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NIOSH CONFERENCE ON DIBROMOCHLOROPROPANE

A Symposium on DBCP Sponsored at Cincinnati, Ohio,

on October 19-20, 1977, by the

National Institute for Occupational Safety and Health

Dr. Channing Meyer, Conference Coordinator

Marion G. Curry and Jeffery A. Lybarger, Editors

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The proceedings of a conference on the human reproductive effects of 1,2-dibromochloropropane (96128) (DBCP) are presented. The conference was held in Cincinnati, Ohio on October 19 and 20, 1977, and was sponsored by NIOSH. Contributed papers on the following topics are included: findings of reproductive surveys of DBCP exposed male workers at Occidental Chemical Company, Dow, and Shell; establishment of human semen quality standards; methods used to determine infertility; DBCP mutagenicity; analytical methods; protective measures; and the effects of ethylene-dibromide (106934) exposure.

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ABSTRACT

The effect of exposure to 1,2-dibromochloropropane (DBCP) on the fertility of male workers formulating or applying DBCP-containing pesticides was the subject of a conference held in Cincinnati, Ohio, in October 1977. Authorities in their respective fields presented 15 discussions on: the experiences of companies involved in DBCP production (the Dow Chemical Company, Shell Chemical Company, and Occidental Chemical Company); the attempts to define normal sperm count, to standardize counting techniques, to conduct epidemiological studies, to monitor exposed persons, and to select control groups; the monitoring, analyzing, and respiratory protection needed for DBCP; and the involvement of the National Institute for Occupational Safety and Health (NIOSH), the Occupational Safety and Health Administration (OSHA), the U.S. Environmental Protection Agency (EPA), the Oil, Chemical and Atomic Workers International Union.

Appendices provide additional information concerning the hazards involved in DBCP exposure: an annotated bibliography of recent DBCP literature related to male fertility; the EPA notice to suspend DBCP; and the background for and the OSHA regulation (29 CFR Part 1910.1044) concerning DBCP.

CONTENTS

ACKNOWLEDGMENTS

Because this Conference on Dibromochloropropane was called to provide a timely forum for the exchange of scientific information and to solve some immediate problems facing people exposed to DBCP, the participants shared their knowledge in informal presentations. Their oral remarks have necessarily undergone extensive editing and have been reviewed by the authors. We wish to acknowledge and extend our appreciation to all of these authors for their willingness to participate and to review the final edited version of their original presentations.

The effort of Dr. Austin Henschel to resolve technical and scientific uncertainties that existed in the original transcript has been of inestimable help. The able and untiring assistance of Elizabeth Ayer in the original editing is acknowledged. Lorice Ede supplied support and background information concerning the legal aspects of DBCP regulations.

Marion G. Curry and
Dr. Jeffery Lybarger,
Editors

OPENING REMARKS

Bobby Craft* and Channing Meyer+

BOBBY CRAFT

This encouraging turnout reflects an increasing interest not only in occupational safety and health in general but in the effects on reproduction of a variety of chemical agents in the workplace.

Some of you have shared this kind of experience before when we discussed problems of vinyl chloride and styrene, butadiene, and other chemicals. One wonders what will be next. When will we be able to move out of this reactive mode of trying to catch up with problems that keep cropping up, rather than moving on to a proactive phase when we can prevent these kinds of occurrences from happening?

The cooperative and rapid fashion that the various groups and organizations involved in this have moved together to attack this question of male fertility and exposure to DBCP is encouraging. In the matter of a few weeks, production of the chemical was voluntarily stopped by the principal producers, Dow and Shell, after they had documented problems among their workers similar to those reported by the Occidental Chemical Company and by the Oil Chemical Atomic Workers Union. The Occupational Safety and Health Administration (OSHA) moved very quickly to promulgate an emergency temporary standard. Even earlier, the State of California banned production of the chemical in their state. EPA and FDA have both moved very quickly to take action to protect their constituencies.

The cooperative flavor of these investigations is, as far as I know, unprecedented. When the workers became concerned about the problem, they and their union asked Dr. Donald Whorton if he would assist in trying to find out what was going on. Later, the Occidental Chemical Company also asked Dr. Whorton if he would help

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them in the investigation. After the National Institute for Occupational Health and Safety (NIOSH) received requests for assistance from both the company and from the Oil Chemical Atomic Workers Union, we also contracted for Dr. Whorton's services. This speaks for Dr. Whorton's universal acceptance as an objective scientist.

The discouraging side to this story is that some time ago, we had enough information to have prevented the problem from occurring. Why did we let it happen? More importantly, how can we prevent similar occurrences from happening in the future, given the information that we have right now on a large number of similar kinds of chemical substances that are being used in the workplace?

Our purpose here today is not to answer these questions; however, by sharing information that various groups have acquired, we can gain some new insight as to how we might possibly prevent such occurrences from happening in the future.

I would like to introduce Dr. Channing Meyer, your chairman for this conference.

DR. CHANNING MEYER

I would like to welcome all of you to a session marked, I believe, by unprecedented cooperation between management, labor, governmental agencies, and all the other parties involved in this effort. It is encouraging to work for the ultimate goal that Dr. Craft suggested--how do we avoid things like this in the future. By investigating, through cooperative efforts, the things that have and are happening, I am hoping we can accomplish that goal.

What we want to happen here is an exchange of good scientific information that has been gathered by government, management, and labor--information that will help us set up programs to avoid similar occurrences in the future. Let us share information. We want your ideas and your participation in setting up surveillance programs for the people who have been exposed to DBCP and who are known to be affected, and we need your help to work on ways to discover other similar agents.

THE OCCIDENTAL CHEMICAL COMPANY EXPERIENCE

M. Donald Whorton* and Ronald M. Krauss+

DR. WHORTON

BACKGROUND

The Occidental Chemical Company is located in the Central Valley of California. Ammonia and ferilizer are produced, and pesticides are formulated. Among Occidental Chemical's Agricultural-Chemical Division (Ag-Chem) workers, there was a rumor that if you worked in the Ag-Chem division you were infertile--unable to have children. (The term "infertility" is used rather than "sterility" because sterility generally implies a permanence, usually with surgical intervention.)

Initial Study of Five Workers

After considerable discussion, the Union (OCAW Local 1-5) decided to have the men provide semen samples for analysis. Semen samples from seven volunteers were sent to a central California laboratory for sperm analysis. Because the laboratory gives results only to doctors and because I had previously been a consultant to the Union, the Union had them sent to me. The laboratory examination slips indicated "azoospermia," "sperm counts less than 5 million," "less than 8 million." Although this was a single laboratory test with no controls, the results indicated a problem of considerable magnitude. After meeting with both Company and Union representatives, I was retained by both to examine these seven volunteers (and later, to examine a larger group).

Of the original seven men, one had been vasectomized and another failed to appear. The five men completed a medical history questionnaire--a special questionnaire concerning the reproductive aspects of the genital-urinary (GU) system--and they provided a semen sample, which was immediately sent for analysis.

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I reviewed each man's medical history questionnaire with him and gave each a complete physical examination. The following laboratory tests were made:

-- a complete blood count (CBC) with a differential (if the exposure is affecting sperm, maybe it is affecting other rapidly producing systems, mainly the hematopoietic system);
-- a urinalysis (looking for any kidney or renal or bladder effect);
-- an SMA 12 (looking for liver and renal effects);
-- a thyroid screen (T-4 and T-3 resin uptake);
-- and follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone assays.

The sperm count results were the same as they had been; all five were either severely oligospermic (low sperm counts) or they were azoospermic (no sperm in the ejaculate).

Second Preliminary Study

After these results were given to the men, the Union, and the Company, I agreed to see additional employees--all the people who were then working in the Ag-Chem division (including all the supervisory personnel, mechanics, and clerical people) and the people in the quality control laboratory who handled the chemicals that came from the Ag-Chem section.

Among these workers (a total of 39 people, 36 males and 3 females), there was no loss of libido, no loss of erectile ability, no problems with ejaculation. In other words, there was no evidence of impotence at all. We were not dealing with impotence, we were dealing with another problem. There was no loss of facial hair, no alteration of body hair, no evidence of gynecomastia, no testicular atrophy. There were really no group abnormal physical findings or laboratory results other than sperm counts, FSH, and LH.

From these 39 workers, 22 nonvasectomized dibromochloropropane (DBCP) formulators were divided into two groups (Table 1). In group A are 11 people who were severely affected; their mean sperm count was 0.2 million/ml; 9 workers had sperm counts of zero, and 2 had sperm counts of 1 million/ml. In group B are Ag-Chem workers or laboratory people, all with normal sperm counts (mean 93 ± 18 million/ml). Each had a sperm count ≥ 40 million/ml.

There are significant differences. The mean exposure time of group A was 8 years; in group B, the exposure time was 0.08 years. Although there is a difference in age, a still later study of a larger group showed this not to be a significant factor. The mean FSH level of group A (11.3) compared with that of group B (2.6) is

Table 1. Mean and standard error for age, years of exposure, sperm counts, and serum FSH, LH, and testosterone levels of 22 nonvasectomized formulators.

Group		Age, yr		Exposure, year		Sperm count, X 10^6/ml		FSH, mIu*/ml		LH, mIu/ml		Testosterone, ng/dl	
	No.	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
A	11	32.7	1.6+	8.0	1.2†	0.2	0.1†~	11.3	1.8†	28.4	3.3+	459	35
B	11	26.7	1.2+	0.08	0.02†	93	18†	2.6	0.4†	14.0	2.8+	463	31

* milli International units.
+ Difference between groups A and B significant at $p<0.01$.
† Difference between groups A and B significant at $p<0.001$.
~ Nine workers with zero sperm/ml; two with 1 X 10^6/ml.

significant at the 0.001 level. The same held for LH. For testosterone, there was no real difference at all.

SPERM PRODUCTION

Sperm generation takes 72 days to go from the primary spermatogonia development at the inner portion of seminiferous tubules out toward the lumen of the tubule, until it is stored in the epididymis. It then takes another 2 to 3 weeks of maturing in the epididymis before the sperm are ejaculated. So there is about a 3-month lag time.

What are some of the factors affecting sperm production (Figure 1)? One factor is heat. Scrotal temperature is about 2 to 2.5°C lower than body temperature. If the testes were to be placed within the body, they would cease to make sperm. With certain types of work, the scrotum becomes heated. Some people avoid hot baths. Although there is debate, there is some question about tight fitting shorts.

HEAT	Baths; shorts; work; role of scrotum
ANATOMICAL	Varicocele; undescended testes, torsion
INFECTION	Post-pubertal mumps
DRUGS	Antimetabolites, lead, arsenic, colchicines, amoebicides, nitrofurantoin, hormones, pesticides.
ENDOCRINE	FSH, LH, testosterone
RADIATION	

Figure 1. Factors affecting sperm production.

Anatomical difficulties that can cause infertility include varicoceles (even a unilateral vericocele); undescended testes; torsion or twisting of the testes; or actual trauma.

Many drugs affect sperm production: antimetabolite-type drugs given to cancer patients; lead; arsenic; colchicine given to people with gout; nitrofurantoin (which should never be used by males concerned about not having children); various sorts of hormones, estrogen, et cetera; and pesticides.

Then there are the endocrines. Dr. Krauss will address his comments to hormonal endocrinology.

DR. KRAUSS

I want to review some of the hormonal events involved in testicular function and spermatogenesis and the significance of some of these hormonal measurements. A number of exogenous factors can affect testicular function, e.g., infection, trauma, genetic causes, and toxins. (Later, the actual mechanical and numerical factors involved in sperm production will be discussed.) There is a hormonal control mechanism that is also susceptible to various influences, and here, I am concentrating on the hormonal events.

One of the two anatomical components we are interested in is the seminiferous tubule, which is involved in the production of spermatozoa (Figure 2). This tubule occupies about 90 percent of the testicle. In the testicle, the important hormone, known as testosterone, is produced by the second component, the Leydig cells. The hormone itself is responsible for all the features we commonly associate with "maleness." This involves hair growth, general body features, secondary sexual development, genitalia, performance, erection, et cetera. All of these functions are influenced by testosterone levels.

FOLLICLE STIMULATING HORMONE (FSH); LUTEINIZING HORMONE; TESTOSTERONE

In terms of sperm production, the major responsible hormone is known as follicle stimulating hormone (FSH). This comes from the pituitary gland that is under the control of other hormones originating from higher in the central nervous system. The pituitary gland is connected to the brain through the hypothalamus, which controls the release of FSH hormone from the pituitary. FSH then acts on the testicle and is critical for the production of sperm.

