |
| 369 | Alpha-Methylbenzyl Alcohol |
| 370 | Benzofuran |
| 371 | Toluene |
| 372 | 3,3-Dimethoxybenzidine Dihydrochloride |
| 373 | Succinic Anhydride |
| 374 | Glycidol |
| 375 | Vinyl Toluene |
| 376 | Allyl Glycidyl Ether |
| 377 | *o*-Chlorobenzalmalononitrile |
| 378 | Benzaldehyde |
| 379 | 2-Chloroacetophenone |
| 380 | Epinephrine Hydrochloride |
| 381 | *d*-Carvone |
| 382 | Furfural |
| 385 | Methyl Bromide |
| 386 | Tetranitromethane |
| 387 | Amphetamine Sulfate |
| 388 | Ethylene Thiourea |
| 389 | Sodium Azide |
| 390 | 3,3′-Dimethylbenzidine Dihydrochloride |
| 391 | Tris(2-chloroethyl) Phosphate |
| 392 | Chlorinated Water and Chloraminated Water |
| 393 | Sodium Fluoride |
| 394 | Acetaminophen |
| 395 | Probenecid |
| 396 | Monochloroacetic Acid |
| 397 | C.I. Direct Blue 15 |
| 398 | Polybrominated Biphenyls |
| 399 | Titanocene Dichloride |
| 401 | 2,4-Diaminophenol Dihydrochloride |
| 402 | Furan |
| 403 | Resorcinol |
| 404 | 5,5-Diphenylhydantoin |
| 405 | C.I. Acid Red 114 |
| 406 | γ-Butyrolactone |
| 407 | C.I. Pigment Red 3 |
| 408 | Mercuric Chloride |
| 409 | Quercetin |
| 410 | Naphthalene |
| 411 | C.I. Pigment Red 23 |
| 412 | 4,4-Diamino-2,2-Stilbenedisulfonic Acid |
| 413 | Ethylene Glycol |
| 414 | Pentachloroanisole |
| 415 | Polysorbate 80 |
| 416 | *o*-Nitroanisole |
| 417 | *p*-Nitrophenol |
| 418 | *p*-Nitroaniline |
| 419 | HC Hellow 4 |
| 421 | Talc |
| 422 | Coumarin |
| 423 | Dihydrocoumarin |
| 427 | Turmeric Oleoresin |
| 431 | Benzyl Acetate |
| 434 | 1,3-Butadiene |
| 443 | Oxazepam |

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