Public Health Goal for 1,2-Dibromo-3-chloropropane (DBCP) In Drinking Water

Prepared by

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PREFACE

Drinking Water Public Health Goals

Pesticide and Environmental Toxicology Section

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs).

Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA web site at www.oehha.ca.gov.

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PUBLIC HEALTH GOAL FOR 1,2-DIBROMO-3-CHLOROPROPANE (DBCP) IN DRINKING WATER

SUMMARY

The Office of Environmental Health Hazard Assessment (OEHHA) has developed a Public Health Goal (PHG) of 1.7 ppt (parts per trillion) for 1,2-dibromo-3-chloropropane (DBCP) in drinking water. The PHG is based on carcinogenic effects observed in experimental animals and reported by Hazleton (1977, 1978). Significant increases in tumor incidence were observed in female mice exposed to DBCP in their food. A dose of 4.8 mg/kg-day to female mice resulted in significant increases in squamous cell carcinomas of the forestomach versus the controls. A cancer potency of 7 $(mg/kg\text{-}day)^{-1}$ for the formation of squamous cell carcinomas of the forestomach was derived from this study by OEHHA (DHS, 1988a) and was used in this risk assessment. These tumors were also observed in male mice and rats of both sexes. DBCP was also mutagenic and was a male reproductive toxicant in laboratory animals and in humans. The PHG was calculated based on a de minimis theoretical excess individual cancer risk level of 10^{-6} from exposure to DBCP, taking into account oral, dermal and inhalation exposures.

A public health protective water concentration based on a non-cancer toxic endpoint was also calculated. This level was 0.2 ppb and was based on the most sensitive non-cancer toxic endpoint, testicular effects in male rabbits (Rao et al., 1982). The NOAEL derived from this study was 0.025 mg/kg-day (the LOAEL was approximately 0.25 mg/kg-day). The calculation of the health protective water concentration based on this endpoint assumes an adult body weight of 70 kg, a relative source contribution of 80%, a drinking water consumption of 6 Leq/day, and applies an uncertainty factor of 1,000 (10 for interspecies variability, 10 for intraspecies variability, 10 for the use of a subchronic NOAEL). The calculated concentration of 0.2 ppb based on this endpoint was not proposed as the PHG because DBCP poses a carcinogenic risk to the public health and the concentration of 1.7 ppt establishes a level that does not pose any significant cancer risk to public health.

INTRODUCTION

The purpose of this document is to propose a Public Health Goal (PHG) for DBCP in drinking water. We evaluated some newer data on the toxicity of DBCP, however, the majority of the assessment is based on a reevaluation of data that can be found in prior assessments (DHS, 1988; Reed et al., 1987). The cancer potency used in this risk assessment was derived previously by OEHHA (DHS, 1988a,b).

A Maximum Contaminant Level (MCL) of 0.0002 mg/L (200 ppt) was established by the California Department of Health Services (DHS) in 1991 (Barclays, 1998a). This MCL was based in part on the results of the risk assessments performed by OEHHA (formerly part of DHS) in 1988 (DHS, 1988a) and by the University of California, Davis, under contract with the department, in 1987 (Reed et al., 1987). The U.S. Environmental Protection Agency (U.S. EPA) has an identical MCL of 0.0002 mg/L and has set the federal Maximum Contaminant Level Goal (MCLG) to zero due to their classification of DBCP as a B2 carcinogen (U.S. EPA, 1985c, 1998).

Under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65), DBCP is listed as a chemical known to the State to cause cancer and male reproductive toxicity. This 1987 listing was due to the material's identification in the Labor Code and its OSHA-driven carcinogen warning requirement (Barclays, 1998b). The International Agency for Research on Cancer (IARC) has classified DBCP as Group 2B, "possibly carcinogenic to humans" (IARC, 1979). DBCP is also listed in the NTP's Seventh Annual Report on Carcinogens as a compound "reasonably anticipated" to be a carcinogen (NTP, 1994). Although U.S. EPA has classified DBCP as a B2 carcinogen, a "probable human carcinogen", it is important to note that U.S. EPA has removed its cancer assessment for the chemical from its Integrated Risk Information System, stating that the assessment is "now under review" (IRIS, 1998).

CHEMICAL PROFILE

Chemical Identity

DBCP is a simple halogenated hydrocarbon that is a liquid at room temperature. The chemical formula, structure, synonyms and identification numbers are listed in Table 1 and were adapted from the ATSDR toxicological profile for the compound (ATSDR, 1992).

Physical and Chemical Properties

DBCP is miscible in water and alcohols and is also very volatile. Other important physical and chemical properties of DBCP are given in Table 2.

Production and Uses

DBCP was originally introduced by the Dow Chemical Company under the trade name Fumazone and by the Shell Development Company under the code number "OS 1897" for use as a soil fumigant for the control of plant parasitic nematodes (USDA, 1978). First produced commercially in the United States in 1955, DBCP production during the years 1974-1975 is estimated to have been between 18 to 20 million pounds annually (IARC, 1979). The major agricultural use was on soybeans at approximately 12 million pounds per year.

Until 1977, DBCP was used extensively as a soil fumigant and nematocide on over 40 different crops in the United States. In addition to soybeans, crops receiving extensive treatment with DBCP included fruits, nuts, vegetables, peanuts, and cotton. On the basis of possible carcinogenic and reproductive effects, U.S. EPA in 1977 suspended registration of products containing DBCP except for pre-planting use as a soil fumigant for pineapples in Hawaii (U.S. EPA 1977, 1979). In 1985, U.S. EPA issued an intent to cancel all registrations for DBCP-containing pesticide products, including those used in the Hawaiian pineapple industry (U.S. EPA, 1985a,b). The chemical is no longer manufactured commercially or used agriculturally in this country (ATSDR, 1992).

In California, the agricultural use of DBCP was suspended in 1977. In its last year of use in the state, approximately 426,000 pounds of active ingredient were used in the state, primarily on tomatoes and grapes (CDFA, 1978).

Small amounts of the chemical are still used for research purposes and as an intermediate in organic synthesis. The exact amount of material currently being used is unknown, but is thought to be very small (ATSDR 1992).

Table 1. Chemical Identity of DBCP

Chemical Name	1,2-dibromo-3-chloropropane
Synonyms	DBCP, BBC 12
Previously registered trade names	Nemagon, Nemafume, Fumazone, Fumagon, Nemabrom, Nemazon, OS 1897
Chemical formula	$C_3H_5Br_2Cl$
Wiswesser line notation	G1YE1E
Chemical structure	$CH_2BrCHBrCH_2Cl$

Table 2. Physical and Chemical Properties of DBCP

Property	**Value or Information**	**References**
Molecular weight	236.36	Windholz, 1983
Color	Colorless liquid when pure, amber to dark-brown or yellow liquid as technical mixture	Sax and Lewis, 1987; Verschueren, 1983; NIOSH, 1985
Physical state	Liquid	Windholz, 1983
Odor	Pungent	Windholz, 1983
Odor threshold	0.965 mg/m^3	Ruth, 1986
Melting point	6^o C	Stenger, 1978
Boiling point	196^o C	Stenger, 1978
Flash point	76.6^o C (open cup)	Sax and Lewis, 1987
Solubility		
Water	1,230 mg/L @ 20^o C	Munnecke and VanGundy, 1979
Organic solvents	Miscible with methanol, ethanol, isopropanol, hydrocarbons, halogenated hydrocarbons, and oils	IARC, 1979; Windholz, 1983
Density	2.093 g/cm^3 @ 14^o C	
Partition coefficients		
Log K_{ow}	2.26 (estimated)	U.S. EPA, 1988b

Property	Value or Information	References
Log K_{oc}	2.17; 2.11	Sabljic, 1984; Wilson et al., 1981
bioconcentration factor	11.2	Bysshe, 1982
Vapor pressure	0.58 mmHg @ 20° C	Munnecke and VanGundy, 1979
Henry's law constant	1.47 x 10^{-4} atm-m^3/mol @ 20° C	Thomas, 1982
Conversion factors	1 ppm = 9.67 mg/m^3; 1 mg/m^3 = 0.103 ppm	ATSDR, 1992

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

DBCP may be released into the air from soils which were treated with the chemical for agricultural purposes. In addition, the chemical may be released into the air from the use of well water contaminated with DBCP. Since DBCP has not been used agriculturally for approximately 20 years and concentrations of the chemical in well water are quite low, significant concentrations of DBCP are probably not volatilized from contaminated water to the ambient atmosphere. Accordingly, the background level for ambient air is expected to be negligible (ATSDR, 1992). A possible exception to this may be the air near hazardous waste sites where DBCP has been disposed. No data appears to be available concerning atmospheric concentrations of DBCP at these sites, however. Although the CLP Statistical Database does not list DBCP among the compounds most frequently found at National Priority List waste sites, at least three of such sites are located in California (CLPSD, 1989). Another exception would be the air in a home where DBCP contaminated water is used. Significant inhalation exposure to volatilized DBCP could occur during showering, bathing, cooking, for example.

Soil

DBCP can be quite persistent in soil under certain conditions. For example, residues of up to 0.5 µg DBCP/kg soil have been found in a field 6-7 years following the last application. Since the material is quite volatile and has not been used agriculturally for a number of years, widespread exposure to DBCP due to soil contamination is unlikely. Ambient soil levels in areas where the chemical has not been used are most likely negligible. In areas where the material has been extensively used, soil concentrations are probably less than 0.5 µg DBCP/kg soil.

Water

DBCP is not currently manufactured or used agriculturally in the United States, accordingly, significant releases into surface or groundwater are not expected. Furthermore, any surface water contamination by DBCP would be expected to have dissipated by this time as the chemical has not been used in significant quantities for a number of years.

Extensive use of DBCP, however, has resulted in contamination of underground aquifers in several areas of this country, in particular the Sacramento Valley of California (Peoples et al., 1980). DBCP, depending upon conditions such as pH and temperature, can be quite persistent in groundwater. Half-life estimates for this material in underground aquifers are as long as 141 years (Burlington et al., 1982). The 1996 Update of the California Well Inventory Database (CDPR, 1997) reported DBCP as, by far, the most frequently detected contaminant, with DBCP detected in 370 out of 1,884 wells tested (20%). Although the majority of detections (70%) were in wells in the San Joaquin Valley (Kern, Fresno, Merced, Tulare, and Stanislaus Counties), contaminated wells were also found in the extreme southern part of the state (Riverside and San Bernardino Counties; 82 detections) and in the Sacramento Valley (Sutter County - 1 detection).