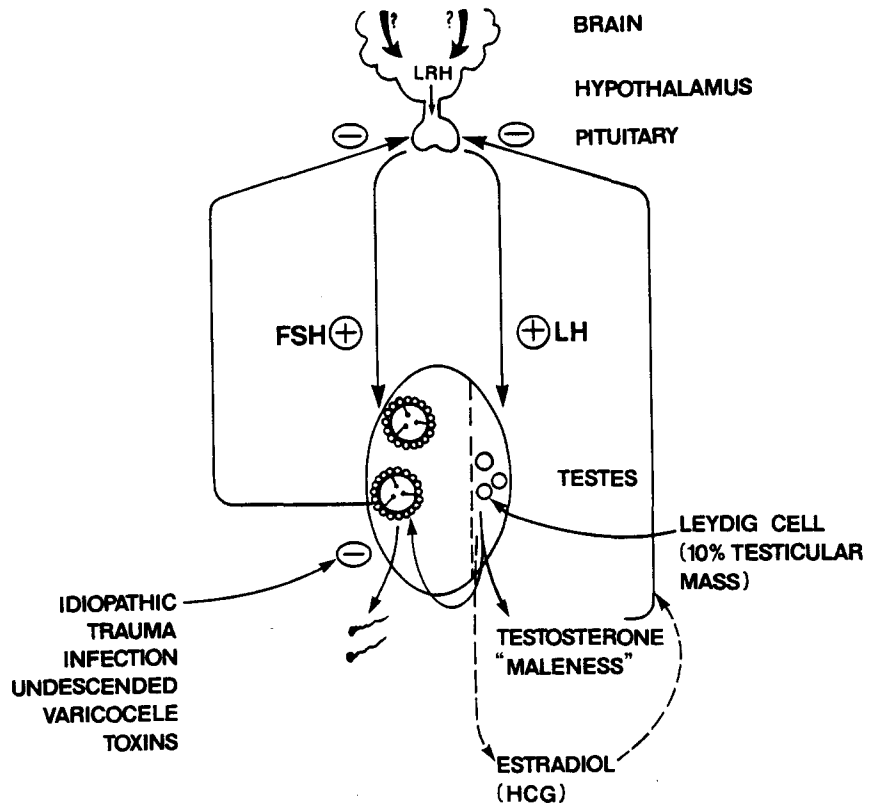

Figure 2. Schematic of development of male spermatozoa.

The same is true for the second hormone, the luteinizing hormone (LH). It is named for its function in females, but in men, we might call it the Leydig cell stimulating hormone. This also originates in the pituitary under the control of a hypothalamic releasing factor. Perhaps it is the same one that releases the FSH. LH is critical for the function of Leydig cells and testosterone production.

NEGATIVE FEEDBACK LOOP

We have, then, a system that produces sperm (seminiferous tubules) under FSH influence; and we have some cells (Leydig cells) that make testosterone under LH influence. How is this regulated? There is a negative feedback loop. (This is really one of the critical elements in the data that we are going to be showing.) All good hormonal systems have a negative feedback loop, and in this case, we have a fair amount of information indicating that the products of Leydig cells turn off pituitary LH production.

It may either be testosterone or, possibly, an estrogen produced by these Leydig cells that is responsible for turning off the

pituitary gland when the testosterone level reaches what is considered to be normal.

Where Leydig cell function is impaired (and this has been documented experimentally), the testosterone level falls just enough to turn on the pituitary gland. In the case of the seminiferous tubules, it is more obscure. A negative feedback chemical, which has been named inhibin, has been identified recently. Much remains to be learned about inhibin; it appears, however, that anything that affects the function of the seminiferous tubules can result in a loss of the negative-feedback effect of this chemical, and FSH levels will increase. When there is a primary damage to the testicle involving seminiferous tubules, the negative feedback response is blunted and FSH is increased, just as LH would be increased in the absence of testosterone.

Another way in which the testicle can be affected is directly through damage to the pituitary or to the brain; this results in the absence of gonadotropic hormones and is, in fact, one cause of infertility and testicular dysfunction.

So there are two, almost opposite, situations concerning the hormonal control system: one, where there is a disruption at the end organ resulting in increases in the pituitary hormone; the other is some sort of damage that results in decreased pituitary hormones--what is called secondary end organ failure.

HORMONAL MEASUREMENT

The three hormones (FSH, LH, and testosterone) can be measured in the laboratory. All are susceptible to serum assays. All are susceptible to radioimmunoassay, a very precise, specific assay. Given the proper anti-sera, and there are very specific anti-sera against FSH, LH, and testosterone, the procedure is extremely useful and very precise.

The serum is sampled, and the hormones are measured. Although there are some problems related to hour-to-hour variation in hormone levels (which does occur with LH and to a much lesser extent with FSH), we believe such variations would average out given the numbers of subjects that were sampled here.

What did we find? We found the hormone levels, particularly the FSH level, to be markedly increased, which is consistent with a primary testicular damage. These hormonal measurements are of interest in several ways. They allow us to:

-- identify the site of action of the suspected toxin;
-- use the hormonal system to gain insight into the whole

mechanism for pituitary-testicular regulation, an area rife with scientific uncertainties; and
-- use one or more of these hormones as the marker for testicular damage when sperm counts, which would probably be the best parameter, are unavailable--either because subjects wouldn't volunteer or because of their having had vasectomies.

There is one other hormone that I want to mention briefly--human chorionic gonadotropin (HCG) produced by the testicle in very small amounts under normal situations. In cases of carcinogenesis or tumors involving the testicle or involving other organs in the body as well, levels of HCG have been used as a tumor marker. This is yet another way to use hormonal measurments. Other hormones, such as ACTH or adrenocorticotropic hormone, have also been shown to be useful as tumor markers. From this hormonal milieu, we can perhaps assess several major aspects having to do with DBCP.

With this background, Dr. Whorton will now present the results.

DR. WHORTON

After we did the health hazard evaluation of the 39 workers, we found there were four questions that needed answering:

-- "Did the infertility problem extend beyond the Ag-Chem division to involve other male employees?"
-- "What was the extent of the infertility problem in employees outside of the Ag-Chem division?"
-- "Was there a hormonal assay available, one that was as effective as a sperm count, for identifying affected individuals?" (Because a blood specimen is easier to get than is a sperm specimen.)
-- "Although DBCP was thought to be the most likely causal agent, could one or more other chemicals also be involved?"

SAMPLING PROGRAM

Although we wanted to sample all those people presently or in the past employed in the Ag-Chem division and those present employees who had never been employed in the Ag-Chem division (Figure 3), this was unsucessful. Since the employment data needed for epidemiological predictors or evaluation were not available, we decided to offer examinations to any employee of Occidental Chemical that wanted to be examined.

The examination included an abbreviated medical history limited to the GU tract and a reproductive history; a physical examination,

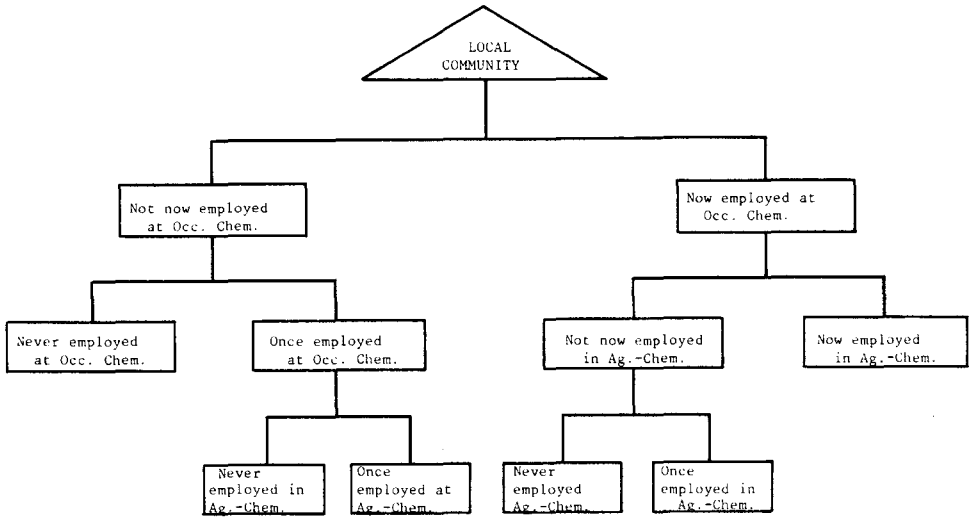

Figure 3. Sampling strategy for the Occidental Chemical Company. More than 3 month's employment needed to be considered "employed."

limited to GU tract, testicular size, body habit (e.g., gynecomastia), and blood pressure; and for laboratory purposes, a sperm count. The sperm sample was collected at home after at least a 2- or, preferably, 3-day period of abstinence (by masturbation, although coitus-interruptus was allowed if masturbation was unacceptable).

After the sperm samples were brought to the workplace on the day of collection, they were sent immediately to a laboratory and all were counted during that day. Only sperm counts were made at this point; morphology evaluations were not done because we believed a count alone was a reasonable screen. The blood samples were all drawn at the same time during the day to lessen the possibilities of diurnal variations. They were then sent to a laboratory where they were spun down, separated, frozen, and later run in batches.

We were doing more than just a pure health hazard survey--we were seeking the problem. We looked at FSH, LH, and testosterone trying to find a marker that would be useful.

Dr. Tom Wilcox, a NIOSH physician, or I then saw all the employees who participated. In Table 2 are listed the 196 people in the sample group, by exposure group and vasectomy status. Of this group, there were nine nonvasectomized-exposed persons who didn't want to give a sperm sample or who, for some other reason, were unable to present a sample. In addition to the 196 men, a group of 5 women with very minimal exposure were checked; all were clerical employees except one. We did FSH's and LH's on them. The three

Table 2. Sample groups exposed to DBCP, by exposure group and vasectomy status.

Number	Vasectomy status	Exposure group
35	Nonvasectomized	Not exposed
107	Nonvasectomized	Exposed
9	Nonvasectomized (no sample)	Exposed
7	Vasectomized	Not exposed
38	Vasectomized	Exposed

that were not on the oral contraceptive pill had normal FSH and LH and also had normal menstrual cycles. The FSH and LH of the two who were on the pill were altered abnormally because of the pill. Two farmers from a neighboring dairy farm were also seen; they were normal.

About 261 hourly employees worked for Occidental Chemical. The response of these hourly employees to the medical examination and to a later questionnaire concerning nonparticipation has been broken down into the areas of the plant in which they worked (Table 3).

Table 3. Number and percent of Occidental Chemical Company hourly employees (by work area) participating in medical or questionnaire phase of the study.

Work area	Total employees	No. examined	Percent examined	No. responding to questionnaire	No. not examined or not responding to questionnaire	Percent of total employees not examined or not responding
Ag Chem	24	24	100	n.a.	0	0
Best Products	12	11	91	1	0	0
Maintenance	135	82	61	25	28	21
Ammonia plant	28	14	50	11	3	11
Warehouse	28	7	25	13	8	29
Fertilizer plant	14	5	35	9	0	0
Acid plant	20	4	20	3	13	65
Total	261	147	56	62	52	20

Because we knew the people who had not participated in the medical examination, we asked them to tell us why (Table 4). (These questionnaires were returned anonymously.) Of the nonmedical participants, 62 responded and 52 did not. Of the 62 responding to this questionnaire, 36 of them had never worked at the Ag-Chem division, 19 had worked for a year or less, 5 for a year or more, and 2 did not state.

Table 4. Reason for nonparticipation in the medical examination.

Reason	Number
Sterile employee (vasectomy)	20
Sterile wife	6
Did not wish to give specimen	3
"Not interested"	22
Religious	1
Other	10
Total	62

Plant Operation

In the Ag-Chem division, about 100 products are made and 200 technical grade chemicals are used, although they are not used all the time. This is where DBCP was used.

Best Products is where products for the home are made, mainly insecticides. Because DBCP is not used, this and the Ag-Chem area are, in a sense, comparable.

Maintenance employees keep the plant working and running; they vary from working all over the plant to working in specific shops. Sometimes it is difficult to determine how many hours each of these workers spend where.

Ammonia is made in the ammonia plant.

There is a generalized warehouse, with the Ag-Chem division having its own separate warehouse. Very few things from Ag-Chem get stored in the general warehouse.

Fertilizer is made in the fertilizer plant. During the evaluation, we learned that for about 3 years, in the early 1960's, DBCP was impregnated into fertilizer pellets. This changed some of

our thoughts about "ever worked in Ag-Chem" to "ever been exposed to DBCP."

Sulfuric acid and some other things are made in the acid plant.

Chemicals Used in Plant Operation

To obtain a concept of the amount and types of chemicals used in the Ag-Chem division, the Company supplied the number of pounds per month for the years 1968 through 1977. These data, combined by quarters, are given here for DBCP, ethylene dibromide, epichlorohydrin, and toxaphene (Table 5).

Epichlorohydrin is similar to and related to alphachlorohydrin, which produces sterility in animals, mainly by acting on the epididymis. The Ag-Chem division also processed ethylene dibromide (which is closely related to DBCP) three or four times a year. It would arrive in a tank car, and three workers would repackage it in a day and a half.

When the total exposure is considered, the exposure to DBCP far exceeded that of other compounds. Thus, when considering the etiological agent, DBCP was most probable. The other compounds with animal evidence of testicular effects are encountered to a markedly lesser degree, either in amount or time.

FINDINGS FROM EXAMINATIONS

One of the things we wanted to know was did the infertility problem extend beyond the Ag-Chem division? Was there an association between those who were exposed and those who were not exposed?

Sperm Count and Age

When we looked at sperm count and age, we found there was no association--not for the entire group nor for the group exposed or the group not exposed. In Figure 4 are cumulative percentage distributions of sperm counts for two groups: a. workers who are now or who once worked in Ag-Chem (N = 51) and b. workers who never worked in Ag-Chem (N = 91). The median sperm count was 45.0 million/ml for the Ag-Chem workers and 73.3 for those never in Ag-Chem.

Sperm Count and Exposure

Because DBCP was once impregnated in pellets in the fertilizer plant, some people who never worked in Ag-Chem were really exposed

Table 5. Four chemicals formulated by the Agricultural Chemical Division, by quarters, from 1968 to 1977 (in pounds).

