Gonadotoxic Effects of DBCP: A Historical Review and Current Concepts

Kathleen Hwang[1], Michael L. Eisenberg[2], Rustin C. Walters[3] and Larry I. Lipshultz[*,4]

[1]*Brown University, Providence, Rhode Island, USA*

[2]*Stanford University, San Francisco, California, USA*

[3]*Naval Medical Center, Portsmouth, Virginia, USA*

[4]*Lester and Sue Smith Chair in Reproductive Medicine, Division of Male Reproductive Medicine and Surgery, Scott Department of Urology, Baylor College of Medicine, Houston, Texas, USA*

Abstract: Dibromo-chloro-propane (DBCP), a persistent liphophilic brominated organochlorine, has been produced for agricultural purposes as a nematocide since the 1950s. Widespread use due to its effectiveness as a pesticide continued until the late 1970s when early reports of its toxicity emerged from the laboratories, particularly its impact on spermatogenesis and other adverse reproductive health effects. Since then innumerable cases and studies have surfaced with clear impact after exposure to DBCP, however, the sustained effect of this exposure has yet to be completely understood. As a result of these studies, environmental agencies banned almost all agricultural uses of DBCP in the United States in the late 1970s. This review will try to balance the known toxicity of DBCP with a scientific assessment of published data and a summary of the legal issues that have resulted.

Keywords: Gonadotoxic, DBCP, sperm, legal.

INTRODUCTION

Dibromo-chloro-propane (DBCP), a highly lipophilic brominated hydrocarbon, is a soil fumigant pesticide with significant lethality for nematodes. DBCP formulation began in the U.S. in 1955, and by 1975 its production had reached 25 million pounds per year [1]. DBCP gave farming an economic advantage, boosting successful fruit harvesting by as much as 20% [2]. By 1977 the widespread applicability of DBCP had targeted over 30 U.S. crops and distribution had spread to many foreign countries, especially in Central America. However, in 1977, following startling toxicity findings in a group of U.S. chemical formulation workers, the Environmental Protection Agency stopped virtually all DBCP agricultural use. The story of DBCP's unique and highly specific toxicity [3, 4], the science that this phenomenon engendered, and the legal cases that resulted continue to make headlines.

Although these headlines reflect the rather emotional and highly volatile nature of these legal proceedings, often these claims of damage have gone far beyond what is supported by available science. This review will try to balance the known toxicity of DBCP with a scientific assessment of published data and a summary of the legal issues that have resulted.

SCIENTIFIC REVIEW OF BASIC MECHANISMS

DBCP is a small lipophilic halocarbon that readily passes from the blood through the blood-testis barrier to the Sertoli and germ cells. DBCP has been shown to metabolize to cytotoxic products in several target tissues [5]. Although severe atrophy of the testes of several species of laboratory animals exposed to DBCP by inhalation were reported as early as 1961 [6], adverse effects on human testicular function were not recognized until the mid-1970s [7].

Metabolism of DBCP occurs largely in the liver *via* the microsomal cytochrome p450 system [8], where liver enzymes catalyze the biotransformation of DBCP to metabolites that are excreted in the bile and urine. DBCP is converted by glutathione S-transferases to a reactive, cytotoxic episulfonium ion in the testicular seminiferous tubules [9, 10], and this metabolite can bind covalently to DNA, producing single-strand breaks [11]. This pathophysiologic activity most likely accounts for DBCP's specific toxicity during the spermatogenic cycle.

Bjorge *et al*. reported that rat testicular cells are more efficient than human cells in metabolically activating DBCP [4]. Furthermore, the activity of glutathione S-transferase is significantly lower in the testes of monkeys and humans than in rats [12]. The ability to convert DBCP to its non-toxic form is dependent on the testicular enzyme epoxide hydrolase. This enzyme catalyzes the hydrolysis and subsequent deactivation of epoxides and has the highest level of activity in the testes of humans and mice and relatively low activity in rats [13]. Hence, rats produce more damaging DBCP metabolites than humans and are less able to detoxify these resulting products, making DBCP theoretically a more potent gonadotoxin in this laboratory animal model.