It has been estimated that more than 200,000 Californians are exposed to DBCP from their water supply (Reed et al., 1987). Concentrations of DBCP found in 1992-93 in Fresno, California, well water range from 6.3×10^{-5} mg/L (the average of 21 active wells is the city limits) to 2.8×10^{-3} mg/L in the most contaminated (not active) well in the city (Kloos, 1995). Using the time-weighted lifetime daily dose factors as developed by Reed et al. (1987), these water concentrations convert to lifetime daily average doses of 1.6×10^{-5} and 1.0×10^{-3} mg/kg-day, respectively.

Food

DBCP has not been used in California agriculturally for approximately twenty years. With the exception of the use of contaminated groundwater for agricultural purposes, no residues of the chemical are expected in foods. In the case that contaminated groundwater was used for agricultural irrigation, residues in harvested products are expected to be negligible.

METABOLISM AND PHARMACOKINETICS

Absorption

Oral

DBCP is rapidly and extensively absorbed following oral exposure in the rat. Peak blood levels occur within five minutes to three hours following dosing (Gingell et al., 1987a; Kato et al. 1979a,b; Ruddick and Newsome, 1979), depending upon the vehicle. Animals dosed with DBCP in water showed maximum blood concentrations within five to forty minutes, while it took approximately three hours for DBCP blood concentrations to peak in those animals exposed to the chemical in corn oil. With a water vehicle, DBCP absorption followed first-order kinetics, the time to peak blood levels was not dose-dependent up to 10 mg/kg. Although the rate of

absorption was slower and more erratic with corn oil as the vehicle, the extent of absorption (as determined by area under the curve estimation) was approximately the same with either vehicle (68-78%).

It is assumed that DBCP is absorbed following oral administration by other laboratory species (guinea pig, rabbit, chick) because of the systemic toxic effects observed in these animals following oral exposure to the compound.

No data is available concerning absorption of DBCP in humans via the oral route. It is presumed that since absorption occurs by this route in experimental animals, it occurs in humans as well. For the purposes of this risk assessment, it is assumed that complete oral absorption of DBCP occurs in humans.

Dermal

No studies regarding the dermal absorption of DBCP in humans or experimental animals are available. It can be inferred that the material is absorbed by this route in the rabbit in toxic amounts, as Torkelson et al. (1961) determined an LD_{50} of 500 - 1400 mg/kg in this species.

Evidence that DBCP can be absorbed by the dermal route in humans is provided by the observation that death occurred in a middle-aged female following a 24 hour dermal (and inhalation) exposure to this material (Torkelson et al., 1961; U.S. EPA, 1976). The victim died two days following exposure from renal and hepatic failure. The individual's liver was at an early cirrhotic stage which likely exacerbated the acute toxicity of DBCP. Dermal absorption of DBCP in humans can also be inferred from worker studies (Whorton and Foliart, 1988).

Inhalation

No specific studies regarding the inhalation absorption of DBCP in humans or experimental animals are available. Absorption by this route can be inferred, however, as DBCP is a potent systemic toxicant in experimental animals when inhaled (Torkelson et al. 1961, Rao et al. 1983).

Evidence that DBCP can be absorbed by humans via the inhalation route is provided by the cases of testicular and reproductive toxicity following occupational exposure to DBCP (Olsen et al. 1990; Takahashi et al., 1981; Whorton et al., 1977, 1979).

Inhalation studies with similar compounds in animals (EDB, TCE, chloroform, etc.) suggest that approximately 50% of inhaled low molecular weight halogenated aliphatic hydrocarbons are actually absorbed (Raabe, 1986; Stott and McKenna, 1984). The average fraction of low molecular weight compounds (including methylene chloride) absorbed over a range of ventilation rates by human volunteers was 50.4% (Astrand, 1975). Accordingly, for the purposes of this risk assessment, 50% absorption of DBCP by the inhalation route is assumed.

Distribution

No information is available regarding the tissue distribution of DBCP in humans. Data regarding the distribution of absorbed DBCP in laboratory animals is limited to studies in the rat following oral and intravenous dosing. The result of those studies are discussed below.

DBCP is rapidly and extensively distributed to all major tissues in the rat (Lipscomb et al., 1977; Kato et al., 1979b, 1980a,b; Ruddick and Newsome, 1979). The apparent volume of distribution is reported as 4.98 L/kg (Gingell et al., 1987b). Six hours after an oral dose of ^{14}C-DBCP, the highest concentrations of radioactivity were found in the liver, kidney, intestine, and stomach (Kato et al., 1979a). The compound was rapidly and extensively metabolized, as only 0.44 % and 0.16 % of the radioactivity present at six hours was due to parent compound in the kidney and liver, respectively. The remainder of the radioactivity was associated with unidentified metabolites or was unextractable. Radioactivity associated with the testes was less than that associated with two other target tissues (liver and kidney).

DBCP is cleared from rat adipose tissue relatively rapidly, with only 3-14% of the peak levels of radioactivity remaining in the fat 24 hours after dosing (Kato et al., 1979b; Ruddick and Newsome, 1979). The estimated half-life of DBCP elimination from fat in rats ranges from three to approximately six hours (Reed et al., 1987). Accordingly, DBCP is not expected to accumulate in adipose tissue.

Metabolism

Following intragastric administration of radioactively labeled DBCP to rats, more than 90% of the radioactivity appeared in metabolites eliminated in expired air, urine and feces. Less than 1% of the administered dose was eliminated by the lungs as unchanged DBCP, almost all of the radioactivity eliminated by the lungs was in CO_2 (Kato et al., 1979, Gingell et al., 1987a). Following i.p. administration of ^{13}C-labeled DBCP to rats, 15 metabolites were detected in bile and 12 in urine. Five metabolites present in both bile and urine were identified as glutathione conjugated derivatives of DBCP (Dohn et al., 1988). Four other metabolites in urine were identified as N-acetylcysteine conjugated derivatives (Weber et al., 1995).

Metabolism of DBCP has been studied by measuring bromide release in the presence of rat liver microsomes and NADPH. Microsomes from rats pretreated with phenobarbital were approximately 20 times as active as those from rats not given phenobarbital (Lag et al., 1989). Addition of glutathione increased bromide release by a factor of 1.79, but addition of the cytochrome P-450 inhibitors SKF 525-A and metyrapone decreased bromide production by factors of 5 and 10, respectively. Incubation of DBCP in the absence of NADPH yielded 3% of the bromide produced in the presence of NADPH (Lag et al., 1989). A potent direct-acting mutagen, 2-bromoacrolein, has been identified as a product of phenobarbital-induced rat liver microsome metabolism of DBCP in the presence of NADPH (Omichinski et al., 1988).

Incubation of DBCP and GSH with the cytosol fraction of tissue homogenates also released bromide. The cytosol from liver was approximately twice as active as that from testis and four times as active as that from kidney of male rats (Lag et al., 1989). When GSH was not added, bromide formation was reduced to 5, 16, and 11% of the level of cytosols in the presence of GSH from liver, kidney and testis, respectively.

Excretion

No studies are available in the literature regarding the excretion of DBCP in humans, nor were any found concerning the excretion of DBCP in experimental animals following inhalation or dermal exposures. The only available information regarding the excretion of DBCP by rats following oral and intravenous exposure is described below.

Radiolabeled products derived from ^{14}C-DBCP are excreted via several routes following administration. Significant amounts of radiolabel was excreted in exhaled air (14% within 4 hours; approximately 20% by 48 hours), however, only trace quantities (<1%) of the radioactivity was associated with unmetabolized DBCP (Jones et al., 1979; Kato et al., 1979b). Following an oral dose of 20 mg/kg ^{14}C-DBCP, urinary and fecal excretion accounted for approximately 51% and 23% of the dose, respectively. Mercapturic acids were detected in the urine (Kato et al., 1979b). Similar results have been observed by other investigators (Gingell et al., 1987b).

Toxicokinetic Modeling

Gingell et al. (1987a) investigated the toxicokinetics of DBCP in the rat after oral and intravenous dosing. DBCP was rapidly absorbed from the gastrointestinal tract in either a water or corn-oil vehicle. Peak blood levels were reached in five to forty minutes (water vehicle). The compound was absorbed more slowly from corn oil, as it took approximately three hours to reach maximum blood levels. Sixty-eight to 85% of the administered dose was absorbed. When given in water, the kinetics of DBCP fit a two compartment, open model. In corn oil, interpretation was more difficult apparently due to erratic absorption. After both intravenous exposure and oral dosing in a water vehicle, blood levels followed a classical biexponential decay; the rate constants for the initial (a) phase and the slower (b) phase can be seen in Table 3, along with several other toxicokinetic parameters. The apparent volume of distribution was approximately 5 L/kg, indicating extensive distribution, presumably to fatty tissues. The whole-body elimination half-life of DBCP was approximately 2.5 hours.

Table 3. Summary of DBCP Toxicokinetic Parameters in the Rat[1]

	Route of Administration		
Parameter (mean value)[2,3]	Intravenous	Oral (in water)	Oral (in corn oil)
a (hr^{-1})	5.03	3.38	nd[4]
b (hr^{-1})	0.32	0.31	nd
k_a (hr^{-1})	nd	152	nd
volume of distribution (L/kg)	4.98	nd	nd
elimination half-life (hr)	2.37	2.64	3.12
clearance (ml/min/kg)	25.3	nd	nd
fraction absorbed (%)	nd	84.5	68.2

[1] Adapted from Gingell et al., 1987a
[2] Mean values of parameters for doses of 0.1, 1.0 and 10.0 mg/kg for water vehicle and for i.v. doses which were given in rat plasma. There were 4-9 animals/dose for these two dosing regimens. With corn oil as a vehicle, a single dose of 1.0 mg/kg was used. The values reported above are the averages from six animals.
[3] For derivation of toxicokinetic parameters, see Gingell et al., 1987a.
[4] nd = not determined

TOXICOLOGY

Exposure to DBCP causes a myriad of adverse effects in numerous organ systems. The toxic endpoints of primary concern for low dose, chronic exposures (cancer and reproductive toxicity) will be discussed in detail below. This section briefly summarizes the many additional adverse outcomes, evident in both animals and humans, resulting from exposure to DBCP. Extensive reviews of these toxicity studies can be found in ATSDR (1992), DHS (1988), Reed et al. (1987), and Wilbur et al. (1985).