Year	Compound	Jan-Mar	Apr-June	July-Sept	Oct-Dec
1968	DBCP	-	-	59499	327520
	Ethylene dibromide	-	-	0	0
	Epichlorohydrin	-	-	1098	3846
	Toxaphene	-	-	41902	5123
1969	DBCP	503450	727554	136916	162815
	Ethylene dibromide	80620	36785	0	3610
	Epichlorohydrin	5915	10196	3532	1856
	Toxaphene	6993	192018	167107	817
1970	DBCP	488076	441971	212798	335275
	Ethylene dibromide	45087	44401	0	0
	Epichlorohydrin	5986	6032	3620	3873
	Toxaphene	224	96174	113767	1360
1971	DBCP	418602	355978	138865	315800
	Ethylene dibromide	0	47542	0	0
	Epichlorohydrin	4900	5562	2558	3670
	Toxaphene	428	157144	174365	0
1972	DBCP	429755	241890	406146	428480
	Ethylene dibromide	0	0	0	0
	Epichlorohydrin	549	1561	463	83
	Toxaphene	8696	190845	42669	522
1973	DBCP	395910	464980	193211	832214
	Ethylene dibromide	39708	0	0	12033
	Epichlorohydrin	4635	5676	2444	9666
	Toxaphene	0	21976	53997	3199
1974	DBCP	622673	678446	422868	1159824
	Ethylene dibromide	414889	0	37543	0
	Epichlorohydrin	7311	8764	4850	12334
	Toxaphene	17427	42130	43933	0
1975	DBCP	852882	602052	553775	503530
	Ethylene dibromide	0	0	0	41166
	Epichlorohydrin	6413	2314	5894	5069
	Toxaphene	240	16709	85457	453
1976	DBCP	620786	445723	961584	266734
	Ethylene dibromide	37543	54869	0	39708
	Epichlorohydrin	4540	4463	11468	3261
	Toxaphene	0	47474	88421	694
1977	DBCP	728790	362341	255401	-
	Ethylene dibromide	80860	0	0	-
	Epichlorohydrin	8450	4435	3132	-
	Toxaphene	0	34135	33092	-

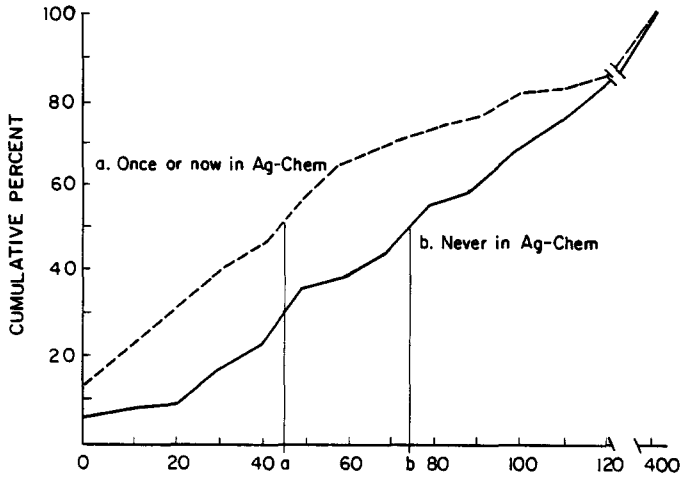

Figure 4. Cumulative percentage distribution for sperm count for two groups: a. once worked or now works in Ag-Chem; b. never worked in Ag-Chem.

to DBCP. There were also 15 applicators who worked out in the fields for the Company who had been exposed but who hadn't worked in Ag-Chem. Determining the applicator's exposure was difficult; gross time was used. In Figure 5, then, are the cumulative percent distributions based on a. DBCP exposure (N = 107) or b. no DBCP exposure (N = 35). The median sperm count was 45.6 million/ml for workers exposed to DBCP and 78.7 for those not exposed. There is a difference between Figures 4 and 5 because some azoospermic and oligospermic men who had never worked in Ag-Chem had exposure to DBCP in the pellet plant or as applicators.

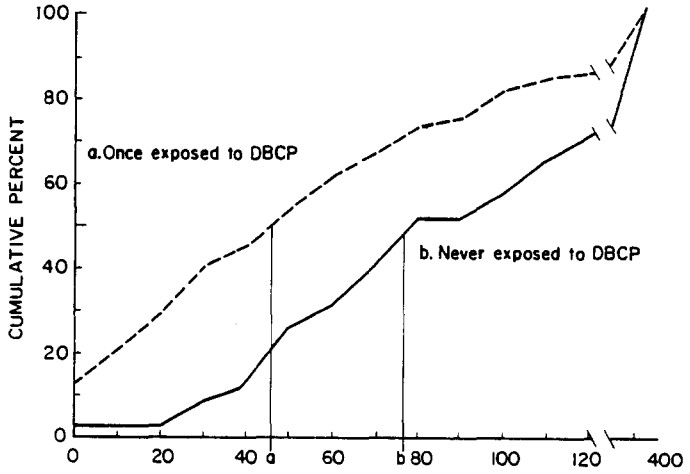

Figure 5. Cumulative percentage distributions for sperm count for two groups: a. exposed to DBCP; b. Never exposed to DBCP.

The mean, the standard error, and range sperm counts for 107 employees with a history of exposure to DBCP are given in Table 6. Median was used in Figures 4 and 5 because, with this type of population, it only takes one 358 and a number of zeros to obtain a mean of 80 million/ml. Here the total mean is 63.8 for those exposed.

Table 6. Mean, standard error, and range of sperm counts (in millions/ml) for 107 employees exposed to DBCP.

Age group	Count	Mean	Standard error	Range	
				Minimum	Maximum
20	34	65.4	10.3	1.0	244.0
30	46	58.5	9.4	0	263.0
40	18	80.8	26.5	0	358.0
50	9	51.2	16.0	0	153.0
Total	107 Avg.	63.8		0	358.0

Sperm Count and Nonexposure

The mean, standard error, and range sperm counts for the 35 who were never exposed to DBCP are given in Table 7. There is a difference: for the exposed, the average mean is 63.8; for the never exposed, the average mean is 106. In this population, however, the use of the median is better than the use of the mean.

Table 7. Mean, standard error, and range of sperm counts (in millions/ml) for 35 employees never exposed to DBCP.

Age group	Count	Mean	Standard error	Range	
				Minimum	Maximum
20	16	89.7	12.0	30.0	184.0
30	8	137.1	38.4	42.0	372.0
40	9	99.0	27.3	25.0	281.0
50	2	147.5	147.5	0	295.0
Total	35 Avg.	106.2		0	372.0

The distribution of sperm count (in millions per milliliter) among the exposed and nonexposed is illustrated in a bar graph (Figure 6). For most of the exposed workers, the count is below 40 million/ml, whereas for the nonexposed, the count is above 40 million/ml.

These tables and figures illustrate that we were finding very different types of sperm counts for the exposed as compared with the nonexposed populations.

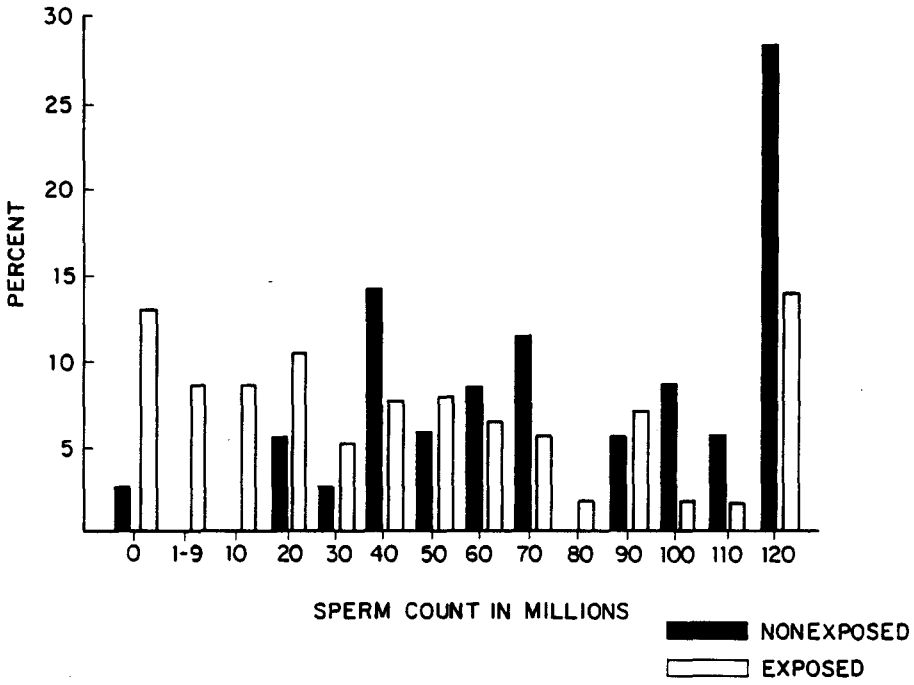

Figure 6. Percent distribution of sperm counts among the sample of 142 Occidental Chemical Company employees, 1977.

Sperm Count and Exposure Time

In Table 8, we have attempted to relate the sperm counts to exposure times. Obtaining good data for DBCP exposure time was difficult. The Company had very good data from the mechanics for the number of hours they spent in the Ag-Chem area in 1976 and 1977. Unfortunately, they didn't have data for earlier exposure times. People's recollections varied about the time they worked in the Ag-Chem area and the time they didn't; the applicators had a very difficult time saying how many months, or how many weeks, or how often they worked with DBCP. When we could not quantitate some people's exposure in any rational fashion, they were dropped from this comparison.

Table 8. Relationship of sperm count to DBCP exposure time in 126 nonvasectomized men.

Sperm count	Exposure time, months					
	None	1-6	6-24	24-42	43	Total
<40 X 10^6/ml	4 (9.1%)	11 (25%)	7 (15.5%)	8 (18.2%)	14 (31.8%)	44 (34.5%)
>40 X 10^6/ml	31 (37.8%)	37 (45.1%)	7 (8.5%)	4 (4.9%)	3 (3.7%)	82 (65.1%)
Total number	35	48	14	12	17	126
Total percent	27.8	38.1	11.1	9.5	13.5	100

Although there is debate about what is a normal sperm count, here we used two large groups: those with sperm counts less than 40 million/ml and those with sperm counts greater than 40 million/ml. Of the 35 persons never exposed, 31 had counts greater than 40 million/ml. For the exposed population, as exposure time increased, the sperm count decreased.

Figure 7 is a graphic representation of the effect of time on sperm counts. Those exposed under 3 months had normal sperm counts; those exposed for about a year had reduced sperm counts; those exposed for more than 3 years had a few or no sperm.

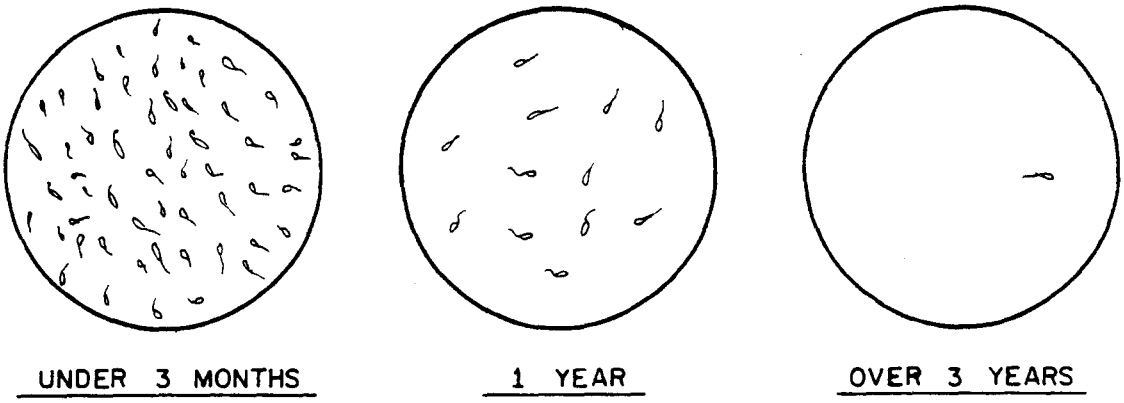

Figure 7. Effect of exposure time on sperm count.

Hormonal Levels of Exposed and Nonexposed Groups

In addition to the infertility problem, we considered the hormonal levels of the exposed and nonexposed groups (Tables 9-12). Although there were 107 nonvasectomized exposed people who gave sperm samples, the 114 considered for hormone levels includes the 7 exposed workers who didn't give sperm samples. For these 114 employees (Table 9), there is some variation of FSH with age. If statistical methods are used, there is a significant rise of FSH with age.

Table 9. Mean, standard error, and range of FSH levels (in mIu/ml) for 114 nonvasectomized employees exposed to DBCP.

Age group	No.	Mean	Standard error	Range	
				Minimum	Maximum
20	36	3.5	0.2	1.3	8.5
30	48	5.5	0.6	1.1	24.3
40	19	7.7	1.4	2.0	28.1
50	11	5.1	1.2	2.4	15.9
Total	114	5.2		1.1	28.1

For 35 nonexposed, nonvasectomized workers (Table 10), statistical methods indicate FSH increases with age. In the age group over 50, one azoospermic man had a very high FSH level. If his level is taken out, there may be no change with age.

Table 10. Mean, standard error, and range of FSH levels (in mIu/ml) for 35 nonvasectomized employees never exposed to DBCP.

Age group	No.	Mean	Standard error	Range	
				Minimum	Maximum
20	16	2.9	0.2	1.6	4.4
30	8	3.5	0.5	1.8	6.9
40	9	3.7	0.2	2.7	4.8
50	2	6.7	4.0	2.7	10.8
Total	35	3.4		1.6	10.8

When LH values were measured for the 35 nonexposed, nonvasectomized men, the results were the same, i.e., not significant with age (Table 11). In the group of 114 exposed, nonvasectomized workers, however, there is a significant rise above age 40 (Table 12).