Toxicology

Investigations of DBCP's gonadotoxic potency have been carried out in several species of animals and have

*Address correspondence to this author at the Quinn Medical Tower at St. Luke's, 6624 Fannin Street, Suite 1700, Houston, Texas 77030, USA; Tel: (713) 798-6163; Fax: (713) 798-6007; E-mail: larryl@bcm.edu

1874-303X/13

demonstrated that the spermatotoxic effects of DBCP are dose-, route-, and species-dependent. Inhaled DBCP is much more toxic than ingested DBCP, as the liver removes much more of the ingested chemical before it reaches and damages the testes [14]. The susceptibility of animals to DBCP is quite species-specific. Rabbits appear to be the most sensitive with an approximately 10-fold higher sensitivity than rats to inhaled DBCP [15, 16]. Foote *et al*. also observed that testicular injury was associated with lower drinking water levels in rabbits than in rats [17]. Interestingly, mice and hamsters are relatively insensitive to testicular damage by DBCP [13, 18].

Investigators have clearly demonstrated that DBCP is biotransformed to a greater extent to metabolites that covalently bind to the cells' DNA in rat testicular cells as compared to human testicular cells *in vitro* [11]. Investigators found a DBCP concentration-dependent increase in single-strand DNA breaks in rat DNA but no significant damage in human DNA was found at any concentration tested [11]. This evidence suggests that testicular epithelium in humans receives a lower DBCP dose, metabolically activates less, detoxifies more, and experiences significantly less DNA damage and cytotoxicity than that in rats in response to equivalent DBCP inhalation exposures.

Taking into account this species specificity and the comparatively low impact of DBCP on human DNA, it is little wonder that Torkelson [6] arbitrarily suggested a five times lower human concentration limit, i.e., 20% of the lowest dose (5ppm) that he tested in rats.

IDENTIFICATION OF INITIAL HEALTH IMPACT

Clinical Experience and Work Exposure

The human gonadotoxicity of DBCP was first discovered at the Occidental Chemical Company in Lathrop, California [7]. Subsequent studies of factory workers established the dose-dependent effects of DBCP on the testis as well as the subsequent recovery of spermatogenesis in many affected men. While the factory studies conclusively established the effects of DBCP on male fertility for those with direct contact, the agricultural studies that followed appear inconclusive, reflecting the variability in DBCP exposure, reporting, and the various methods of DBCP application and formulation. Moreover, other methodologic limitations have been noted (vide infra). To date, it is uncertain if routine agricultural DBCP exposure involves concentrations high enough to impair a male worker's reproductive potential.

Factory Studies

In 1977, several workers at a chemical plant in California were noted to have impaired fertility [7]. The number of employees manufacturing DBCP was relatively small, but many of them were of reproductive age. A relatively high percentage of these formulators discovered that they were having difficulty conceiving after they began working in the DBCP production division. Eventually, six formulators were evaluated with semen analyses, and surprisingly, all men were found to be azoospermic or severely oligospermic. An outside medical consultant was then hired, and eventually the entire division was evaluated. Of the 36 men in the division, 11 had previously undergone vasectomy. Semen analyses from the remaining 25 men showed 9 (36%) with azoospermia and 3 (12%) with oligospermia (<20 million sperm/mL). Interestingly, there was a time-dependent effect. Those workers with the longest exposure (≥36 months) had the most severely depressed counts (<1 million), while those with the shortest exposure had normal semen parameters. Serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels were elevated in the affected men, while testosterone and physical examinations were normal. Biava *et al*. biopsied the testes of several of the Lathrop workers and found altered or absent spermatogenesis, with the most severely affected men having no remaining spermatogenic cells [19].

Subsequently, a comprehensive study of a larger group of of the plant's 310 employees was undertaken. Of 196 men examined, 142 underwent a semen analysis. Of the 142 men who had not had a previous vasectomy, 107 had been exposed to DBCP and 35 had had no exposure. Of the exposed men, 13.1% were azoospermic and 32.6% were oligospermic. In contrast, the nonexposed group included only 2.9% azoospermic and 5.7% oligospermic men [20].