Toxicological Effects in Animals

Acute Toxicity

Lethality has been studied in animals exposed to DBCP by various routes of administration (Kodama and Dunlap, 1956, Torkelson et al., 1961; Rakhmatullaev, 1971). Estimates of the mean oral LD_{50} values are 170-350 mg/kg in rats, 180-440 mg/kg in rabbits, 60 mg/kg in chickens, 210-316 mg/kg in guinea pigs, and 410 mg/kg in mice. Inhalation LD_{50} values in rats range from approximately 10-23 mg/kg (using different dosing regimens). LD_{50} values for dermal exposure range from approximately 500-1400 mg/kg.

Subchronic Toxicity

Cellular damage and impaired function of the kidneys have been observed in animals exposed to DBCP. Increased kidney weight was observed in rats fed DBCP in the diet for 90 days at concentrations of 450 and 1350 ppm (Kodama and Dunlap, 1956) or in the drinking water for 60 days at 19 mg/kg body weight (Johnson et al., 1986). No adverse renal effects were observed in these two studies at lower dosages. Single injections of DBCP given to rats at doses of 80 to 320 mg/kg subcutaneously or 40 to 80 mg/kg intraperitoneally resulted in tubular necrosis of the proximal tubules, reduced kidney weight and/or impaired renal function (Kluwe, 1981a,b, 1985; Saegusa, 1986; Saegusa et al., 1982; Holme et al., 1991; Lag et al., 1991; Kaplanski et al., 1991). However, lower subcutaneous doses in other studies did not result in alterations to the kidney: 10 mg/kg (single injection) or 10-40 mg/kg (7 daily injections) (Kluwe et al., 1981a,b); daily injections for 6 months at doses of 1, 5 and 25 mg/kg (Warren et al., 1984), or at 20 mg/kg 1 d/wk for 3 wk (Shemi et al., 1982). Rats administered DBCP subcutaneously 2 d/wk for 12 weeks at doses of 10, 30 and 100 mg/kg showed increased kidney weight and morphological changes at all doses and primary renal lesions at the highest dose (Saegusa, 1989). Decreased kidney weight and tubular necrosis were also observed in rats exposed to DBCP by inhalation (Torkelson et al., 1961; Reznik et al., 1980; Saegusa et al., 1982).

Administration of DBCP to rats resulted in various alterations to the liver and liver function. DBCP fed to rats for 90 days via the diet at concentrations of 5, 20, 150, 450 or 1350 ppm caused increased liver weight at doses of 450 ppm and higher (Kodama and Dunlap, 1956; Torkelson et al., 1961). Hepatocellular necrosis was observed in rats fed DBCP at 70 mg/kg for 45 days (Faydysh et al., 1970) and in rats exposed to DBCP via inhalation at 5 and 25 ppm for 13 wk, 6 hr/day, 5 d/wk (Reznik et al., 1980). Single doses of DBCP administered subcutaneously to male

rats caused hepatocellular swelling at 40 mg/kg and cellular necrosis and increases in enzyme activity at 80 to 320 mg/kg (Kluwe 1981a,b, 1985; Saegusa, 1986; Saegusa et al., 1987). A single i.p. dose of 50 mg/kg to rats significantly increased liver weight compared to that of controls (Kaplanski et al., 1991).

Rodents exposed to DBCP via inhalation resulted in toxicity to the respiratory tract. Rats and mice exposed to 1, 5, and 25 ppm DBCP, 6 hr/day, 5d/wk for 13 weeks resulted in hyperplasia and metaplasia of the nasal cavity at 1 ppm and severe atrophy of epithelial cells in the 5 and 25 ppm dose groups (Reznik et al., 1980). Rats exposed to 10 ppm DBCP 24 hr/day for 14 days resulted in necrosis of the bronchiolar epithelium and emphysematous alveolar distention (Saegusa et al., 1982).

Additional organ systems have also been reported to be affected by DBCP exposures. These included irritation to the eyes and skin, central nervous system depression and behavioral changes

(Torkelson et al., 1961; Reznik and Sprinchan, 1975). Tissue lesions of the thymus, duodenum, and bone marrow have been reported in rats administered DBCP (Saegusa, 1986; Saegusa et al., 1987). Also, weights of the spleen and adrenal glands were increased in rats administered DBCP (Kaplanski et al., 1991).

Genetic Toxicity

DBCP has been demonstrated to be a mutagen and clastogen in multiple test systems, including prokaryotic and eukaryotic *in vitro* tests, *in vivo* animal experiments, and in humans exposed occupationally.

The genotoxicity of DBCP has been extensively reviewed in previous publications (Dybing et al., 1989; Reed et al., 1987; Teramoto and Shirasu, 1989). Table 6 summarizes the extensive evidence that DBCP is a mutagen and clastogen.

Some formulations of technical grade DBCP were stabilized with 1% epichlorhydrin, a potent mutagen. Biles et al. (1978) demonstrated that much of the direct acting mutagenesis observed in bacterial test systems was due to epichlorhydrin. In the presence of metabolic activation systems, metabolites of DBCP were primarily responsible for the observed mutations, since the mutagenicity of pure DBCP and technical-grade DBCP (containing 1% epichlorhyrin) were equal.

Metabolic activation of DBCP to DNA reactive species is believed to proceed through two mechanisms. In one, DBCP can be oxidatively metabolized by the cytochrome P-450 enzymes, primarily in the liver, to 2-bromoacrolein with loss of HBr and HCl in the process (Omichinski et al., 1988a,b). The product, 2-Bromoacrolein is a potent, direct-acting mutagen. A second mechanism involves conjugation of DBCP with glutathion which rearranges to form a reactive episulfonium ion (Dybing et al., 1989).

Table 4. Genotoxicity of DBCP

Test System	Response	References
Bacteria (with activation)		
Ames Assay (*S. typhimurium*, TA98, TA100, TA1535)	+	Biles et al., 1978; Stolzenberg and Hine, 1979; McKee et al., 1987; Ratpan and Plaumann, 1988; Zeiger et al., 1988; Lag et al., 1994
Ara Test (*S. typhimurium*)	+	Roldan-Arjona et al.,1991
Modified Ames Assay (*E. coli*, WP2her)	+	Moriya et al., 1983
Drosophila melanogaster		
Recessive Lethal Assay	+	Inoue et al., 1982; Kale and Baum, 1982; Zimmering, 1983;
Heritable Translocation	+	Kale and Baum, 1982; Zimmering, 1983
Crossing Over / Inter-chromosomal Mitotic Recombination	+	Kale and Baum, 1982; Vogel and Nivard, 1993
Chromosome Loss	+	Zimmering, 1983
Mammalian Cells (in vitro)		
Human Testicular Cells		
Single-strand breaks and alkali labile sites	-	Bjorge et al., 1996a, 1996b
Rat Testicular and Renal Cells		
Single-strand breaks and alkali labile sites	+	Brunborg et al., 1998; Bjorge et al., 1995, 1996a, 1996b
Rabbit Lung Cells (in vitro)		
DNA Damage (Alkaline Elution Technique)	+	Becher et al., 1993
Chinese Hamster V79 Cells		
Chromosomal Aberrations	+	Tezuka et al., 1980; Loveday et al., 1989
Sister Chromatid Exchange	+	Tezuka et al., 1980; Loveday et al., 1989
Polypoid Test	-	Tezuka et al., 1980
Syrian Hamster Embryo Cells		
Cell Transformation Assay	+	McKee et al., 1987

Test System	Response	References
Mouse Lymphoma Cells (L5178, TK Locus)		
Gene Mutation Assay	+	McKee et al., 1987; Myhr and Caspary, 1991
Rat (in vivo)		
Chromosomal Aberrations	+	Kapp, 1979
Dominant Lethal Assay	+	Teramoto et al., 1980; Saito-Suzuki et al., 1982; Rao et al., 1979.
DNA Damage[1] (Alkaline and/or Neutral Filter Elution Techniques) (Kidney, Liver, Testes, Lung, Spleen, Brain, Bone-Marrow, Bladder, Stomach, Intestines)	+	Omichinski et al., 1987; Brunborg et al., 1988; Soderlund et al., 1988; Lag et al., 1989; Brunborg et al., 1990; Soderlund et al., 1990; Holme et al., 1991; Kitchin and Brown, 1994; Kouzi et al., 1995; Brunborg et al., 1996
Micronucleus Assay (bone marrow)	+	Albanese et al., 1988; George et al., 1990; Waters et al.,1994
Unscheduled DNA Synthesis (germ-cell/spermatocytes)	+	Bentley and Working, 1988
Mice (in vivo)		
DNA Damage (Alkaline Elution Technique) (Kidney)	+	Soderlund et al., 1990
Unscheduled DNA synthesis (in germ cells)	+/-[2]	Lee and Suzuki, 1979
Sister Chromatid Exchange	+	Abbott and Mcfee, 1989
Micronucleus Assay and/or Chromosome Aberrations (bone marrow)	-	Albanese et al., 1988; Shelby et al., 1993[3]; Waters et al., 1994; Shelby and Witt, 1995
Micronucleus Assay (forestomach and liver)	+	Belitsky et al., 1994
Dominant lethal	-	Teramoto et al., 1980; Generoso et al., 1985; Au et al., 1990
Sperm Morphology	-	Osterloh et al., 1983
Gene-mutation Induction (Germline/Spermatogonia)	-	Russel et al., 1986

[1] Single-strand breaks, double-strand breaks, alkali-labile sites and crosslinks.

[2] Significant increases observed in prepubertal male CD-1 mice dosed with DBCP, but not with adult mice.

[3] The results from this study were equivocal, as there was some evidence of micronuclei formation in one of the dose groups for both bone marrow and peripheral blood, but trend tests were not significant.