Table 11. Mean, standard error, and range of LH levels (in mIu/ml) for 35 nonvasectomized employees never exposed to DBCP.

Age group	No.	Mean	Standard error	Range	
				Minimum	Maximum
20	16	13.2	1.5	4.6	21.8
30	8	14.5	3.2	3.5	29.2
40	9	14.1	2.5	5.5	28.0
50	2	18.4	7.7	10.7	26.1
Total	35	14.0		3.5	29.2

Table 12. Mean, standard error, and range of LH levels (in mIu/ml) for 114 nonvasectomized employees exposed to DBCP.

Age group	No.	Mean	Standard error	Range	
				Minimum	Maximum
20	36	14.4	1.3	1.5	37.8
30	48	14.5	1.2	1.0	37.4
40	19	18.8	3.3	6.0	56.0
50	11	20.2	3.9	3.1	53.2
Total	114	15.7		1.0	56.0

For serum testosterone, there was a significant decrease with age for the exposed. There is no decrease with age for the nonexposed. Normally, some decrease in testosterone might be expected with age.

When mean sperm counts are compared by groups, those who were azoospermic who were exposed had a mean FSH of 13.9. For workers with sperm counts from 1 to 9 million/ml, the mean was only 4.4 mIu. Because the FSH level doesn't rise very much until the sperm count gets to zero, it would appear that a man would have to be

almost azoospermic to have a predictable, significant rise in FSH. The same thing, though not to quite the same extreme, occurred for LH. We did not see any change for testosterone.

In Table 13 are correlation coefficients for age, sperm count, FSH, LH, and testosterone in 35 nonexposed individuals. There is a significant correlation at the 0.01 level for FSH and age and for testosterone and LH (asterisked items). At the 0.05 level, there was a significant correlation for FSH and sperm count--as sperm count decreases, FSH increases. (There was one azoospermic in the group and his FSH was quite high.)

Table 13. Correlation coefficients for age, sperm count, FSH, LH, and testosterone for 35 nonexposed individuals.

Coefficient	Age	Sperm count	LH	Testosterone
Sperm count	0.17	-	-	-
LH	0.10	0.16	-	-
Testosterone	-0.23	-0.16	0.51*	-
FSH	0.40*	-0.33+	0.25	0.10

*Significant correlation at 0.01.
+Significant at 0.05.

Most of the correlation coefficients (for age, sperm counts, known exposure, FSH, LH, and testosterone) in 91 individuals with quantifiable exposure are significant at the 0.01 level--the sperm count decreases with increased exposure (Table 14). Sperm count decreases with a rise in FSH. Sperm count decreases with a rise in LH. LH increases with exposure. LH increases with rise in FSH. FSH increases with a rise in exposure.

Hormones as Predictors

Another question needing an answer is, is there a predictor? Can a hormonal assay (a FSH or LH or testosterone or some combination thereof) be used to predict a sperm count without doing a sperm count?

Tables 15 and 16 show prediction analyses for all men with both sperm count and hormone results. In Table 15 there are two groups: people who have sperm counts between zero and 19 million/ml and those greater than 19 million/ml.

Table 14. Correlation coefficients for age, sperm count, known exposure, FSH, LH, and testosterone in 91 exposed individuals with quantifiable exposure.

Coefficient	Age	Sperm count	LH	Testosterone	FSH
Sperm count	0.09	-	-	-	-
LH	0.16	-0.36	-	-	-
Testosterone	-0.14	-0.22	-0.04	-	-
FSH	0.18	-0.35*	0.63*	-0.02	-
Exposure	0.23	-0.38*	0.52*	-0.02	0.60*

*Significant at 0.01.

Table 15. Prediction results of sperm counts by discriminant analysis of FSH, LH, and testosterone levels for 140 men (two groups).

Group	Sperm count	Actual group membership	Predicted group membership	
			Group I	Group II
I	1-19 X 10^6/ml	32	17 (53.1%)	15 (46.9%)
II	>19 X 10^6/ml	108	6 (5.6%)	102 (94.4%)

In Table 16 there are three groups: from one to 19 million/ml, greater than 19 million/ml, and azoospermics. For groups I and II (1 to 19 and >19 million/ml, respectively), the results are the same--inconclusive. The azoospermics, however, were the most predictive. This only corroborates some of the other data that have been discussed.

The two-group breakdown was used for FSH (Table 17) and for LH (Table 18). The results, again, were not sensitive, with LH not being as good a predictor as was FSH.

Table 16. Prediction results of sperm counts by discriminant analysis of FSH, LH, and testosterone levels for 140 men (three groups).

Group	Sperm count	Actual group membership	Predicted group membership	
			Group I	Group II
I	1-19 X 10^6/ml	17	8 (47.1%)	9 (52.9%)
II	>19 X 10^6/ml	108	27 (25.0%)	81 (75.0%)
III	Azoospermia	15	14 (93.3%)	1 (6.7%)

Table 17. Prediction results of sperm counts by discriminant analysis of FSH for 140 men.

Group	Sperm count	Actual group membership	Predicted group membership	
			Group I	Group II
I	1-19 X 10^6/ml	32	16 (50.0%)	16 (50.0%)
II	>19 X 10^6/ml	108	3 (2.8%)	105 (75.0%)

Table 18. Prediction results of sperm counts by discriminant analysis of LH for 140 men.

Group	Sperm count	Actual group membership	Predicted group membership	
			Group I	Group II
I	1-19 X 10^6/ml	32	17 (53.1%)	15 (46.9%)
II	>19 X 10^6/ml	108	20 (18.5%)	88 (81.5%)

BIOPSIES

In an attempt to determine why people were azoospermic or oligospermic, we performed biopsies (Figure 8). A testicular biopsy is done under general anesthesia so the tissue will not be distorted. The procedure is: take the testicle; palpate it to make sure you have the testicle and not the epididymis; incise though the scrotum; and then make a small incision in the tunica. The testicular tissue oozes out. With a scissors, snip the tissue. Oversew it and repair the scrotum. It is not a major procedure.

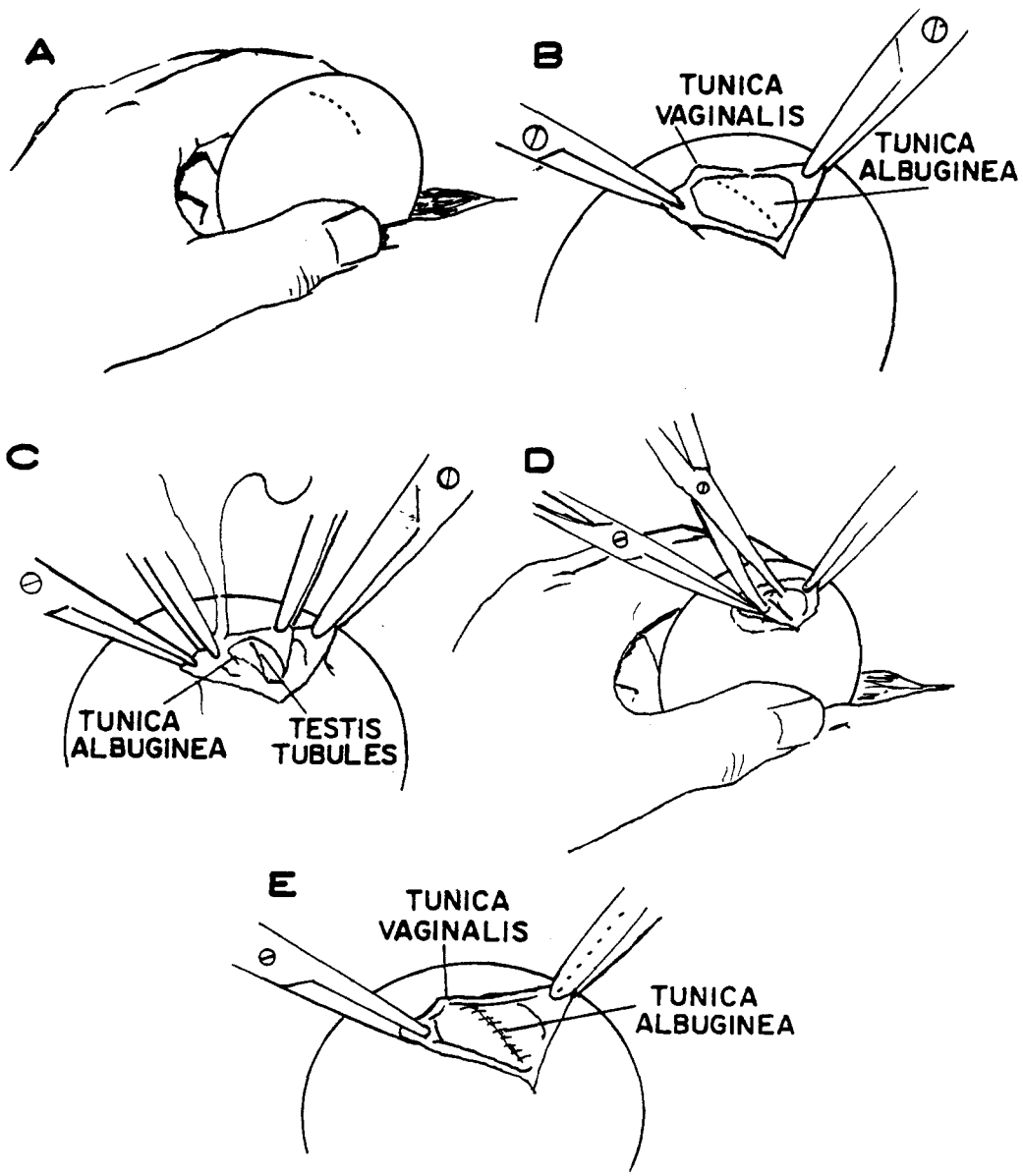

Figure 8. Technique for performing a FSH biopsy.

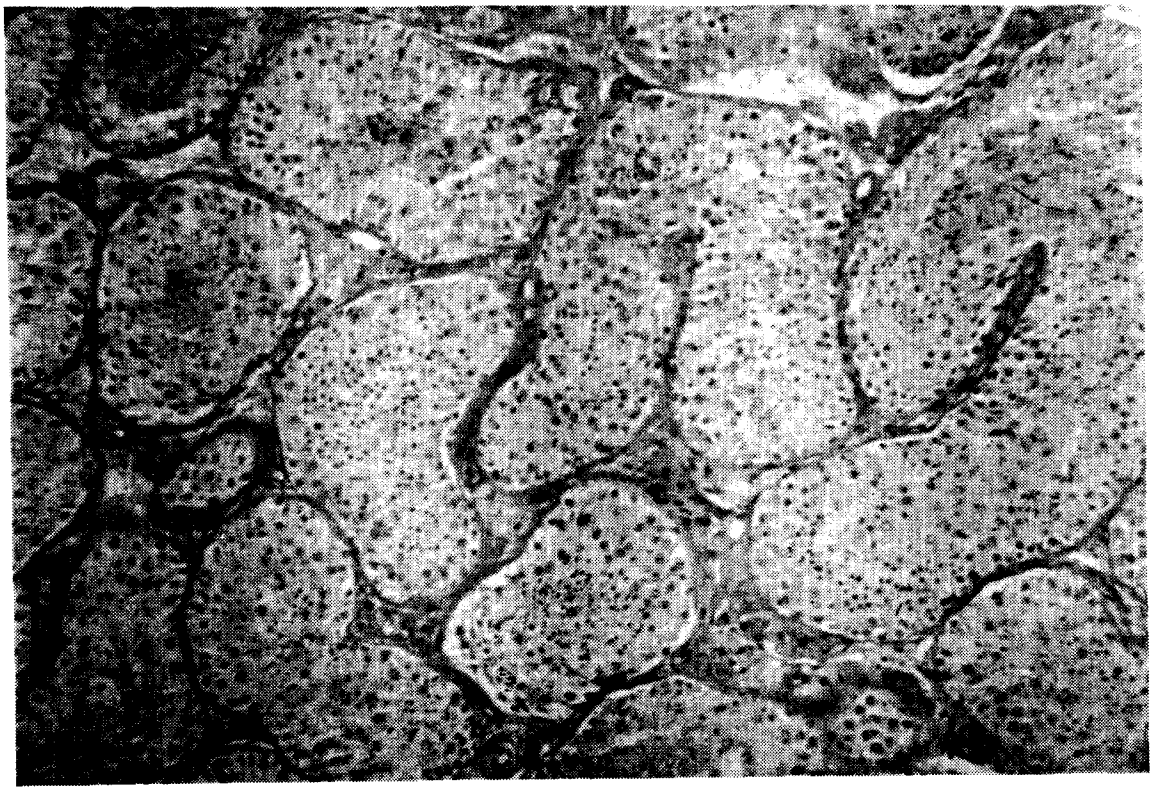

Figure 9. Tissue from normal testis (100X).

Figure 9 illustrates tissue from a normal appearing testes. The various sorts of cells, large and small, evidence of spermatids, and primary spermatogonia on the side are apparent. This man had been exposed for 3 years and away from exposure for 3-1/2 years.