When these men were first identified, the role of DBCP as an important gonadotoxin was uncertain, as over 100 chemicals were being used or manufactured in the plant. The existing air levels of DBCP in the factory were measured at 0.4ppm (8-hour time-weighted average), well below the 1ppm level recommended by Torkelson *et al*. [6]. After a review of all the affected workers' employment history, it was determined that DBCP was a common exposure and the likely cause of their testicular failure [21].

Almost concurrently, and with some uncertainty remaining about the magnitude of DBCP's gonadotoxic effects, Lipshultz *et al*. in 1979 further explored the relationship of DBCP and altered testicular function in two diverse factory settings. The authors studied DBCP production workers at chemical plants in Colorado and Alabama. The Colorado plant manufactured DBCP from 1956 to 1976, and the Alabama plant manufactured DBCP from 1976 to 1977. In all, the exposed group included 64 men from Colorado and 71 from Alabama. The unexposed group included 20 men from Colorado and 37 from Alabama. Of the exposed men from Colorado, 22% were oligospermic (<20 million/mL) compared to 10% of nonexposed men. In addition, 7% of the exposed men were azoospermic in contrast to none of the unexposed. At the Alabama facility, 17% of the exposed men and 9% of the nonexposed men were oligospermic. In Mobile, furthermore, 2% of the exposed men were azoospermic in contrast to none of the unexposed. The authors went on to determine that duration as well as the level of exposure to DBCP predicted the degree of testicular failure. This "quality of exposure" was factored into the evaluation of data from both sites by using a job-related magnitude-of-exposure factor. Indeed, employees at both facilities with greater exposure had lower sperm densities. Interestingly, the exposure required to impair sperm production was less at the Alabama site, probably because of its more recent production and suggesting that recovery of spermatogenesis, as most likely had occurred in Denver, was also possible [22]. This concept of "recovery" was supported by a subsequent study of 14 workers in Mobile by Lantz *et al*. These investigators

demonstrated improvement of sperm count when they reevaluated men 18 to 21 months after their last DBCP exposure [23].

Egnatz *et al.* examined the Dow Chemical Company experience at a Midland, Michigan, factory. Production occurred at the facility from 1957 to 1975, and the study was undertaken beginning in 1977. In all, 232 workers with potential DBCP exposure were compared to 97 nonexposed workers. The authors found that those workers with the highest and most recent DBCP exposure had significantly lower concentrations of sperm production. In contrast, men with more distant, indirect, or intermittent exposure had semen counts that were not significantly different from the nonexposed groups. The lack of association with distant or even intermittent exposure again suggested the recovery of testicular function following cessation of DBCP exposure [24].

Scharnberger *et al*. studied workers at an Arkansas plant [25]. The authors stratified the 86 Arkansas workers into three exposure categories, based on time and quality of exposure. Of the men in the highest exposure category, 14 of the 18 men (78%) were found to be azoospermic. In a very different part of the world, Potashnik and colleagues examined 23 employees of an Israeli DBCP manufacturing plant. Focusing on men in the highest exposure group (>100 hours), they found 12 men (52%) to be azoospermic. Five of these azoospermic men had last been exposed 1 to 5 years prior to evaluation [26].

Follow-up from many of these factory studies has since been published. As suggested by earlier works, recovery from oligospermia or azoospermia following cessation of DBCP exposure is possible (Table **1**) [27-30]. This improvement in sperm production usually is seen within 16 months [21, 23]. In fact, only one study found no differences in semen parameters when DBCP-exposed and nonexposed men were compared several years after cessation of DBCP manufacturing [24]. Nevertheless, despite multiple reports documenting recovery of spermatogenesis, reinitiation of spermatogenesis did not occur in all affected men.

Agricultural Studies

A study of California pesticide applicators by Glass *et al*. concluded that men who had been exposed to DBCP for more than 2 months in the previous year had a statistically significant but clinically unimportant decrease in sperm count and an increase in FSH compared to that in other men at other exposure durations. Importantly, the authors concluded that there was no significant alteration in the rate of clinical infertility [31]. Closer examination suggests the transiency of the gonadotoxic effect of DBCP because only recent heavy exposure was correlated with decreasing sperm counts. However, the small sample size (n=96) limits the conclusions of the paper — a fact demonstrated when the authors were unable to correlate sperm count with patient age or days of abstinence, both of which are well known to affect sperm density [32, 33].