Test System	Response	References
Mutagenicity Spot Test	+	Sasaki et al., 1986
Guinea Pig (in vivo)		
DNA Damage (Alkaline Elution Technique) (Kidney)	+	Soderlund et al., 1990
Hamster (in vivo)		
DNA Damage (Alkaline Elution Technique) (Kidney)	+	Soderlund et al., 1990
Humans (in vivo)		
Y-chromosomal non-disjunction	+	Kapp et al., 1979; Kapp and Jacobson, 1980

Developmental and Reproductive Toxicity

In animals, exposure to DBCP causes testicular damage and male infertility as well as adverse reproductive outcomes. Adverse effects observed in animals following DBCP exposure include reduced sperm number, changes in sperm motility and morphology, decreased ability to impregnate females, reductions in testicular, epididymis and seminal vesicle weight, damage to the seminiferous tubules, reduction in testosterone and luteinizing hormone levels, testicular DNA damage and increased number of dead embryos. The effects on male reproductive system in animals appear to occur at doses somewhat higher than those associated with similar effects in humans. This may indicate that humans are more sensitive to the adverse reproductive effects of exposure to DBCP, especially DBCP-induced testicular toxicity, or may simply reflect the poor exposure estimates in the human studies. An alternate explanation may relate to the longer exposure periods that humans often experience compared to animals, as there is significant animal evidence for cumulative testicular toxicity increasing with continued or repeated exposure.

Inhalation

Rao et al. (1982, 1983) studied adverse reproductive effects in male rabbits and rats exposed to 0.1 and 1 ppm DBCP for 14 weeks of exposure (5 days/week, 6 hours/day). Adverse effects of decreased sperm production and testicular atrophy were observed in both rats and rabbits at the 1 ppm level, but not in rabbits or rats exposed to 0.1 ppm for the same duration, although the rabbits exposed to 0.1 ppm showed an equivocal increase in abnormal sperm after 14 weeks. Reed et al. (1987) estimated that the rabbits in the 1 ppm group were exposed to 0.54 mg/kg-day and absorbed 0.27 mg/kg-day of DBCP.

Oral

Rakhmatullaev (1971) administered a Soviet formulation of DBCP in drinking water daily for 8 months to male albino rats. Various indicators of reproductive toxicity were observed, including

reduced sperm motility and the decreased ability to impregnate female rats; 0.05 mg/kg-day was identified as a “threshold dose" and 0.005 mg/kg-day was identified to be without any toxic effect. These results are difficult to interpret because the number of animals affected was not reported and statistical analyses were not provided. The duration of this study was longer than any other oral study. The effects observed in the Rao et al. (1982) inhalation study are considered consistent with the results of this drinking water study in that doses of similar magnitude were associated with reproductive toxicity.

Johnston et al. (1986) administered DBCP to male and female Sprague-Dawley rats, 10 animals per group, at target doses of 0.02, 0.2, 2.0 and 20.0 mg/kg-day in drinking water for 60 days prior to mating and during mating. No adverse effects were observed with respect to fertility, gestational survival, pup viability, or testicular weight.

Foote et al. (1986a,b) exposed male Dutch rabbits, 6 animals per group, to DBCP via drinking water at doses of 0, 0.94, 1.88, 3.75, 7.50 and 15.0 mg/kg body weight 5 day/wk for 10 weeks. No effects were observed for the rabbits dosed with 0.94 mg/kg-day. Alterations to sperm morphology were observed at 1.88 mg/kg.

Amann and Berndtson (1986) administered DBCP diluted in corn oil to rats (15 animals per group) via gavage at doses of 0, 0.94, 1.88, 3.75, 7.5, or 15.0 mg/kg-day for 77 days. From day 65 to 77, each male rat was allowed to mate with two untreated females. Sperm production and epididymal spermatozoal reserves were measured in males. Pregnancy rate, number of corpora lutea, and number of live and dead embryos were counted in the females. Adverse effects in male compared to controls included statistically significant increases in testicular weight, parenchymal weight of the testes, sperm production, and mean diameter of the seminiferous tubules. With regard to pregnancy outcomes, the number of dead embryos was increased. All of these effects were observed to be statistically significant by dose-response trend analysis, however, the effects were significantly increased over controls in pair-wise statistical testing for the 15 mg/kg-day group only.

Heindel et al. (1989) administered DBCP to male Sprague-Dawley rats via the drinking water. The rate of water consumption was reduced in rats drinking higher concentrations of DBCP. Average daily doses were estimated to be 0, 0.4 3.3, 5.4 and 9.7 mg/kg-day for the 64-day exposure period. A slight statistically significant increase in absolute testicular weight was observed for rats in the highest dose group, but was not significant when corrected for body weight. No adverse effects were observed for other male reproductive endpoints, such as sperm counts, follicular hormone or testosterone levels, or histopathological changes in testicular seminiferous epithelium.

Other Routes of Exposure

Lui and Wysocki (1987) administered subcutaneous (s.c.) injections of DBCP to male Sprague-Dawley rats, 5 animals per dose group, during the early postnatal period, a time in which the male reproductive tract normally undergoes developmental changes. Doses were 0, 1, 5, 10 or 20 mg/kg and were given on alternate days from day 2 to day 20 of life. Statistically significant reduction in testis weight was seen at 1 mg/kg. Severe reduction in the testis, epididymis and seminal vesicle weights was seen at the higher doses, including complete obliteration of the seminiferous tubules in the 10 mg/kg dose group. The results of this study indicate that a critical period exists (the first 10 days of life) in which male rats are highly susceptible to the reproductive toxic effects of DBCP.

In a study of the effects of *in utero* exposure to DBCP on the development of male rat sexual differentiation, Warren et al. (1988) administered daily subcutaneous injection of 25 mg/kg DBCP to pregnant Sprague-Dawley rats. One group was dosed beginning at day 14.5 of gestation through day 19.5, another group dosed from day 16.5 to day 19.5 of gestation and a third group dosed days 18.5 and 19.5 of gestation. There were 5 pregnant females per dose group. Additional groups of control animals were given corn oil under the same dosing regimen as the DBCP-dosed rats. Male offspring of DBCP-exposed dams showed significantly reduced testis weight, testis testosterone levels, and luteinizing hormone receptor content. The most striking observation was that 7 of 9 male offspring treated for 6 days during gestation and 3 of the 6 male animals treated for 4 days during gestation were devoid of seminiferous tubules.

Ahmad et al. (1988) studied the morphological and biochemical changes in the male rat reproductive system following exposure to DBCP, epichlorhydrin and allyl chloride (contaminants and/or metabolites of technical-grade DBCP). Male Long-Evans rats were injected subcutaneously with 1, 5, or 25 mg/kg-body weight DBCP or with 25 mg/kg epichlorhydrin or 25 mg/kg allyl chloride daily for 1, 3, or 6 months. No adverse effects were observed in rats in the 1 mg/kg dose group. At 5 mg/kg, by 3 months some rats showed abnormal morphological changes of the seminiferous tubules of the testes. The highest dose, 25 mg/kg, gave rise to testicular regression at 1 month, progressing to an extreme condition by 6 months of treatment.

Epichlorhydrin and allyl chloride did not produce adverse effects indicating that the reproductive effects of technical DBCP is likely due to DBCP itself and not contaminants.

Shaked et al. (1988) administered doses of DBCP to pregnant female rats under 5 different experimental dosing regimens. In the first experiment, tritiated DBCP (0.2 mL/ 100 g body weight) was injected (i.p.) on day 13 of gestation. Some of the labeled DBCP was observed to cross the blood-placenta barrier as radioactivity was detected in the fetuses. In the next experiment, pregnant rats were injected (s.c.) with a single dose of DBCP (40 mg/kg) on one day between day 12 and day 20 of gestation. No specific day of injection produced different effects than the others. However, when the data were pooled (N=42 rats) and compared with controls (N=37), the number of DBCP-exposed pups that were born was lower than that of controls and postimplantation and perinatal losses were significantly increased compared with those of control animals. DBCP was administered to pregnant rats in eight s.c. injections (10 mg/kg-day) on eight consecutive days of gestation (L_{11}-L_{18}) in the third experiment. All pups of DBCP-exposed animals died within hours of birth. No histological differences in the ovaries of the mothers were observed compared to controls. In the fourth experiment, DBCP was directly injected into the amniotic sac on day 13 of gestation at a dose of 0.1 mg DBCP per fetus. This did not have any adverse effect on pregnancy outcome. In the final experiment, proestrus rats were injected s.c. with a single dose of 40 mg/kg of DBCP or DMSO (vehicle control) at a time which would affect the completion of the first meiotic division. Females were caged overnight with fertile males. Sixty percent of the DBCP-treated rats conceived compared to 100 % of the controls.

Sod-Moriah et al. (1988) studied the long-term effects to the male rat reproductive system following DBCP exposure. Male rats were administered subcutaneous injections of 20 mg/kg DBCP once per week for 3 weeks and were sacrificed at 5, 9, 13, 17, 25 and 50 weeks after the last dose. Testes weights were reduced and remained low despite recovery of body weight compared with controls. Most males were infertile and serum follicular stimulating hormone and luteinizing hormone levels remained high for infertile males.

Saegusa (1989) administered DBCP to Sprague-Dawley rats by subcutaneous injection, twice weekly for 12 weeks, at doses of 0 (vehicle), 10, 30 or 100 mg/kg-bw. Five rats from each group were sacrificed at the 12th, 24th and 36th week. Reduction of testes weights and increase in atrophy of the seminiferous tubules were reported and responded as a function of the dose level of DBCP and exposure duration.

Kaplanski et al. (1991) measured gonadotoxicity of male Sprague-Dawley rats given a single injection of 50 mg/kg of DBCP. Testes weights and sperm counts were decreased and histological damage was observed 4 weeks following the injection.

Lag et al. (1991) studied DBCP as part of a larger study of halogenated propanes and their ability to produce renal and testicular toxicity. Groups of 5 male rats were administered a single i.p. injection of DBCP at 0 (vehicle control), 14.5 or 40 mg/kg. Necrosis and atrophy of the seminiferous tubules were evident in the 40 mg/kg dose group 48 hours after dosing. Testicular DNA damage, as measured by the alkaline elution method, increased with dose of DBCP. DNA damage was also observed *in vitro* from pooled testicular cells treated with DBCP. Testicular DNA damage *in vivo* correlated well with the observed histological alterations. The authors indicated that DNA damage might be an initial event in the development of DBCP-induced organ necrosis. Also, DNA damage observed *in vivo* correlated well with that produced *in vitro*, suggesting that toxicity may be due to *in situ* activation of DBCP. Additional studies indicating DNA damage in the testis following exposure are listed in the prior section on genotoxicity.

Omura et al. (1995) administered eight male Wistar rats with a single s.c. injection of 80 mg/kg DBCP. Nine rats served as controls. Six weeks after the injection, testes and epididymis weights were significantly reduced. Sperm counts in the head and tail of the epididymis were severely reduced in the DBCP-dosed group compared with controls. Also, nearly 90 % of sperm from the DBCP-dosed rats were without a tail, whereas only about 1% of sperm from control rats showed this abnormality.