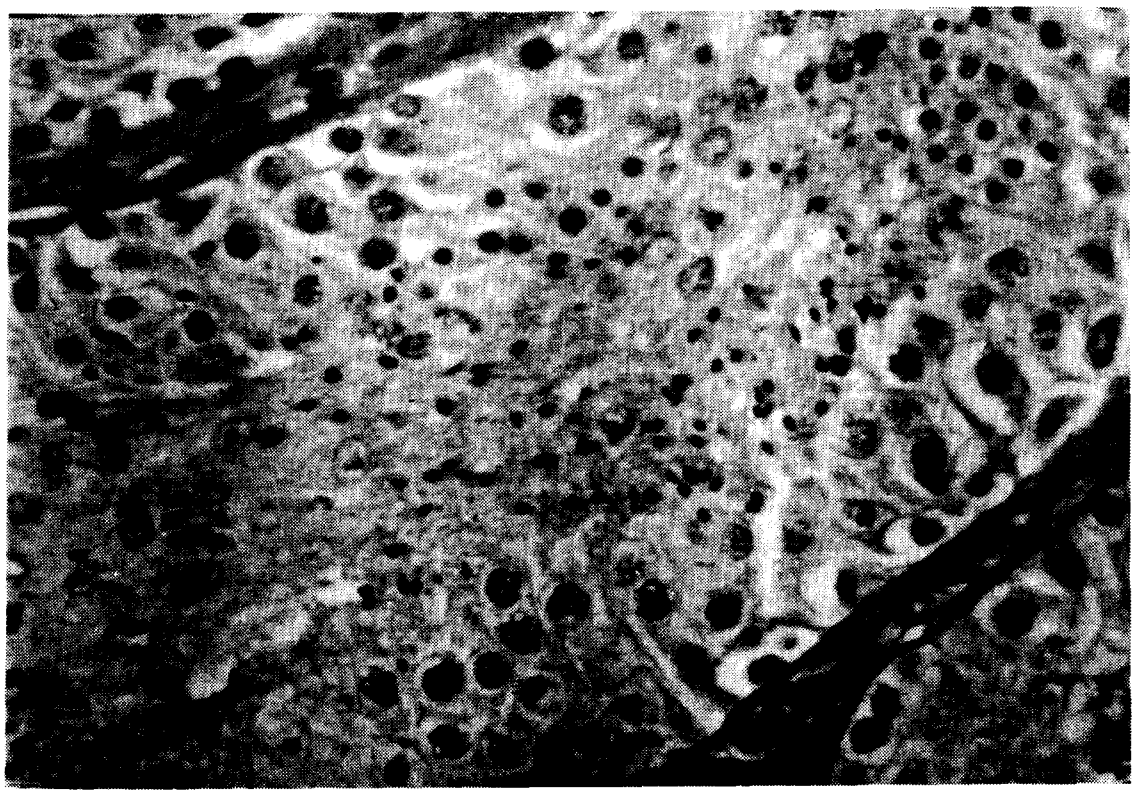

Figure 10. Tissue from a normal testis, seminiferous tubules (400X).

Figure 10 (a higher power of the same patient seen in Figure 9) illustrates seminiferous tubule tissue from a normal appearing testis--the larger cells on the periphery and the little, small spermatids in the middle. There is no thickening of the membrane; the interstititium looks fine. There is no inflammation et cetera.

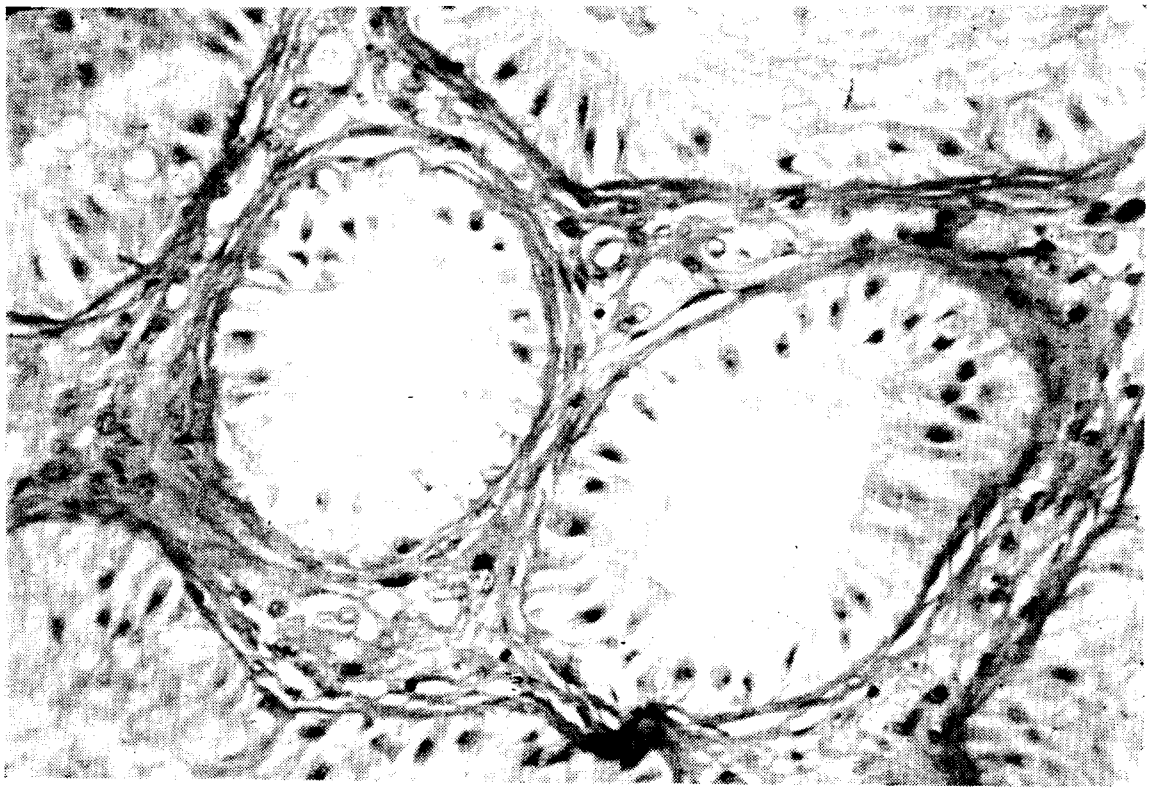

Figure 11. Tissue from a severely affected worker, Sertoli cells (250X).

Figure 11 illustrates tissue taken from a more severely affected individual. Where are all the spermatogonia? Where are the spermatids? Basically, they are not there. What is shown in Figure 11 are Sertoli cells, which are normally present. They act as "nurse cells." There probably is an increase in peritubular fibrosis. Again, however, looking at the the interstitium presents no information. There is no increase in scarring, fibrosis, et cetera.

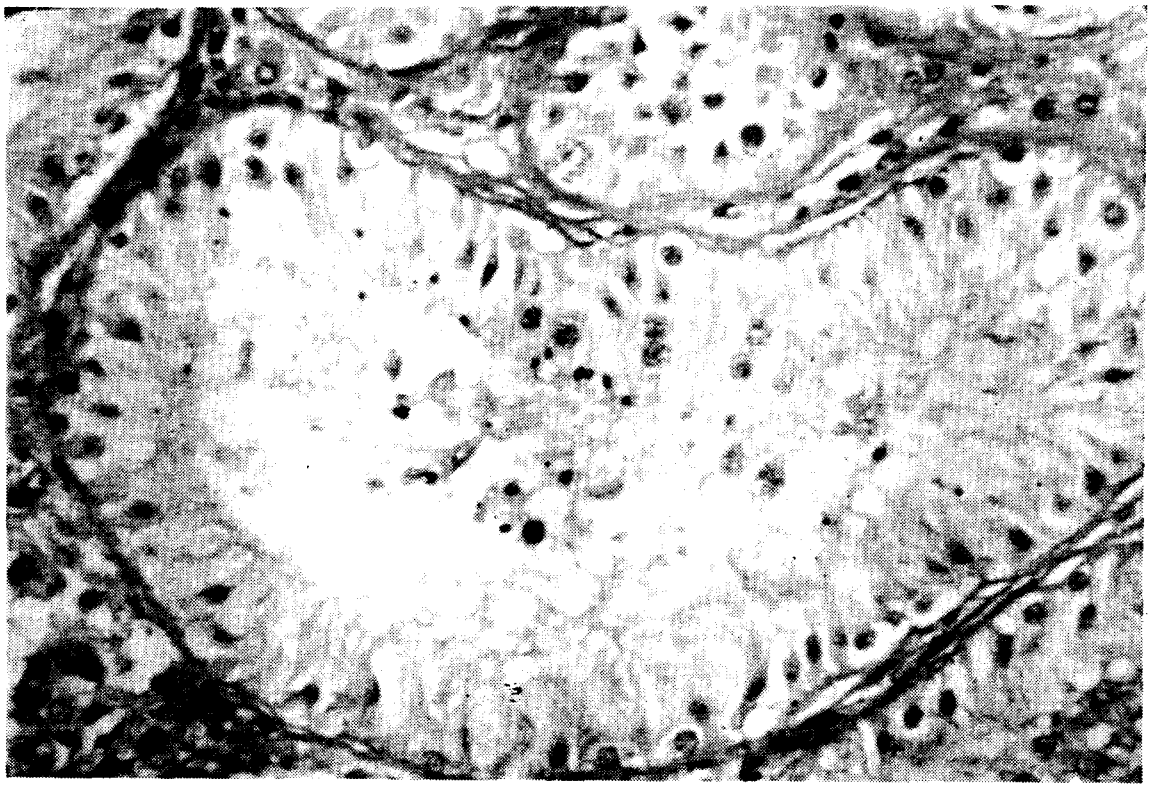

Figure 12. Tissue from a worker exposed for 1 year (250X).

Figure 12 illustrates tissue from an individual who has been exposed for 1 year. When this Figure is compared with Figure 9, the relative decrease in the number of spermatogonia and the number of active spermatogenesis can be seen. Again, there is no inflammatory process going on.

CONCLUSIONS

What was the extent of the problem? We found that 13 percent of those who were exposed were azoospermic; 16.8 percent were severely oligospermic, with sperm counts of between 1 to 19 million/ml; and 15.8 percent were low normal (if you are willing to agree that that is 20 to 39 million/ml).

DBCP is most likely the causal factor. This finding could not be based on data from this one plant alone. Data from studies by Dow and Shell (see The Dow Experience, p. 30, and The Shell Experience, p. 43) lead us to believe that it most likely is DBCP.

In a population in which there is reluctance to producing a semen sample, FSH could be used as a screening tool, a predictor. However, that population would have to have a large number of azoospermics to be meaningful plus there would be a large number of false negatives. FSH and LH together don't add much information. There is no reason, based on our data, to include testosterone at all. If something abnormal is found, the only way to confirm it is with sperm count or a biopsy.

Collecting sperm samples on a large scale basis can't be done unless there is tremendous cooperation. Even in our situation where the Company and the Union, at all levels, were pushing very hard for everybody to participate, we still had a considerable number of people who didn't want to talk to us and another group of people who wouldn't even fill out an anonymous questionnaire.

Our data, which indicate that DBCP is a selective sperm cell or spermatogonia toxin, do not really provide an answer to reversibility. From the antimetabolite data, one would assume that there should be reversibility. Based on some of the people I have seen, however, I would imagine there is a point of no return. At a certain end stage, there will not be recovery; however, before he gets there, I think a recovery is reasonable. We don't know, however, whether those who are going to recover will have genetically normal sperm. It may be that the spermatogonia that survive are really super spermatogonia; there may be super sperm cells or very severly damaged sperm cells. I don't know.

From the data in this study, we cannot comment on the carcinogenicity of DBCP, other than to say we haven't seen any. There was no evidence nor anything that would indicate it in any of the biopsies.

The only way to answer some of these questions is a long-term follow-up of all the exposed population. For statistical purposes, the population at Oxy-Chem isn't large enough. We need a long term follow-up on some sort of a nation-wide basis that would include all the people who have been exposed. Otherwise, I don't think these questions can be answered.

THE DOW EXPERIENCE

H. Charles Scharnweber*

I would like to begin with a chronology of Dow's actions concerning dibromochloropropane (DBCP). We became aware that there was a problem on July 18, 1977, when Dr. Whorton, acting as Occidental Chemical Company's medical consultant, telephoned us to ask for information about DBCP and to express his concerns and findings about a sterility problem. On August 1, 1977, I asked the supervisor of our Magnolia, Arkansas, plant (where DBCP was being manufactured) for sperm counts on employees and arranged for Dr. Jack Walker to do the testing.

On August 8, Dr. Walker reported that he had indeed found low sperm counts in our Magnolia population. On August 12, 1977, both Dow and Shell (see The Shell Experience by Joyner, Kusnetz, and Lipshultz, p. 43) suspended production of this material.

BACKGROUND

Some evidence of the effects of DBCP were revealed in a 1961 joint report[1] of two toxicologic investigations conducted concurrently and independently--one by the Dow Chemical Company and the other (which was supported in part by the Shell Development Company) by the University of California School of Medicine in San Francisco.

Based on single and repeated exposure of laboratory animals, Dr. Torkelson et al., concluded that DBCP was:

> ". . .highly toxic on repeated exposure, producing damage even at 5 ppm, the lowest level studied. Excessive exposure to the vapors resulted in damage to the liver, kidneys, and various tissues including sperm cells and seminiferous tubules, dermis, bronchioles, renal collecting tubules, lens and cornea, and alimentary canal. Injury caused by this compound was noted to be particularly slow in healing. Precautions for safe handling of this compound are discussed."

*M.D., Dow Chemical Company, Midland, Michigan.

As shown in Table 1 (Laboratory A data from the University of California laboratory, which did the studies for Shell), increased liver and kidney weight was apparent in male rats exposed to various concentrations of DBCP. In addition, there was an obvious decrease in testicular weight. Severe injury to these organs as well as the lungs was seen microscopically and described by the authors.