Sandifer and colleagues evaluated men with different occupations who were all involved in the DBCP agricultural setting to determine how specific exposure may play a role in promoting testicular failure. Seventy-six DBCP workers from 6 states were examined. The median sperm counts for formulators (12.1 million/mL), applicators (2.7 million/mL), and farmers (17.8 million/mL) were below those for researchers (101.5 million/mL) and salesmen (73.0 million/mL) [34]. As in the Glass *et al*. study, the authors found no persons who desired more children but were "infertile," suggesting that there was no effect on clinical fertility. The study is somewhat difficult to interpret, given that rather than using a geographically relevant control, a reference group from New York City was used. Moreover, just as there are known geographic variations in semen production, there are also known socioeconomic and lifestyle factors, such as social class or lifestyle habits, that affect semen parameters yet were not considered [35]. It is important to note that formulators, farmers, and applicators likely represent socioeconomic groups distinctly different from those of salesmen or researchers.

Investigations performed on Hawaiian workers showed conflicting results. Takahashi and colleagues performed a study on men working in Molokai. Unfortunately, DBCP exposure could not be quantified. Nevertheless, they found that 23% of the agricultural workers were oligospermic, and 54% had low sperm counts compared to 14% of a reference group. While the investigators found significant differences in sperm concentration, there were no effects on the cohort's fertility, infant mortality, or birth defects. While the authors attempted to account for marijuana use, only self-reported drug use data was collected, and the men were excluded rather than controlled for the exposure in the analysis of DBCP exposure. In addition, a convenience sample, consisting of infertile men evaluated at a gynecologic clinic and volunteers from the general public who lived in the area, was utilized rather than non-DBCP-exposed agricultural workers, who would have made an ideal control group. Because there was no accounting for other exposures of agricultural workers (i.e., other pesticides or recreational drugs) and sociodemographic variables, the reference comparison group likely was not valid [36].

Table 1. Factory Studies that Address Recovery of Spermatogenesis

Study	Year	Follow-Up (Years)	Exposed Men	Azoospermic Men (n)	Azoospermia Recovery % (n)	Oligospermic Men (n)	Oligospermia Recovery % (n)
Whorton & Milby [29]	1980	1	21	12	0 (0)	9	67 (6)
Potashnik [30]	1983	4	20	13	31 (4)	7	71 (5)
Potashnik & Yanai-Inbar [31]	1987	8	15	8	38 (3)	7	43 (4)
Potashnik & Porath [32]	1995	17	15	9	33 (3)	6	50 (3)

In contrast, other studies on Hawaiian pineapple workers followed the men longitudinally and collected semen analyses at intervals and compared estimated DBCP exposures. In these instances, no significant differences were found in semen values based on DBCP exposure levels [21].

In addition to its application and formulation in developed countries, DBCP was also used in less developed countries. Ramirez and Ramirez studied 72 men who presented to a health clinic in Costa Rica "quejandose de no poder engendrar" (complaining about their inability to procreate). The men had applied DBCP in the district of Rio Frio. The authors found a negative correlation between exposure to DBCP and sperm counts, and on the basis of these findings, they looked at another 600 workers without fertility concerns and found "similar results" [37].

The article has been criticized due to several methodologic limitations. Of the original 72 men in the cohort, 20 (27.8%) were excluded for "ailments that have a close etiologic relationship with sterility"; these exclusion criteria were poorly defined. The term "sterile" was used loosely and included men with oligospermia. In addition, a correlation coefficient to examine the association between two continuous variables (i.e., sperm count and DBCP exposure) can be inaccurate, as it can be quite sensitive to outliers [38]. Furthermore, no data on the methods of quantitating DBCP exposure or timing of DBCP exposure in relation to semen analyses were given, nor was other information on the sociodemographic characteristics of the applicators provided. Even the age of the applicators was not examined, a fact that is relevant, given that animal data suggests that the age of exposure significantly impacts DBCP's potential gonadotoxicity [39]. Marijuana use is known to be common in this region of Costa Rica, and this variable was not assessed. Moreover, the lead author of the study acknowledged that men with multiple episodes of gonorrhea urethritis were also from the highest DBCP exposure group, suggesting that other common risk factors may also explain the putative relationship between DBCP exposure and sperm quality but were not critically examined.