Chronic Toxicity

The most relevant effects associated with chronic DBCP exposure are reproductive toxicity and cancer, which are discussed in their respective sections.

Carcinogenicity

Hazleton laboratories, under contract with Dow Chemical Company, performed a bioassay of 95% pure DBCP mixed with feed of rats and mice of both sexes (Hazleton, 1977; 1978).

Groups of 60 male and 60 female Charles River rats were fed diets supplemented with DBCP at levels estimated to produce a dose of 0.3, 1.0 or 3.0 mg/kg-day. The estimates were made using the data on group mean body weight to calculate the concentration of DBCP corresponding to the target dose rate. Feed was mixed on Monday and again on Thursday of each week, and for the first 31 weeks no adjustment was made for the amount of DBCP lost due to volatilization. From week 32 to the end of the study, the amount of DBCP added to the feed in each dose group was increased by 20% to compensate for the amount lost due to volatilization (approximately 40% in three days). Calculated time-weighted average dose rates for the low- mid- and high-dose groups were 0.24, 0.80 and 2.39 mg/kg/day (HSDB, 1997), respectively. Groups of 60 male and female

rats were observed as controls. All surviving animals were killed at 104 weeks and examined for tumors. The incidences of squamous-cell carcinomas of the stomach (or forestomach) in control, low-dose, mid-dose and high-dose animals were 0/48, 0/46, 3/46 and 20/41, respectively, in males and in females 0/48, 0/45, 0/47 and 8/43. The incidence of squamous-cell carcinomas or papillomas of the stomach in control, low-dose, mid-dose and high-dose animals were 0/48, 0/46, 3/46 and 21/41, respectively, in males and in females 0/48, 0/45, 0/47 and 10/43. The incidences of hepatocellular carcinomas in control, low-dose, mid-dose and high-dose animals were 0/48, 1/46, 2/46 and 5/41, respectively, in males and in females 0/48, 1/45, 3/47 and 0/43. The incidences of hepatocellular carcinomas or neoplastic nodules in control, low-dose, mid-dose and high-dose animals were 0/48, 5/46, 4/46 and 8/41, respectively, in males and in females 0/48, 3/45, 5/47 and 3/43. The incidences of renal tubular-cell carcinomas in control, low-dose, mid-dose and high-dose animals were 0/48, 1/46, 3/46 and 9/41, respectively, in males and in females 0/48, 1/45, 0/47 and 5/43. The incidences of renal tubular-cell carcinomas or adenomas in control, low-dose, mid-dose and high-dose animals were 0/48, 1/46, 4/46 and 15/41, respectively, in males and in females 0/48, 1/45, 0/47 and 12/43.

Groups of 50 male and 50 female HaM/ICR Swiss mice were given diets supplemented with DBCP at levels calculated to produce a dose of 0.3, 1.0 or 3.0 mg/kg-day for the first 27 weeks, and then were given levels calculated to produce a dose of 0.6, 2.0 or 6.0 mg/kg-day for the remainder of the experiment. To compensate for DBCP lost from feed as a result of volatilization (approximately 40% over three days), the amount of DBCP added to the feed for each dose group (mixed each Monday and Friday) was increased by 40 % above the amount calculated to give the target dose. Time-weighted average dose rates calculated from data in the Hazleton Laboratories report for the low- mid- and high-dose groups were 0.48, 1.6 and 4.8 mg/kg/day. Groups of 50 male and female mice were observed as controls. All surviving animals were killed at 78 weeks and examined for tumors. The incidences of squamous-cell carcinomas of the stomach in control and high-dose animals were 0/50 and 26/49, respectively, in males and in females 0/50 and 19/50. The incidences of squamous-cell papillomas of the stomach in control and high-dose animals were 0/50 and 5/49, respectively, in males and in females 0/50 and 6/50. The incidences of carcinomas or papillomas combined and results of histopathological examination of animals in the low- and mid-dose groups were not reported. The tumor incidences from the Hazleton bioassays are shown in table 5.

Table 5 Tumor Incidences in Rats and Mice Administered DBCP in the Diet (Hazleton 1977, 1978)

		Doses (mg/kg-day)			
Tumor diagnosis and site	**Sex/Species**	**Control**	**0.24**	**0.80**	**2.39**
Squamous cell carcinoma of stomach or forestomach	Male rats	0/48	0/46	3/46	20/41**
	Female rats	0/48	0/45	0/47	8/43*
Squamous cell carcinoma or papilloma of stomach or forestomach	Male rats	0/48	0/46	3/46	21/41**
	Female rats	0/48	0/45	0/47	10/43**
hepatocellular carcinomas	Male rats	0/48	1/46	2/46	5/41*
	Female rats	0/48	1/45	3/47	0/43
hepatocellular carcinomas or neoplastic nodules	Male rats	0/48	5/46	4/46	8/41*
	Female rats	0/48	3/45	5/47*	3/43
Renal tubular cell carcinomas	Male rats	0/48	1/46	3/46	9/41**
	Female rats	0/45	1/45	0/47	5/43
Renal tubular cell carcinomas or adenomas	Male rats	0/48	1/46	4/46	15/41**
	Female rats	0/48	1/45	0/47	12/43**
			Controls	**4.8**[a]	
Squamous cell carcinomas of the stomach or forestomach	Male mice		0/50	26/49**	
	Female mice		0/50	19/50**	
Squamous cell papillomas of the stomach or forestomach	Male mice		0/50	5/49*	
	Female mice		0/50	6/50*	

* Statistically significant increase in incidence ($p<0.05$)
** Statistically significant increase in incidence ($p<0.001$)
[a] Results of histopathological examination were reported only for the high dose group and controls, but not the two lower dose groups.

The National Cancer Institute (NCI, 1978) performed a gavage bioassay with DBCP in both sexes of rats and mice. Groups of 50 male and 50 female Osborne-Mendel rats were given 12 mg/kg (low dose) or 24 mg/kg (high dose) DBCP (>90% pure) in corn oil by intragastric intubation 5

days per week starting at 6-7 weeks of age. After 9 weeks of treatment, these doses were increased to 15 and 30 mg/kg, respectively. Groups of 20 male and female rats were given corn oil alone by intubation 5 days per week for up to 78 weeks. Time-weighted average daily doses were approximately 10.7 mg/kg in the low-dose groups and 20.7 mg/kg in high-dose groups (U.S. EPA, 1988). Additional groups of 20 mice/sex did not receive any treatment. Surviving corn-oil treated males and females and low-dose males (5/50) were killed 83 weeks after treatment began, and surviving high-dose males (8/50) were killed after 62 weeks. Surviving low-dose females (8/50) and high-dose females (3/50) were killed after 73 and 64 weeks of treatment, respectively. Vehicle-treated controls and untreated controls were killed after 83 weeks and 109 weeks, respectively. There was increased mortality in treated rats of both sexes. At 60 weeks, survival in untreated, vehicle-treated, low-dose and high dose groups was 96%, 84%, 84% and 24%, respectively, in males and 100%, 80%, 50% and 20% in these groups of females. Early deaths in these animals are thought to be either tumor-related and/or associated with the renal necrosis observed in the treated groups.

The incidences of squamous-cell carcinomas of the forestomach were 47/50 in both low-dose and high-dose groups of males and 38/50 and 29/49 in low- and high-dose groups of females, respectively. No tumors of the stomach or forestomach were seen in control groups of either sex. The incidences of mammary adenocarcinomas were 24/50 and 31/50 in low- and high-dose females, respectively. The incidences were 0/20 and 2/20 in vehicle-treated and in untreated groups of females, respectively. The decreased incidence of forestomach tumors in high-dose females may be due to the severe early mortality in this study.

Groups of 50 male and 50 female B6C3F1 mice were given 80 mg/kg (low dose) or 160 mg/kg (high dose) DBCP (>90% pure) in corn oil by intragastric intubation 5 days per week for 11 weeks (starting at 6-7 weeks of age). Starting at week 12 of treatment, the doses were increased to 100 mg/kg (low dose) or 200 mg/kg (high dose) for the next 14 weeks. From week 26 to the end of the experiment, the doses were again increased to 130 mg/kg (low dose) or 260 mg/kg (high dose). Groups of 20 mice/sex received the vehicle alone and groups of 20 mice/sex were observed as untreated controls. Surviving mice in vehicle control, low-dose and high-dose groups were killed at 59, 60 and 47 weeks, respectively, and those in the untreated male and female control groups were killed after 78 and 90 weeks, respectively. Time-weighted average daily doses were approximately 81.4 and 156.4 mg/kg in low- and high-dose males, respectively, and 78.6 and 149.3 mg/kg in low- and high-dose females (U.S. EPA, 1988). There was increased mortality in treated mice of both sexes. At 45 weeks, survival in untreated, vehicle-treated, low-dose and high dose groups was 96%, 90%, 80% and 40%, respectively, in males and 100%, 96%, 86% and 50% in these groups of females, respectively. Early deaths in these animals are thought to be either tumor-related and/or associated with the renal necrosis observed in the treated groups.

The incidences of squamous-cell carcinomas of the forestomach were 43/46 and 47/49 in low- and high-dose males, respectively, and 50/50 and 47/48 in low- and high-dose females. No tumors of the stomach or forestomach were seen in any of the control groups. The tumor incidences from the NCI bioassays can be seen in table 6.

Table 6 Tumor Incidences in Rats and Mice Administered DBCP by Gavage (NCI, 1978)

		Doses (mg/kg-day)		
Tumor diagnosis and site	**Sex/Species**	**Control**	**10.7**	**20.7**
Squamous cell carcinomas of the forestomach	Male rats	0/20	47/50*	47/50*
	Female rats	0/20	38/50*	29/49*
Adenocarcinomas of mammary gland	Female rats	0/20	24/50*	31/50*
		Controls	**81.4**	**156.4**
Squamous cell carcinomas of the forestomach	Male mice	0/20	43/46*	47/49*
		Controls	**78.6**	**149.3**
	Female mice	0/20	50/50*	47/48*

* Statistically significant increase in incidence ($p<0.001$)

An inhalation bioassay of DBCP was performed by the National Toxicology Program in both sexes of rats and mice (NTP, 1982). Groups of 50 male and female Fisher 344/N rats were exposed for 6 hours per day, 5 days per week to either 0.6 ppm (low dose) or 3.0 ppm (high dose) technical grade DBCP. Groups of 50 males and females were observed as untreated controls. Surviving high-dose males and females were killed at 84 weeks. Surviving control and low-dose animals were killed at 104 weeks. Survival was reduced in the high-dose group of both sexes with 30% of high-dose males and 36% of high-dose females alive after 75 weeks of treatment compared with greater than 90% survival in control and low-dose groups of both sexes. Early deaths were associated with respiratory tract tumors. Interference with breathing and metastasis to the brain were major contributing factors to these deaths.