Similar effects were observed in studies in the Dow laboratory. (See Table 1, Laboratory B.) Decreased testicular weight and increased lung and kidney weight were reported. The animals exposed to 12 ppm were made quite ill; deaths due to pneumonia were common in rats. These were probably secondary to liver and kidney injury in this species as well as in the two female monkeys, which had to be sacrificed after becoming so ill exposure could not be continued.

Histological examination confirmed the injury to the testes, liver, kidney, and lungs. The University of California's data for rats indicated a significant atrophy of the testes, with a less significant atrophy for the rabbits. The Dow results also showed testicular atrophy, although the correlation between exposure and atrophy does not appear to be great. Although the decreased testes weight in the exposed rats doesn't appear significant, it was because of the extreme debility of the animals.

This same publication reported that the material penetrated the skin of rabbits and cautioned against skin contact. Because of their concern about skin absorption and the potential damage resulting from the material entering the body in that manner, the following recommendations were made (Reference 1, pages 557-558):

> "Since minimal effects were still apparent in animals exposed repeatedly to 5 ppm in air, it is suggested that the concentration of 1,2-dibromo-3-chloropropane be kept below 1 ppm if repeated, prolonged exposure is likely. If this precaution is observed, there would seem to be little likelihood of injury. Until further experience is obtained, close observation of the health of people exposed to this compound should be maintained."

> "Protective clothing impermeable to the material should be worn if the likelihood of skin contact exists. Standard rubber or neoprene gloves do not offer adequate protection and should not be relied upon for keeping the material off the skin. Compar rubber and polyethylene appear to offer the most practical protection. 1,2-Dibromo-3-cloropropane should never be allowed to remain on the skin. Clothing and shoes should not be allowed to become contaminated with the material, and if they do, they should be promptly removed and not worn again until completely free of the material."

Table 1. Mortality, weight gain, and organ:body weight ratios of animals given 50 to 66 7-hour exposures to 1,2-dibromo-3-chloropropane in air.*

Species	Number of exposures	Vapor concentration, ppm	Sex	Mortality ratio	Body weight change: net gain / original wt. X 100	Organ weights (g/100 g body weight) Liver	Kidney	Lung	Spleen	Testes	Heart
Laboratory A											
Rat	50	0	M	0/15	108	3.57	0.63	0.63	---	1.02	---
	50	5	M	0/15	82+	3.94+	0.64	0.64	---	0.83	---
	50	10	M	2/15	15+	4.06+	0.83+	0.75	---	0.53+	---
	50	20	M	10/15	39+	4.74+	0.84+	0.84	---	0.52+	---
	15	40	M	13/15							
Laboratory B											
Rabbit	0	0	M	0/3	---	2.43	0.46	0.41	0.02	0.19	0.20
	0	0	F	0/3	---	Controls were not sacrificed					
	66	12	M	0/3	---	2.53	0.56	0.41	0.04	0.04+	0.20
	66	12	F	0/3	---	3.07	0.48	0.39	0.04	---	0.18
Guinea pig	0	0	M	0/10	120	3.09	0.62	0.59	0.10	0.56	0.31
	0	0	F	1/10	116	3.65	0.67	0.66	0.13	---	0.28
	66	12	M	0/10	122	3.48	0.64	0.58	0.20	0.37+	0.32
	66	12	F	0/10	113	3.45	0.68	0.69	0.14	---	0.21
Rat	0	0	M	0/20	150	3.42	0.72	0.55	0.36	0.94	0.33
	0	0	F	0/20	85	3.42	0.74	0.72	0.43	---	0.42
	50	12	M	8/20	76+	3.67	0.83+	1.01+	0.36	0.99†	0.40+
	50	12	F	10/20	40+	3.62	0.86+	1.24+	0.40	---	0.44

*Reprinted with permission from Toxicology and Applied Pharmacology, 3:550, 1961.
+Significantly different from control value ($P < 0.05$).
†Not statistically significant owing to decreased body weight. Marked pathological changes occurred.

THE MAGNOLIA PLANT

At the Magnolia plant, we tried to categorize the people's exposures. They were exposed not only to DBCP but to other materials as well, including ethylenedibromide (EDB). The five categories of potential exposure and the results of each group's sperm counts are given in Table 2. The results fit the same patterns evident in Dr. Wharton's work. In the low potential group, there was only one zero sperm count. There were 13 people with counts less than 50 million, our breakpoint in the beginning. Since then, our breakpoint has been closer to 20 or 30 million, although we haven't determined what our final breakpoint should be.

Table 2. Sperm counts of five groups of Magnolia employees exposed to DBCP (using a 50 million/ml breakpoint).

	Sperm count			
Exposure potential	0	<50 million/ml	>50 million/ml	Total
Office help (no exposure anticipated)	1	13	11	25
In plant occasionally, but not in Fumazone* area (e.g., brinefield workers)	2	7	9	18
Occasional proximity to Fumazone (e.g., contract people)	2	9	2	13
In plant continuously or involved in startup and research (e.g., control room workers)	2	7	3	12
Involved in production of Fumazone (e.g., packaging and warehouse workers)	14	4	0	18
Total	21 (24%)	40 (46%)	25 (29%)	86 (99%)

*Trademark for a soil fumigant produced by Dow Chemical Company.

The alarming figure is in the high exposure group--14 of these men had a sperm count of zero. In all, 21 men had sperm counts of zero (24 percent), 46 percent had a sperm count less than 50 million/ml, and the other 29 percent had a count above 50 million/ml. Thus, 70 percent of the men are considered subfertile if 50 million is used as a breakpoint. When a breakpoint of 20 million/ml is used, the results look somewhat different: 41 men have a count of 0 to 10 million/ml and another 6 men have a count of 10 to 20 million/ml, totalling only 55 percent subfertile (Table 3). The remainder had counts above 20 to 30 million/ml and consequently were not affected.

Table 3. Sperm counts of Magnolia employees exposed to DBCP (using a 20 million/ml breakpoint).

Sperm count, million/ml	No. of men	%<20 million/ml	%>20 million/ml
0-10	41	48	--
10-20	6	7	--
20-30	5	--	6
30-40	4	--	5
40-50	5	--	6
>50	25	--	29
Total	86	55	46*

*Percentages have been rounded off.

Dr. John M. Lanham, my associate in the Corporate Medical Department, has given me some idea of his preliminary clinical impressions of the Magnolia population. He has examined all of them personally, much along the lines Dr. Whorton outlined (including a reproductive history and tests for gynecomastia). He also employed two methods to measure testicle size: using a caliper to estimate testicle size, since it is impossible to measure it exactly, and using one of the tools we found more accurate than calipers, i.e., the Dow-Corning artificial testicles. The artificial testicles are made in a range of sizes (one through four) out of silastic, a soft material that has the approximate consistency of the human testicle. By actually holding one of the various sizes of the prostheses in one's hands and comparing that with the size of the

testicles one is examining, a clinical estimate can be made of the size of the testicles on that individual.

To clarify some of Dr. Lanham's clinical impressions, he used the normal range and mean sizes of the adult human male testicle given by Paulsen of the University of Washington[4]:

Range:	3.6 cm - 5.5 cm, length 2.1 cm - 3.2 cm, width
Mean:	4.6 cm, length 2.6 cm, width

We also measured luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone levels. We used the normal ranges from the Bio-Science Laboratory for our guidelines:

Testosterone, 300 to 1200 ng/100 ml
Follicle stiumlating hormone (FSH), 4 to 25 Iu/ml
Luteinizing hormone (LH), up to 11 mIu/ml

On the basis of preliminary impressions (at the time of this presentation, these data were still being analyzed), the testosterone levels apparently are all normal, substantiating Dr. Whorton's study. FSH levels appear to be elevated in the exposure group most severely affected, which again correlates with Dr. Whorton's findings. We may have some figures that indicate FSH levels are elevated about two and a half times above normal, perhaps higher than some of Occidental's were. LH levels appear to be normal; a preliminary review of the results does not reveal them to be elevated.

Dr. Lanham's opinion is that testicular size is decreased in the high exposure/low sperm count group, in contrast to the low exposure or normal sperm count groups (i.e., any count over 20 million/ml). The reason for the apparent reduction in testicular size is not evident, but Dr. Lanham points out that the turgor of these testicles is not normal. Turgor, in this sense, refers to the physical consistency of the testicle. A good illustration of turgor would be to fill a plastic bag or balloon with silicone fluid, and then note the difference in the way it feels before and after removing some of that silicone. Dr. Lanham's clinical impression is that there is evidence of reduction in testicular size, but he believes that it may not actually be smaller but simply without turgor.

Assuming reversibility of this process, as the testicle fills up again with functioning spermatogonia, spermatids, and sperm cells, the turgor may return. Again, our findings support those that Dr. Whorton outlined: we do not see any significant loss of potency or

libido in this population, and perhaps if the process is reversible, we hope these people will be restored to normal function levels.

We are very concerned about our employees in Magnolia. Originally, we did only sperm counts to try to verify Dr. Whorton's findings quickly. The sperm counts exposed the basic problem, and the rest of the tests simply confirmed and embellished the problem. Since sperm generation takes about 70 days and perhaps another 20 or 30 days to get the sperm into the ejaculate, we are rather arbitrarily saying that in 90 days we are returning to Magnolia to repeat the sperm counts. We have already repeated the counts for people who requested them, and we have done some to confirm the laboratory's reports, but we will return and take those counts again also.

WESTERN DIVISION

After discontinuing production in Magnolia, we looked at our Western Division plant in Pittsburg, California, which had, in the past, produced DBCP and stored it in warehouses. Workers at the plant had not had any exposure for more than 2 years before our investigation. The investigation of this plant was in line with our efforts to find some answer to the question "Is this process reversible?" Unfortunately, the circumstances did not allow us to answer that question since we did not know what these people's sperm counts were before or while they were working with the material. Table 4 shows the results of our tests on the 30 men exposed 2 years ago.

Table 4. 1978 sperm counts of 30 men exposed to DBCP in 1976 at the Western Division plant.

Sperm counts, million/ml	No. of men
0 - 10	7*
10 - 40	4
40 - 120	15
>120	4

*Four men had had vasectomies; two had known medical cause of oligospermia; one man had a very low count.

We were surprised at the high incidence of vasectomy. Of the seven men with sperm counts of 0 to 10, further investigation revealed that four of them had had vasectomies; two of the others had medical reasons for oligospermia (one of these had had fertility problems for many years because of trauma to testicles and the other man had many episodes of severe bilateral epididymitis and was known to have azoospermia as a result of that infection); and the last of the seven men had a very low count with no clinical evidence to explain it.

MICHIGAN DIVISION

Dow has another population exposed to DBCP, the Michigan Division, at Midland. Production of DBCP was stopped at the Michigan Division in January 1976. We are in the process of studying that population with as unbiased an approach as possible, hoping to shed a little light on the reversibility question. We are, however, doing it blind as far as the sperm counts are concerned since we do not know what the workers' sperm counts were when they were working with DBCP almost 2 years ago.

We are trying to match the people in the exposed population with an unexposed population of similar ages. It is relatively easy to get the people who are at risk to submit to this procedure, but it becomes much more difficult to get controls to volunteer to provide a specimen. The motivation is obviously not the same. We are getting excellent cooperation from the men, however, and fortunately the union has been completely cooperative in our testing.

Approximately 520 people have been identified as having had potential exposure in the Michigan Division. We started reviewing their health histories in September 1977; these include a complete reproductive history and a genetic history. We also examined their habitus and testicular size and looked for gynecomastia. We also obtained blood specimens for the three hormone assays previously mentioned while simultaneously doing SMA-12's. Although the previous studies (Dr. Whorton's and ours) did not find any correlation with the use of these parameters, these tests are included to ensure that we don't miss anything since they are relatively simple to perform. We are trying to do the study blind. The examining physician's lack of knowledge of the man's sperm count will obviously make a difference in his interpretation of the estimates of turgor and testicular size.

Because we have only one opportunity to do this type of study, we are doing it as carefully as we can. We have examined 270 people to date. Examination appointments are being made until October 21, although the appointments will go on after that date if requested. A cut-off date was selected because we have had about as much

cooperation as we are going to get. A number of older men say "I don't care what my sperm count is. I don't want to know." Or we hear "My wife just had a baby last year. I know I have no problems, and I am not arguing with you, for obvious reasons." So, there is a problem from people not wanting to know. I think physicians and occupational physicians must be aware that we may have a social problem on our hands in this situation. If there were a correlation between the FSH levels and testicular involvement, it would be a godsend, since it would be much easier to get people to submit to a blood specimen than it presently is to get them to submit to a semen analysis.

When the results of this study are available to us, each of the men examined will receive his results in writing, and we will attempt to keep the findings as confidential as we can. I think confidentiality is important. I can't overemphasize how much mental anguish some of the people at our Arkansas plant have had, partly because we are dealing with male machismo and pride. If decreased sperm counts becomes a continuing problem, some people will have great psychological difficulty dealing with their lack of "maleness." I am sure all of my fellow physicians share my concerns for these subtle problems that we have yet to encounter in further studies.

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DISCUSSION

Question (Dr. Zavon, Hooker Chemical and Plastics Corporation): Did you have any subjects in the Magnolia population that had had vasectomies?

Answer (Dr. Scharnweber): We did not have the same percentage of vasectomies in Magnolia as we had in the Western Division.