In summary, studies examining agricultural DBCP exposure suffer from methodologic deficiencies that limit the interpretation of their conclusions. Lack of adequate control groups and the inability to provide control of sociodemographic and illicit drug use all weaken the current studies. In addition, there is no allowance for the great variability in DBCP exposure and reporting resulting from the various methods of DBCP application and formulation (e.g., manual injection of nematicide at the base of the tree versus use of irrigation systems; controlled preparatory mixing practices, and inconsistent use of protective clothing, etc.).

While DBCP exposure in factory workers is certain, and prior exposure has caused prolonged yet reversible oligospermia and azoospermia, any sustained significant effect on agricultural workers remains to be clearly identified and understood.

LEGAL JOURNEY

Just as fascinating as the physiologic impacts of DBCP are the legal ramifications following its identification as a human gonadotoxin. After the initial findings of toxicity in factory workers at the Occidental Chemical plant in Lathrop, California, the Environmental Protection Agency (EPA) and the State of California ordered a temporary ban on the sale and use of DBCP in 1977 [40]. In 1979, this temporary ban was made permanent by the EPA everywhere in the United States, except for a one year extension for pineapple farming in Hawaii [40].

The first punitive legal action involving the effects of DBCP exposure was *Arnett v. Dow Chemical Company* in 1983 [41]. The plaintiffs included six factory workers from the Occidental Corporation factory in Lathrop, California, where workers were exposed to DBCP while formulating pesticides. Subsequent tests showed that these workers had zero or "below-normal" sperm counts. The court ruled in favor of the six plaintiffs in the form of a substantial judgment. From this point, the focus of DBCP-related cases shifted not only from industrial to agricultural exposure but also to foreign plaintiffs, a shift that depended on poorly conceived and executed scientific studies.

Despite the lack of substantive scientific data indicating a causal relationship between testis failure and the agricultural application of DBCP, extensive litigation continued and extends even to the present day. Driven by suspect putative data, international political ambitions, and potentially large settlements, the legal journey reads like a Hollywood movie. The first case to be litigated involved mainly Central American plaintiffs and settled before trial. In 2001, however, fueled by a local surge of support, the Nicaraguan government enacted Special Law No. 364, which retrospectively imposed liabilities on foreign companies that had manufactured or used DBCP in Nicaragua [41]. Not only was Nicaraguan jurisdiction in question but also whether the legal standard of "innocent until proven guilty" had been breached. Agricultural-based legal cases, however, became headline news with several rulings in California, including *Tellez v. Dole*, *Mejia v. Dole*, and *Rivera v. Dole*. Inconsistencies in the plaintiffs' stories and suspicions of the defendants' lawyers led to the discovery of plaintiff lawyer misconduct and witness fraud (some of the "sterile" plaintiffs were found to have fathered children), as well as falsified laboratory reports and work certificates [42].

The one case that did rule on the scientific implications of agricultural exposure is the case *Osorio v. Dole*. In 2009, U.S. District Court Judge Paul Huck noted, "To date, over 20 medical studies have attempted to analyze the relationship between DBCP and male sterility. But of the six types of sperm impairments listed in the Judgment, only azoospermia has been linked to DBCP exposure, and only in the factory setting — never to farm workers" [43]. Another legal issue dealt with plaintiffs who fathered children after being exposed to DBCP, and Judge Huck reported, "Reoccurrence of sterility following childbirth cannot, as a matter of medical and scientific fact, be the result of prior DBCP exposure" [43].

Although there have been multiple twists and turns in the legal journey of DBCP, the ride is not over. Trials of other "plaintiffs" — whether real or contrived — are waiting. What the eventual outcome will be is far from certain, but the courtroom drama of the DBCP story is a fascinating study in the confluence of science, multinational corporations, and the legal system.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

Declared none.

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Received: October 10, 2012 Revised: November 29, 2012 Accepted: December 1, 2012