The incidences of squamous-cell carcinomas of the nasal cavity were 0/50, 2/50 and 22/49 in control, low-dose and high-dose males and 0/50, 0/50 and 23/50 in control, low-dose and high-dose females, respectively. The incidences of malignant and benign tumors, combined, of the nasal cavity were 0/50, 32/50 and 39/49 in control, low-dose and high-dose males and 1/50, 21/50 and 32/50 in females, respectively. The increases in the incidence of these tumors are highly statistically significant, as are the dose-related trends ($p <0.001$). The incidences of squamous-cell carcinomas or adenomas of the tongue in control, low-dose and high-dose males were 0/50, 1/50 (0 carcinomas) and 11/49 (3 carcinomas) and 0/50, 4/50 (1 carcinoma) and 9/50 (3 carcinomas) in control, low-dose and high-dose females, respectively. The incidence of squamous-cell carcinomas and papillomas of the pharynx (8/50, 2 carcinomas) in high-dose females was significantly increased above the incidence in controls (0/50). In addition, in females there was a significant increase in the incidence of adrenal cortical adenomas at both the low dose (7/50) and the high dose (5/48) compared to the incidence in controls (0/50). The incidences of mammary carcinomas in control, low-dose and high-dose females were 1/50, 1/50 and 4/50 and the incidence of mammary fibroadenomas were 4/50, 13/50 and 4/50, respectively. The decrease in the incidence of fibroadenomas at the high dose may be due to poor survival.

Groups of 50 male and female B6C3F1 mice were exposed for 6 hours per day, 5 days per week to either 0.6 ppm (low dose) or 3.0 ppm (high dose) technical grade DBCP. Groups of 50 males and females were observed as untreated controls. Surviving low- and high-dose males and high-dose females were killed at 76 weeks. Surviving male and female controls and low-dose females were killed at 104 weeks. Survival was poor in males with 42%, 32% and 50% alive in control, low-dose and high-dose groups, respectively, at 60 weeks. At 60 weeks, 64% of high-dose females were alive, compared with greater than 90% of control and low-dose females. Early deaths were associated with respiratory tract tumors. Interference with breathing and metastasis to the brain were major contributing factors to these deaths. Urogenital infection also appeared to be associated with some deaths in male mice. In high-dose males, the incidence of squamous-cell carcinomas of the nasal cavity (6/48) was significantly increased above the incidence in controls (0/45) and the incidence of carcinomas (not further specified) of the nasal cavity (7/48) was also increased above the incidence in controls (0/48). The incidences of malignant and benign nasal cavity tumors in control, low-dose and high-dose males were 0/45, 1/42 and 23/48, respectively. The increase in the high-dose group is highly significant as is the dose-related trend. In females the incidences of squamous-cell tumors (6/50) adenocarcinomas (6/50) and carcinomas not further specified (17/50) were significantly increased above the incidence of these tumor types in controls (0/50). The incidences of malignant and benign tumors of the nasal cavity in control, low-dose and high-dose females were 0/50, 11/50 and 38/50, respectively. The increase in the high-dose group is highly significant as is the dose-related trend.

The incidences of alveolar/bronchiolar carcinomas or adenomas (combined) in males were 0/41, 3/40 (1 carcinoma) and 7/45 (1 carcinoma) in control, low-dose and high-dose animals and in females was 4/49 (1 carcinomas), 5/49 (2 carcinomas) and 13/47 (4 carcinomas), respectively. The increases in the incidences in high-dose males and females are statistically significant ($p=0.008$ and $p=0.012$, respectively) as are the dose-related trends. The incidence of alveolar/bronchiolar carcinomas or adenomas, papillary carcinomas and squamous-cell carcinomas (combined) of the lung in males was 0/41, 3/40 and 11/45 in control, low-dose and high-dose animals, respectively, and in females was 4/49, 12/49 and 18/47. The increases in the incidences in high-dose males and females are highly statistically significant ($p<0.001$), and the increase in low-dose females is significant ($p=0.027$), as are the dose-related trends in both sexes.

The incidences of squamous-cell papillomas and carcinomas of the stomach were 0/0/37, 0/41, and 3/44 (1 carcinoma) in control, low-dose and high-dose males and in females was 0/50, 1/46 (papilloma) and 3/46 (2 carcinomas), respectively. The tumor incidences from the NTP bioassays can be seen in table 7.

Table 7 Tumor Incidences in Rats and Mice Administered DBCP by Inhalation (NTP, 1982)

		Exposure (ppm)		
Tumor diagnosis and site	**Sex/Species**	**Control**	**0.6**	**3.0**
Squamous cell carcinoma of nasal cavity	Male rats	0/50	2/50	22/49***
	Female rats	0/50	0/50	23/50***
Malignant and benign tumors of the nasal cavity	Male rats	0/50	32/50***	39/49***
	Female rats	1/50	21/50***	32/50***
Squamous cell carcinomas or adenomas of the tongue	Male rats	0/50	1/50	11/49***
	Female rats	0/50	4/50	9/50*
Adenoma of the renal cortex	Female rats	0/50	7/50**	5/48*
Carcinoma of mammary gland	Female rats	1/50	1/50	4/50
Fibroadenoma of mammary gland	Female rats	4/50	13/50	4/50
Malignant and benign tumors of nasal cavity	Male mice	0/45	1/42	23/48***
	Female mice	0/50	11/50***	38/50***
Alveolar/bronchiolar carcinomas or adenomas	Male mice	0/41	3/40	7/45**
	Female mice	4/49	5/49	13/47*
Combined adenomas or carcinomas of the lung	Male mice	0/41	3/40	11/45***
	Female mice	4/49	12/49*	18/47***
Squamous cell carcinoma or papilloma of the stomach or forestomach	Male mice	0/37	0/41	3/44
	Female mice	0/50	1/46	3/46

* Statistically significant increase in incidence ($p<0.05$)
** Statistically significant increase in incidence ($p<0.01$)
*** Statistically significant increase in incidence ($p<0.001$)

Toxicological Effects in Humans

Acute Toxicity

Acute toxic effects in humans have been documented following inhalation and/or dermal exposures to DBCP. Symptoms of acute exposure include, dyspnea, drowsiness, nausea, vomiting, abdominal cramps, diarrhea, irritations to the eye, skin and respiratory system, central nervous system depression, and death (Reed et al., 1987).

Subchronic Toxicity

In humans, subchronic DBCP exposure has been reported to cause adverse effects in a number of organ systems, including the liver, kidney, lungs, eyes and skin. The male reproductive system appears to be the most sensitive to the effects of DBCP and will be discussed in detail in a separate section on reproductive effects. Reports from manufacturers of DBCP have indicated that exposure to DBCP in air may cause eye irritation and damage, pulmonary congestion and edema, and possible kidney damage (Reed et al., 1987). US EPA (1976) reported on several cases of skin irritation, skin burns, conjunctivitis and possibly respiratory tract irritation among agricultural and factory works exposed to DBCP.

Developmental and Reproductive Toxicity

Exposure to DBCP has been shown to produce testicular toxicity and infertility in human males and a change in the sex ratio (an increase in the number of females) of children fathered by DBCP-exposed males. Testicular toxicity is reported most frequently and appears to occur at lower exposures than that of other non-cancer endpoints. DBCP-induced testicular damage and infertility, as evidenced by numerous human studies, have been expressed as reduced (oligospermia) or no sperm counts (azoospermia - which is often irreversible), altered sperm motility, damage to the seminiferous tubules, and hormonal disruption. Paternal exposure to DBCP has not resulted in increases in birth defects in offspring, although the numbers of individuals studied for this purpose has been small. Nearly all information regarding DBCP-induced reproductive effects comes from occupational exposures. Exposure estimates from these studies unfortunately are limited or are not available.

Inhalation

Eight-hour time-weighted average measurements of DBCP concentrations ranged from 290 to 400 ppb at the Occidental Petroleum plant in Lathrop, California, where 14 of 25 non-vasectomized men were found to be either infertile and/or showed significantly reduced sperm counts (U.S. OSHA, 1978; Whorton et al., 1979). DHS (1988a) estimated, based on the average air concentrations reported for this facility, that the workers at the Lathrop facility were exposed to approximately 0.4 mg/kg-day DBCP by the inhalation route. The actual dose, however, was undoubtedly larger than this value because of concomitant dermal exposure.

In a series of studies, Whorton et al. (1977), Marshall et al. (1978), Whorton et al. (1979), and Whorton and Milby (1980), evaluated male and female workers exposed to DBCP and other agricultural chemicals in a California pesticide plant. DBCP air concentrations at the plant were measured to be 0.4 ppm in 1977 (8 hr TWA), although exposures were likely to be quite varied and dependent on task and market demand. Thirty-six men and three women were tested for urine and serum levels of thryoxine, testosterone, follicular stimulating hormone, and luteinizing hormone and were given a medical examination and completed a medical history questionnaire. No adverse effects on the female reproductive system were found. All men (11) who had worked in the agriculturalchemical department for 3 or more years had profound testicular effects (azoo- or oligospermic). No effects were seen in the eleven men who had worked at the facility for less than three months. Eleven men had prior vasectomies and the other three had mild to moderate testicular effects.

In a detailed study of all 196 male workers employed at the facility (Whorton et al., 1979), 13% of the exposed men were azoospermic and 17 % were oligospermic, compared with 3 % and 0 % in the controls, respectively. Testicular biopsies taken from men exposed to DBCP for three months or less showed no obvious damage. However, those men exposed for more than 12 months showed decreased sperm counts and sperm activity. Spermatocytes and spermatogonia were almost totally absent among men exposed for three or more years. Recovery from DBCP-induced testicular dysfunction after the cessation of exposure was reported for time points of 1-year (Whorton and Milby, 1980), and 5 to 8 years (Eaton et al., 1986). Of the 44 workers reassessed, 1 of 8 who were azoospermic recovered to normal sperm levels, 1 showed slight improvement, 6 remain azoospermic. All workers with low sperm counts in 1977 continued to have low sperm counts in the follow-up studies.