Question (Dr. Buncher, University of Cincinnati): To pursue the vasectomy question, is there any indication of self-selection of the workers into this work group? Dr. Whorton mentioned that there were rumors about the Ag-Chem area at Occidental Chemical Company before his investigation. How do workers get into this particular production rather than something else? Is there any selection?

Comment (Dr. Whorton, University of California at Berkeley): The only selection I know of in the Ag-Chem area at Oxy-Chem resulted from one long-time worker's recruitment for his baseball team. If anything, the Ag-Chem area was a little more sports-minded than the rest of the plant and had some employees that were large, athletic men. Also it seemed that there were more men in the California plant that had had vasectomies.

Question (Dr. Buncher): Is there any indication that the vasectomy rate is actually higher in California? Are there any comparative figures for California?

Answer (Dr. Whorton): I don't know.

Question (Dr. Buncher): So that is a perfectly usual rate?

Answer (Dr. Whorton): It seemed like an unusually high rate for a rural area.

Question (Dr. Infante, NIOSH): Would you comment on the testicular cancer that I believe has been identified in one of your employees from your facility in Arkansas? What are you planning to do to assess the carcinogenic risks in your population?

Answer (Dr. Scharnweber): We are going to continue to monitor that population in every way we can until we answer the question sufficiently. We do have a testicular tumor in one of the people at the Magnolia location. This tumor was found by Dr. Lanham in his

examinations. I am not at liberty because of confidentiality to go into any further detail. While in the hospital, this man has already been somewhat harassed with numerous calls from the media. I think this is inappropriate. This man is suffering enough. I do not wish to go into this in any more detail at this time.

Comment (Dr. Whorton): Let me add to that answer. At a recent meeting in San Francisco, Dr. Ed Schmuckler, who is head of pathology at University of California, San Francisco, and very involved in chlorinated hydrocarbons, stated that he knows of no chemically induced cancer in the testes of animals or people. He was surprised at finding and skeptical of this one case. The testicular cancer rate is three in one hundred thousand. One incident of cancer in the small number of people we've studied is way out of proportion, and the only way to discover whether it has any significance is to follow all the populations with long-term DBCP exposure.

Question (Dr. Infante): In other words, there is just a question mark about whether or not that cancer is related to exposure? I wonder, then, how that one incident is being interpreted, given the selectivity of DBCP for the germinal cells and the fact that the cell type here is the embryonal cell carcinoma. That is the cell type, isn't it? What type would you expect on an epidemiological basis? What is the dominant cell type?

Answer (Dr. Whorton): The predominant cancer in the testes is seminoma. Probably the second most common type is embryonal carcinoma. Testicular cancer is diagnosed by the predominant cell type, but there is a wide variation that depends on which piece of the testes you are looking at. Consequently, making an absolute diagnosis of testicular cancer is not always easy. However, seminoma is the most common type, and this subject is in the right age group for having testicular cancer.

Question (Dr. Infante): But it was an unusual cell type, wasn't it, and not the dominant cell type? Was it an embryonal cell carcimona?

Answer (Dr. Whorton): When you consider three in one hundred thousand, you are not talking about common tumors. Since seminona is the most common tumor (about 50%) and embryonal is the second most common, an embryonal tumor is not an unusual cancer. But, again, this type of cancer of the testes is not a common cancer.

Question (Mr. Kusnetz, Shell Chemical Company): Dr. Scharnweber, I sympathize with the intent to keep this man's life private, but after the San Francisco hearings last week, Mr. Brubaker, President of your Western Division, did make public some details that I think should be added here.

First, the individual was exposed to other materials, with his exposure to DBCP short-term in comparison with the rest. Second, there was trauma to the the man's genitalia early in life, a fact that caused some speculation in the hearings. At least that much more information has been made public and perhaps should be commented on.

Answer (Dr. Scharnweber): Because Mr. Brubaker is not a physician, he doesn't operate under the same restraints I do. Yes, there was a history of testicular trauma. I think most physicians would say that, in general, it is very difficult to find a normal adult male who hasn't had trauma to his testicles at one time or another in his lifetime. To ascribe this tumor to trauma any more than to ascribe it to a very short-term exposure to DBCP is, at least, premature and maybe fallacious.

The usual latency period for the most malignant materials known is anywhere from 15 to 20 or 30 years. If DBCP is that potent, we should be seeing many people with testicular tumors, and I have not noticed in any literature an increased incidence of testicular tumors in any population of the United States. If there are figures to refute that, I would certainly welcome them.

Question (Dr. MacLeod, Cornell Medical College): Were you using the figures of Nelson and Bunge as reference points for the sperm count data in your populations of DBCP-exposed subjects in Magnolia and elsewhere?

Answer (Dr. Scharnweber): I was using them primarily to show that there is an apparent change, a shifting to the left, in the normal sperm count of the adult male in the United States, and then to show that our Magnolia data skews it even further to the left.

Comment (Dr. MacLeod): To emphasize a point that you are already aware of, it would be rather precarious to use the Nelson and Bunge count frequency distribution curve as a "norm" to be met by your DBCP-exposed population. Of all the modern (1970-1977; see references 5-7, 9, p. 61) pre-vasectomy populations (known fertility) studied and published, the Nelson and Bunge curve lies in the most extreme "left" position, i.e., the poorest "fertile" population on record in terms of sperm count distribution. As you have shown in Table 2 (see p. 33), and as you have just stated, your Magnolia population is skewed to the left of the Nelson and Bunge curve. On that table, the fact that 14 of the 18 subjects (77%) with the greatest and perhaps longest possible exposure to DBCP were azoospermic is an extraordinary indictment of the sterilizing potentials of the compound.

It would be very risky to use that population as a reference point. You only have to look at one figure in their frequency

distribution (greater than 100 million/ml) to see that there is something wrong with that population. I think that we will find pre-vasectomy populations used as reference points to be rather suspect for measuring semen quality.

Answer (Dr. Scharnweber): Channing Meyer and I were hoping that this symposium could help us understand the complex problem of defining a normal sperm count and the normal means, modes, and ranges. Perhaps this meeting can help us pinpoint what we should use as comparison figures.

Comment (Dr. Whorton): At the recent San Francisco meeting, a urologist discussed the various sperm count levels and suggested that one hazard in vasectomy findings is that often, because men know they are going to be sore after a vasectomy, they ejaculate a lot before being tested. He also believes that the percentage of men that have sperm counts of less than 10 million but have fathered children is suspect.

The data are questionable; sperm counts are probably no different from other data in this respect. The data we call normal are taken from unrepresentative populations: hospital populations, pre-vasectomy populations, or infertility populations.

Question (Dr. Blum, University of California at Berkeley): Do you know the number of years that the man who had the testicular cancer had been exposed to EDB and DBCP?

Answer (Dr. Scharnweber): He was not in a high exposure group, but he had some exposure to DBCP for less than 2 years. He had exposure to EDB for a longer period of time, but less than 10 years. He had worked in the plant for 7 or 8 years.

Question (Dr. Troen, Montefiore Hospital): What was his sperm count, and what did the tissue show?

Answer (Dr. Scharnweber): His sperm count was very low. It was an embryonal tumor.

Question (Dr. Troen): But were the spermatogonia gone?

Answer (Dr. Scharnweber): I don't know.

THE SHELL EXPERIENCE

Roy Joyner,* Howard Kusnetz,+ and Larry Lipshultz†

DR. ROY JOYNER

Because the chronology of events concerning DBCP at Shell so closely parallels the events given by Dr. Scharnweber in his presentation of The Dow Experience (p. 30), I will omit these details. As background, however, Shell has manufactured DBCP at two plants--Denver and Mobile. Manufacturing operations began at the Denver Plant in 1955 and ended in February 1976, although there were limited reprocessing operations in April and November 1976 and limited repackaging operations in March 1977. Production for both the product and the raw material was stopped at Denver because of the location of the markets and the transportation costs. They were moved to our Mobile Plant, where operations began in April 1976 and ended early in July 1977.

When we became aware of depressed sperm counts in Occidental Chemical Company's California DBCP workers in mid-July 1977, our first response was to immediately establish the fact that all manufacturing operations were in abeyance and that there was, therefore, no current employee exposure with respect to the manufacture of this product.

Our next action was to attempt to determine the degree of past exposure among our employee group. Mr. Kusnetz, Manager of Safety and Industrial Hygiene for Shell, will present this information.

HOWARD KUSNETZ

Industrial hygiene, in its present form, started at Shell in 1971. The DBCP environmental data that we have been able to measure and the records that we have been able to find at our two manufacturing plants (in Denver and Mobile) show that since 1971

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levels have been consistently under 1 ppm, which was then the working level. A company morbidity and mortality study shows negative results for both our Denver and Mobile plants with respect to testicular disease, oligospermia, and other genito-urinary diseases. This report covered the period from 1973 to the present.

Monitoring of air samples at the Denver plant in 1972, shortly after our industrial hygiene programs began, showed levels of approximately 0.22 and 0.42 ppm; they have been consistently in that range since then. Air samples at Mobile, where production of DBCP did not begin until April 1976, showed no levels greater than 0.6 ppm.

Although the production of DBCP had been effectively stopped by the State of California, we were still concerned with the exposure to field applicators, even though this was not in the OSHA Emergency Temporary Standard. On September 22, 1977, with permission of California authorities, we measured DBCP in field applications at our experimental farm in Modesto (Table 1). Some of our supervisory people, wearing full protective equipment (air supplied respirators and impermeable suits) so their actual exposure would be less, essentially mimicked what a tractor driver and helper would do. The concentrations in Table 1 represent the environments around the operator and do not represent the operator's exposure. Because the application season for DBCP is generally in cool weather (September is much too warm) these concentrations, too, do not reflect actual working conditions. Within a single work cycle of approximately 1-1/2 hours on the 5-acre field, the concentration in the environment around a tractor driver was 8 ppb, and the concentration around a helper for the same period was 34 ppb. Shorter activities within the cycle ranged up to 53 ppb.

Table 1. DBCP field applications, September 22, 1977. Application rate, 2 gallons per acre.

Operator	Operation	Sample type	Sample time, min	Concentration, ppb
NA	Background	A*		<1
A	Tractor driver(overall)	P+	96	8
A	Tank filler	P	24	9
A	Driver-applicator	P	74	10
B	Helper (overall)	P	96	34
B	Helper, filling tank	P	18	53
B	Helper, sealing	P	40	17
B	Cleaning up spill	P	21	1340

*Area sample.
+Personal sample.

The major tasks involve the filling of the tank on the tractor, the application itself, and the sealing by the helper in a second tractor that follows the first. Standard farm practices were used for handling the chisels on the tractors. Basically, these chisels are a series of hollow points that are inserted into the ground behind the tractor. The DBCP is injected underground through these points. A second machine, following, then seals the furrows. We had two samplers on each employee: one to do the full work cycle for Employee A and Employee B, and the other to try to estimate separate work practice operations within that complete work cycle.

Background in the field was less than 1 ppb, our low limit of analytic capability. The helper's exposure was higher--both in the overall full cycle and in the subactivities. Working behind the chisels and points while sealing, he may have been getting what was blown back from the lead tractor. Part of this problem results because the chisels are raised from the ground to enable the tractor to make a turn in the field. Although we tried to have the tractor driver make sure that the chisels were shut off so that there was no liquid coming out during the turns, we were not totally successful. We are continuing to work on this as a mechanical problem.

An accidental spill occurred during our field study. While the helper was filling the tank, he became so interested in watching the sampler being put on the driver that he forgot to watch what he was doing, and the tank ran over. This happened during clean up and is certainly typical of what could happen in the field.

These are not meant to be definitive numbers; they are the results of a single test run under test conditions. They do, however, give an estimate of the exposures.

DR. JOYNER

MOBILE (ALABAMA) PLANT

DBCP manufacturing operations began at the Mobile plant in April 1976, and ended in early July 1977. At the Mobile plant, we tested 76 employees with histories of exposure to DBCP and 18 volunteers presumably unexposed. These volunteers were drawn from both office personnel and from production personnel who had no history of exposure to DBCP.

The results of that first test are shown in Table 2. Analysis of these findings varies greatly depending upon which authority we choose as a reference point. The mean sperm count of 53.7 million/ml is higher than that found in the Nelson-Bunge[1] study

and lower than that described in the MacLeod and Gold[2] study. Fourteen of the 76 employees tested were found to have sperm counts below 20 million/ml. This figure represents 18% of the group and is comparable to the Nelson-Bunge findings of about 20% below 20 million/ml. The motilities are observed to be essentially normal with even the lower count groups showing a motility in the 60 to 70% range.

Table 2. Sperm count results from first test of 72 exposed employees at the Mobile Plant.

Range, million/ml	No. of employees	Mean motility of range group, %
Zero	2	---
0- 9	6	68%
10-19	6	63%
20-29	9	65%
30-39	13	70%
40-49	8	77%
50-59	3	80%
60-69	6	76%
70-79	2	85%
80-89	5	83%
90-99	5	72%
100+	7	87%

When a cumulative percentage distribution by sperm density was plotted for the Mobile employees, the plot for the Mobile employees fell between the Nelson-Bunge cumulative percentage distribution and the MacLeod-Gold distribution (Figure 1.)

Table 3 shows our data for the nonexposed volunteer group. These data could be interpreted as being somewhat better than the exposed group, with a mean of 112.2 million/ml, although the smaller number of individuals in this group makes the significance of any difference somewhat questionable. At Mobile, for both the exposed and nonexposed groups, motility appears to be within normal limits.