The health of workers exposed to DBCP in a production facility in Israel was studied extensively and followed over time. Azoospermia and elevated follicular stimulating hormone were seen in 6 of 6 men exposed to DBCP for 2 to 10 years. Testicular biopsies revealed complete atrophy of the seminiferous epithelium, with most tubules containing only Sertoli cells (Potashnik et al., 1978). In the report of Potashnik et al. (1979), 12 (52%) of 23 male workers on the production line examined for testicular function were azoospermatic. Exposure concentrations were not available. Recovery of testicular function was examined in a series of follow-up studies at 4 years (Postashnik, 1983), 8 years (Potashnik and Yannai-Inbar, 1987) and 17 years (Postashnik and Porath, 1995). After four years, 4 of 13 workers initially azoospermic showed improved sperm count and 5 of 7 improved among those who were initially oligospermic. Those men (either azoospermic or oligospermic) who had more than 120 hours of exposure showed no signs of improvement in 5 years since cessation of exposure (Potashnik, 1983). After 17 years, sperm count recovery was evident within 36 to 45 months in 3 of the 9 azoospermic and 3 of the 6 oligospermic men, with no improvement thereafter (Potashnik and Porath, 1995).

At the Dow Chemical facility in Magnolia, Arkansas, where DBCP was being manufactured, 50% of the 106 workers examined were found to be either oligospermic or azoospermic. Eight-hour time weighted averages measured at the site ranged from 40 to 400 ppb during production (US OSHA, 1978). Concentrations of less than 1 ppm in the air have been estimated for other facilities where adverse reproductive effects have been observed (US OSHA, 1978). Dermal exposures contributed an unknown, but potentially significant amount, to the total dose.

Low sperm count was reported in male pesticide applicators and other agricultural workers exposed to DBCP (Glass et al., 1979; Sandifer et al., 1979). An additional study found low sperm counts in DBCP exposed workers from a Dow Chemical plant in Michigan (Egnatz et al., 1980).

Abnormally high luteinizing hormone levels and hyperplastic Leydig cells from testicular biopsies were observed in workers in a DBCP factory in Mexico (Cortes-Gallegos et al., 1980).

Lipshultz et al. (1980) examined 228 workers, comprised of DBCP-exposed and non-exposed men, from DBCP manufacturing sites in Denver, Colorado, and Mobile, Alabama. The Denver site had produced DBCP from 1956 to 1976 and the Mobile site from 1976 to 1977. Of the non-vasectomized men, oligospermia was observed in 22 % of the exposed workers in the Denver plant and 17 % of exposed workers in the Mobile plant, compared with 9 and 10%, respectively, in non-exposed controls. Azoospermia was seen in 7 % of the Denver exposed workers and 2 % of the Mobile exposed workers and none in the controls from either location.

From a longitudinal study, Whorton and Foliart (1983) reported that no adverse testicular effects were observed by NIOSH in Hawaiian pineapple workers exposed to DBCP at levels of approximately 1 ppb. Because of the unreliability of the industrial hygiene measurements, the lack of dermal exposure characterization, and the fact that these workers were not exposed for as long a period as individuals exposed throughout life to DBCP in their drinking water, it is not known if this is a true chronic human NOEL.

Two studies, Potashnik et al. (1984) and Goldsmith et al. (1984), reported a reduction in the sex ratio of male to female offspring fathered by DBCP-exposed men. In 30 families studied, the preexposure percentage of male offspring was 53 % compared with the postexposure percentage of male offspring of 35 % (Potashnik et al., 1984). No congenital abnormalities were observed in the children of DBCP-exposed men in these studies. Potashnik and Philip (1988) did not find any difference in the incidence of birth defects in the 34 children born to fathers following exposure to DBCP compared to the incidence in 51 children born to the same families prior to DBCP exposure.

Thrupp (1991) reviewed various scientific, legal and ethical issues surrounding a large scale case in which approximately 1,500 male workers in the Atlantic banana-growing region of Costa Rica were permanently sterilized from application of DBCP to banana crops. This exposure translates to a high regional incidence of infertility, affecting 20 to 25 % of the workers. DBCP was used as a nematocide on Standard Fruit Company's plantations in Costa Rica from 1967 to 1979. As of 1990, 1,500 workers were still affected with 60 to 70 % being azoospermatic and the remainder oligospermic.

Oral

Wong et al. (1988) and Whorton et al. (1989) investigated the relationship between DBCP contamination in the drinking water and birth outcomes of the population of Fresno County, California. No correlation between birth outcomes (including sex ratio) and DBCP contamination was found. DBCP concentrations measured in 532 municipal water systems and 14,000 private wells in Fresno County ranged from 0.004 to 5.8 ppb (Whorton et al., 1988).

Chronic Toxicity

The chronic toxicity of DBCP in humans is limited to the reports regarding the reproductive and carcinogenic effects of the chemical. Reproductive effects are described in detail in the preceding section and the potential human carcinogenicity of DBCP is described below.

Carcinogenicity

Evidence regarding the potential human carcinogenicity of DBCP is found in four epidemiologic reports. Two studies reported on drinking water contaminated with DBCP and cancer mortality (Jackson et al., 1982; Wong et al., 1989) and two were cohort mortality studies of workers exposed to DBCP at production facilities (Hearn et al., 1984; Wong et al., 1984).

The ecological study by the California Department of Health Services (Jackson et al., 1982) found an association between DBCP concentrations in groundwater and the incidence of stomach cancers and leukemia. The data in the DHS study was reevaluated by Environmental Health Associates (EHA, 1986; Wong et al., 1989), which, in contrast to DHS, concluded that there was no association between gastric cancer and leukemia and DBCP concentrations in groundwater. It should be noted, however, that in the EHA report, a trend in increasing cancer risk (gastric and leukemia) versus DBCP water concentration was seen, but was not significant. Although the EHA report corrected some of the methodological flaws found in the DHS report, neither study can be considered conclusive.

Wong et al. (1984) conducted a cohort mortality study of plant workers exposed to DBCP. No significant excess cancer risk of any type was found. In the Hearn et al. (1984) study, non-significant increases in respiratory cancer was noted as a function of increased DBCP exposure. A recent update to this study (Olsen et al., 1995) concludes that there is no suggestion of an increased risk of malignant neoplasm mortality among the workers studied. The authors caution, however, that the conclusions remain limited due to the size of the cohort (548 workers).

In summary, the epidemiologic data have not demonstrated DBCP to be carcinogenic in humans. Animal evidence, however, clearly shows DBCP to be a carcinogen in mammals.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

The most sensitive animal species appear to be rabbits and rats. Based on available dose estimates in epidemiological studies, humans seem to be equally sensitive if not more sensitive than these two experimental species. However, use of human studies in this regard is problematic because the exposure data in the available studies is inadequate. A number of animal studies of varying quality are available and provide an estimate of the chronic NOAEL. These studies report NOAELs of similar magnitudes.

The study by Rakhmatullaev (1971) in which DBCP was administered to rats for six months via drinking water reported a “threshold dose” of 0.005 mg/kg-day. Although this study was of appropriate length, it was inadequately reported. In the inhalation study in rabbits by Rao et al. (1982), the NOAEL estimated from the study at termination (14 weeks), 0.1 ppm, was an order of magnitude less than that observed at the end of the tenth week, demonstrating the cumulative effects of DBCP exposure. This NOAEL was roughly estimated by Reed et al. (1987) to be 0.027 mg/kg-day absorbed DBCP. In an additional inhalation study by Rao et al. (1983) in rats, the NOAEL was also observed to be 0.1 ppm (estimated to be 0.05 mg/kg-day in males) for reproductive effects. The Foote et al. (1986a,b) studies, in which rabbits were administered DBCP via the drinking water for 10 weeks indicated a NOAEL of 0.94 mg/kg-day since the

Foote et al. studies were relatively short, OEHHA makes the assumption that had they been carried out an additional four weeks, the NOAEL would have been an order of magnitude lower, or 0.094 mg/kg-day, as was observed in the inhalation study of Rao et al. (1982). Thus, the NOAELs derived from the Foote et al. (1986a,b) and from the Rao et al. (1982) studies are considered to be similar. The latter study has been selected as the basis for the estimation of a safe exposure level for reproductive effects of DBCP, since it appears to provide the lowest chronic NOAEL and it was adequately reported. Indeed, this is the critical study selected by U.S. EPA for the derivation of the RfC (IRIS, 1998). Although the route of the Rao et al. (1982) study is inhalation, this route is not inappropriate as approximately 30% of the absorbed DBCP dose from the use of contaminated groundwater is estimated to be from the inhalation route.

Studies by Lui and Wysocki (1987) and Warren et al. (1988) provide strong evidence for an additional level of concern in that each study pointed to a different critical period during the development of the male reproductive system (at least in the rat) in which the fetus or developing animal is highly susceptible to the effects of DBCP exposure.

These studies indicate that critical pre- and postnatal periods exist in which male rats are highly susceptible to the toxic effects of DBCP on the reproductive system. The Lui and Wysocki (1987) study is of special concern because it demonstrated a low-dose NOAEL of 1 mg/kg-day+ after only 10 days of exposure during a critical developmental stage. Thus, this report takes the position that a full uncertainty factor of 10 for sensitive subpopulations is needed to account for exposures during the critical developmental periods. These periods were not accounted for in the subchronic studies described above.

Adjusting for compound purity (97.3%) and converting to mg/m^3, the NOAEL of 0.1 ppm in the 13-week subchronic rabbit inhalation study of Rao et al.(1982) is:

$$\text{NOAEL} = (0.1 \text{ ppm}) \left(9.67 \frac{\text{mg} / \text{m}^3}{\text{ppm}}\right) (0.973) = 0.94 \text{ mg/m}^3$$

Adjusting the NOAEL for and exposure of six hours/day and five days week gives the following adjusted NOAEL:

$$\text{NOAEL (adj)} = 0.94 \text{ mg/m}^3 \times 6 \text{ hours}/24 \text{ hours} \times 5 \text{ days}/7 \text{ days} = 0.17 \text{ mg/m}^3$$

No dosimetric adjustment was used by U.S. EPA in converting this animal NOAEL to a human equivalent concentration (hec) since the values which would be used for the adjustment are unknown. OEHHA agrees with this approach, accordingly:

$$\text{NOAEL (adj)} = \text{NOAEL (hec)} = 0.17 \text{ mg/m}^3$$

Uncertainty associated with this lack of adjustment is addressed in the selection of uncertainty factors in the calculation of the PHG.

The NOAEL is converted into a human daily dose using the default factors of 70 kg body weight and 20 m^3/day as an inhalation rate:

$$\text{NOAEL (adj)} = \frac{\text{NOAEL (mg/m}^3\text{) x breathing rate (m}^3\text{/day)}}{\text{body weight (kg)}}$$

$$= \frac{0.17 \text{ mg/m3 x } 20 \text{ m3/day}}{70 \text{ kg}} = 0.05 \text{ mg/kg-day}$$

From studies of similar compounds in human volunteers (Astrand, 1975), absorption of DBCP by the inhalation route is estimated to be 50%. Accordingly, the adjusted NOAEL reflecting the absorbed DBCP dose is :

NOAEL = NOAEL (adj) x 0.50 = 0.025 mg/kg-day

Note that this value is essentially the same as that estimated by Reed et al. (1987), who calculated the NOAEL in this experiment to be 0.027 mg/kg-day. Also note that this NOAEL is converted to a RfD of 1.9 µg/day using the standard assumption of a body weight of 70 kg and an uncertainty factor of 1,000, which is less than twice the value of an RfD of 1.1 µg/day as estimated from the same data by Pease et al. (1991) utilizing benchmark dose methodology.

Carcinogenic Effects

No cancer bioassays of DBCP have been published since the last review of the literature and risk assessments by OEHHA (DHS, 1988a,b). Accordingly, the cancer potency derived in these prior documents is used for the calculation of the PHG.

The human carcinogenic potency of 7 $(\text{mg/kg-day})^{-1}$ derived by OEHHA (DHS, 1988a,b) is based on the development of squamous cell carcinomas in the forestomachs of female mice as observed in the Hazleton (1977, 1978) studies. The multistage model was fit to the carcinogenicity dose-response data and the 95% upper confidence limit on the linear term (q1) was calculated using the standard likelihood procedure employed by U.S. EPA. The result termed $q1^*$ is the animal cancer potency. This potency estimate in animals was adjusted to a lifetime potency by using U.S. EPA's standard assumption that potency tends to increase with the third power of the observation time in a bioassay (Anderson et al., 1983). The estimate of lifetime animal carcinogenic potency was converted to an estimate of potency in humans by the factor, $(70 \text{ kg/animal body weight})^{1/3}$. This conversion follows from the assumption that a dose rate calculated as daily intake of DBCP divided by $(\text{body weight})^{2/3}$ has the same potency in rodents and humans. The procedures followed were those outlined in the 1986 U.S. EPA cancer guidelines (U.S. EPA, 1986) and the 1985 DHS guidelines for chemical carcinogen risk assessment (DHS, 1985).

CALCULATION OF PHG

Calculations of concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or noncarcinogens must take into account the toxicity of the chemical itself, as well as the potential exposure of individuals using the water. Tap water is used

directly as drinking water, for preparing foods and beverages. It is also used and for bathing or showering, and in washing, flushing toilets and other household uses resulting in potential dermal and inhalation exposures.

Noncarcinogenic Effects

Calculation of a public health-protective concentration (C, in mg/L) for DBCP in drinking water for noncarcinogenic endpoints follows the general equation:

$$C = \frac{NOAEL \times BW \times RSC}{UF \times W}$$

where,

NOAEL	=	No-observed-adverse-effect-level
BW	=	Adult body weight (a default of 70 kg)
RSC	=	Relative source contribution (defaults of 20, 60 or 80%)
UF	=	Uncertainty factors (defaults of a 10 to account for inter-species extrapolation, a 10 for the use of a subchronic NOAEL and a 10 for potentially sensitive human subpopulations)
W	=	Daily water consumption rate: Default of 2 L/day; higher values of L-equivalents/day (Leq/day) are used for volatile organics to account for inhalation and dermal exposures from the use of contaminated tap water.

For DBCP, the NOAEL from the principal study is 0.025 mg/kg-day for testicular effects in the male rabbit (Rao et al., 1982). The adult human body weight (BW) default is 70 kg. The relative source contribution (RSC) is 80% since the sole anticipated source of exposure is ground water. A cumulative uncertainty factor of 1,000 has been applied, incorporating uncertainty contributions from interspecies extrapolation (10), the use of a subchronic NOAEL in the place of a chronic NOAEL (10), and sensitive human subpopulations (10). A daily water consumption rate of 6 Leq (liter equivalents) is used since 2 L/day is the standard default value for ingestion and, as estimated by earlier work (DHS, 1988; Reed et al. 1987, McKone, 1987), direct ingestion accounts for approximately one-third of the total exposure from household use of DBCP contaminated water (2 L direct ingestion; 2 Leq dermal; 2 Leq inhalation). A health protective water concentration is therefore calculated as:

$$C = \frac{NOAEL \times BW \times RSC}{UF \times W} = \frac{0.025 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.80}{1{,}000 \times 6 \text{ Leq/day}}$$

$$= 2.3 \times 10^{-4} \text{ mg/L} = 0.23 \text{ ppb} = 0.2 \text{ ppb (rounded)}$$

Carcinogenic Effects

For carcinogens, the following general equation can be used to calculate the public health-protective concentration (C) for a carcinogen in drinking water (in mg/L):

$$C = \frac{R \times BW}{CSF \times W}$$

where,

BW	=	Adult body weight (a default of 70 kg)
R	=	De minimis level for lifetime excess individual cancer risk (a default of 10^{-6})
CSF	=	Cancer potency ($q1^*$): 7 $(mg/kg\text{-}day)^{-1}$ from DHS, 1988a for the development of squamous cell carcinomas of the stomach in female mice.
W	=	Daily volume of water consumed (L/day or Leq/day; see above).

For DBCP, the human cancer potency ($q1^*$) derived from the principal study (Hazleton, 1977, 1978) for the development of squamous cell carcinomas of the forestomach in female mice is 7 $(mg/kg\text{-}day)^{-1}$ (DHS, 1988a,b). The adult human body weight is 70 kg and it is assumed, as previously noted, that 6 Leq/day water is "consumed" by a combination of the oral, dermal and inhalation routes.

Therefore,

$$PHG = \frac{10^{-6} \times 70\ kg}{7\ (mg/kg\text{-}day)^{-1} \times 6\ Leq/day}$$

$$= 1.7 \times 10^{-6}\ mg/L = 1.7\ ppt\ (parts\ per\ trillion)$$

The PHG for DBCP is therefore 1.7 ppt.

RISK CHARACTERIZATION

The primary sources of uncertainty in the development of the PHG for DBCP in drinking water are also the general issues of uncertainty in many risk assessments, particularly inter- and intra-species extrapolation. In the case of DBCP, an additional source of uncertainty arises in the estimation of water "consumption." The estimate of adult water consumption was increased from 2 L/d to 6 Leq/day based on the work of McKone (1987). This was done in order to account for any additional exposure from the inhalation and dermal routes. This correction contributes an unknown amount of uncertainty into the calculation of the final PHG.

The PHG of 1.7 ppt was calculated based on the carcinogenic potency of DBCP. The calculated concentration of 0.2 ppb based on the reproductive endpoint was not proposed, as the PHG since the concentration calculated (1.7 ppt) based on the carcinogenic endpoint was lower and was necessary to protect against DBCP-induced carcinogenesis. In calculating the PHG, a *de minimis* theoretical excess individual cancer risk level of 10^{-6} was used. The corresponding levels for cancer risk levels of 10^{-5} or 10^{-4} are 17 and 170 ppt, respectively.

For PHGs, our use of the RSC has, with a few exceptions, followed U.S. EPA drinking water risk assessment methodology. U.S. EPA has treated carcinogens differently from noncarcinogens with respect to the use of RSCs. For noncarcinogens, RfDs (in mg/kg-day), drinking water equivalent levels (DWELs, in mg/L) and MCLGs (in mg/L) are calculated using uncertainty factors (UFs), body weights and water consumption rates (L/day), and the RSC, respectively. The RSC defaults are 20%, 40%, and 80% (0.2, 04, and 0.8); other values may be used depending on the scientific evidence.

U.S. EPA follows a general procedure in promulgating MCLGs:

1. If Group A and B carcinogens (i.e., strong evidence of carcinogenicity) MCLGs are set to zero.
2. If Group C (i.e., limited evidence of carcinogenicity), either an RfD approach is used (as with a noncarcinogen) but an additional UF of 1 to 10 (usually 10) is applied to account for the limited evidence of carcinogenicity, or a quantitative method (potency and low-dose extrapolation) is used and the MCLG is set in the 10^{-5} to 10^{-6} cancer risk range.
3. If Group D (i.e., inadequate or no animal evidence) an RfD approach is used to promulgate the MCLG.

For approaches that use low-dose extrapolation based on quantitative risk assessment, U.S. EPA does not factor in an RSC. The use of low-dose extrapolation is considered by U.S. EPA to be adequately health-protective without the additional source contributions. In developing PHGs, we have adopted the assumption that RSCs should not be factored in for carcinogens grouped in U.S. EPA categories A and B, and for C carcinogens for which we have calculated a cancer potency based on low-dose extrapolation. This is an area of uncertainty and scientific debate and it is not clear how this assumption impacts the overall health risk assessment.

OTHER REGULATORY STANDARDS

The U.S. Environmental Protection Agency's (U.S. EPA's) Maximum Contaminant Level (MCL) for DBCP is 0.0002 mg/L (200 ppt). U.S. EPA's Maximum Contaminant Level Goal (MCLG) for DBCP, a B2 carcinogen, is set to zero. The current California MCL is also 0.0002 mg/L or 200 ppt. The U.S. EPA's MCL of 200ppt is based on Best Available Technology (BAT) and has

been set to "...reduce the risk of cancer or other adverse health effects which have been observed in laboratory animals", but it is not a health-based standard, *per se*.

Several states have set guidelines for DBCP concentrations in drinking water, which are shown in the table below.

Table 8. State Drinking Water Guidelines

State	Drinking Water Guideline
Arizona	25 ppt
Hawaii	40 ppt
Maine	200 ppt
Minnesota	300 ppt
North Carolina	25 ppt
Wisconsin	200 ppt

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