Based on our consultant's opinion that at least three semen specimens should be examined before making a conclusion about an individual, a series of repeat tests has begun in Mobile. Twenty employees have had their second test; there is little or no variation in count from the first test.

Table 3. Sperm count results from first test of 18 control-group individuals at Mobile Plant.

Range, million/ ml	No. of employees	Mean motility of range group, %
Zero	0	--
0 - 9	0	--
10-19	1	90
20-29	1	75
30-39	2	62
40-49	1	90
50-59	2	90
60-69	4	74
70-79	0	--
80-89	2	87
90-99	1	85
100+	4	85

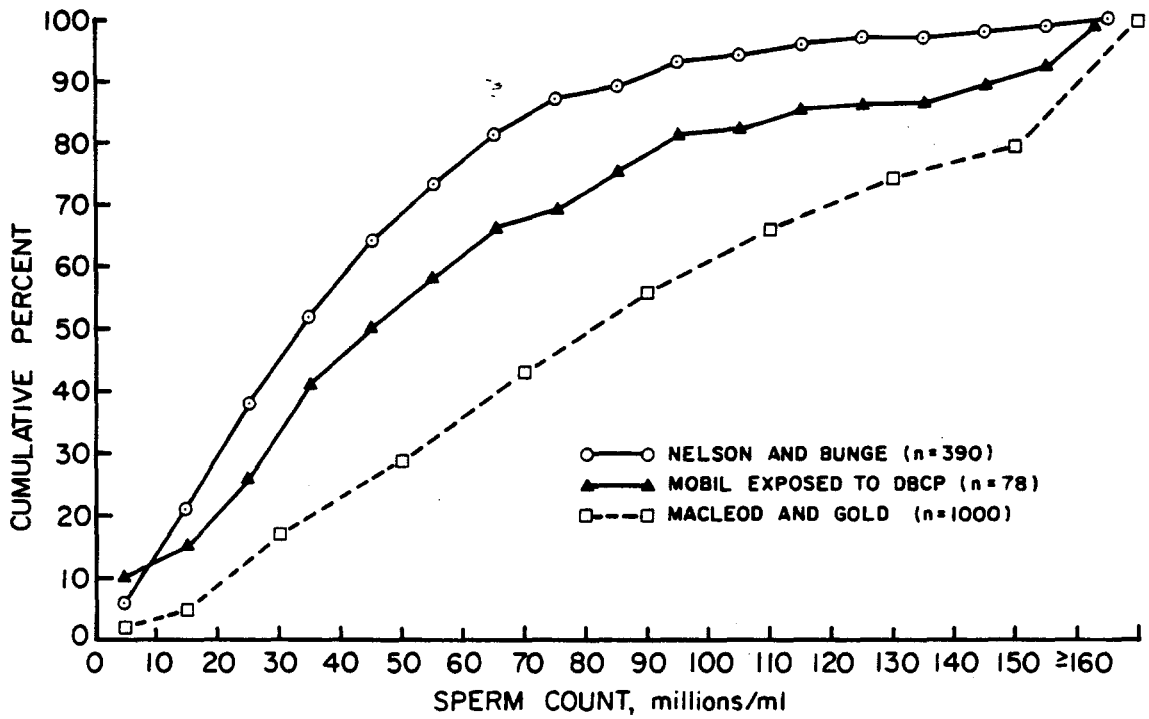

Figure 1. Cumulative percent distribution by sperm density of 92% of Mobile employees exposed to DBCP, Nelson and Bunge data, and MacLeod and Gold data.

Seven field salesmen previously engaged in the sale and demonstration of DBCP (with exposure levels somewhat comparable to those of the applicators) were also tested by urologists. The results of the tests on this very small group included one individual with a sperm count of 27 million and 6 with sperm counts of 50 million or more. All the motilities in the group were also found to be 50 percent or better.

DENVER (COLORADO) PLANT

The plant in Denver operated from 1955 until February 1967. The testing program was similar to the one at Mobile. Thirty-nine employees with a history of possible exposure to DBCP and 28 unexposed volunteers were examined. The approximate percentage of office versus unexposed production people was the same as that in Mobile.

Included in the Denver results (Table 4) are six individuals (actually nine including three that had had vasectomies) in the zero range. One who had had a vasectomy did have a count between 10 and 19 million.

Table 4. Sperm count results from first test of 39 exposed employees at the Denver Plant.

Range, million/ml	No. of employees	Mean motility of range group, %
Zero	6*	--
0-10	3	49%
10-19	5+	28%
20-29	10	26%
30-39	5	28%
40-49	10	43%
50-59	0	--
60-69	0	--
70-79	0	--
80-89	0	--
90-99	0	--
100+	0	--

*Plus 3 vasectomies.
+Plus 1 vasectomy.

The data are quite different from the data from Mobile. Not only were these counts apparently depressed (the highest was less than 50 million/ml, and the mean was 25.2 million/ml), but there was

also a pronounced decrease in motility. This occurred not only in the exposed group, but in the nonexposed volunteer group as well (Table 5). In fact, the two groups were fairly similar in terms of mean counts and motility (Figure 2).

Table 5. Sperm count results from first test of 28 unexposed employees at the Denver Plant.

Range, million/ ml	No. of employees	Mean motility of range group, %
Zero	3*	--
0- 9	3	25%
10-19	7	11%
20-29	4	15%
30-39	4	26%
40-49	7	46%
50-59	0	--
60-69	0	--
70-79	0	--
80-89	0	--
90-99	0	--
100+	0	--

*Plus 1 vasectomy.

Because these findings were a source of considerable concern, we arranged for Dr. Ross from the Shell Oil Corporate Medical Department and our consultant, Dr. Larry Lipshultz, to visit the plant and evaluate the program.

Another major concern must be mentioned: the lack of scientific consensus surrounding the issue of normal sperm counts. So many discrepancies exist in the literature that until this conflict is resolved and a fairly firm consensus on what actually constitutes impaired fertility is arrived at, we are going to have an extremely difficult time determining whether DBCP has affected a given individual. Shell believes that some further study is certainly necessary to solve this problem. Industry should sponsor a study in this field, and our company is prepared to lend our support to that study.

Dr. Lipshultz will give his comments on the Denver problem.

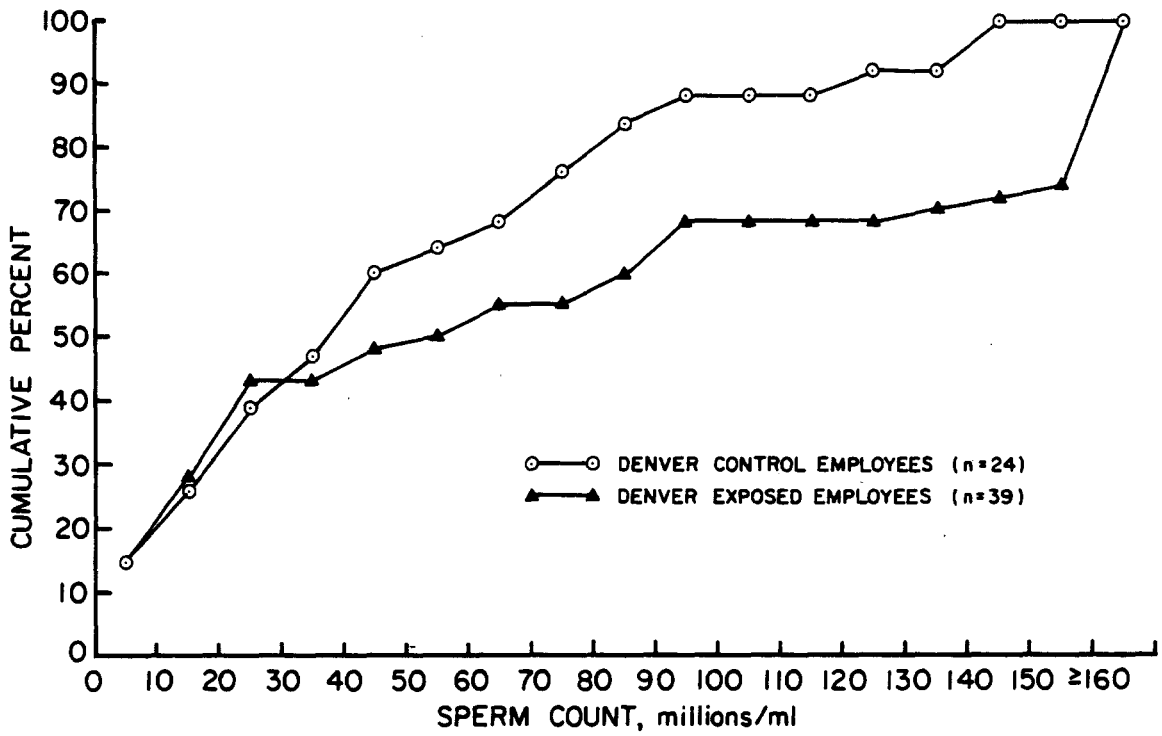

Figure 2. Cumulative percent distribution by sperm count of Denver employees exposed to DBCP and Denver employees not exposed to DBCP. (Sperm analyses were conducted in the Pathology Clinic.)

DR. LIPSHULTZ

DENVER STUDY RESULTS

The results from this test on the Denver population were frightening, especially considering that the results from the control population with no exposure were very similar to those of the exposed group. Because these results were so similar (Figure 2), we went to Denver where we reviewed the semen analyses with the technicians of the laboratory doing these tests. They assured us that they had done the tests the same way they had always done them. They were aware that the results were different, but they didn't know any cause for the change.

After further questioning, we discovered that the only difference between the evaluation of the study population and the laboratory's routine fertility evaluations was that the routine patients brought their specimens from home. About 90% of the specimens of the Shell study patients were collected in the office

during office hours, and the technician examining the office-collected specimens did the studies during office hours, admittedly not waiting until they liquified.

Semen is ejaculated as a coagulant. It takes about 20 to 30 mintues before an accurate analysis of not only motility, but also sperm density, can be made. This technician was sampling the immediate liquified portion, which is the material located between the coagulum of sperm, and finding a very low count and very low motility. This created a predominance of patients with all parameters of their semen quality impaired. The difference between the office-collected specimens and those taken at home led us to the clue that there may have been differences in the counting technique.

In Figure 3 the cumulative percent distribution by sperm density of 21% of the Denver employees exposed to DBCP can be compared with the Nelson and Bunge data and the MacLeod and Gold data. It is similar to Figure 1 for the Mobile employees.

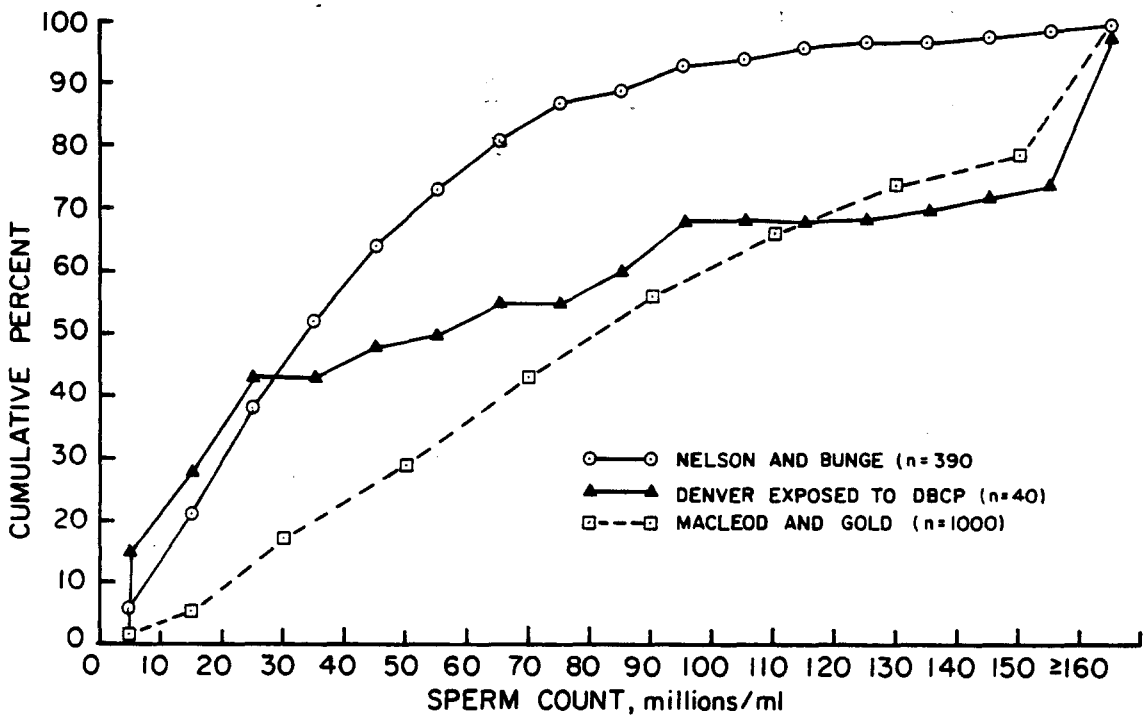

Figure 3. Cumulative percent distribution by sperm density of 21% of Denver employees exposed to DBCP, Nelson and Bunge data, and MacLeod and Gold data. (Sperm analyses conducted at the Pathology Clinic.)

Forty employees have been retested so far. I went to the laboratory (a new laboratory in Denver) to instruct the technicians in a proper method of doing semen analysis (incidentally, the same way that Dr. MacLeod does it). It is essential that the people doing these tests are well trained and consistent in their analyses. Table 6 shows the more reasonable figures from this second set of studies. The mean of the first set of tests was 18 million/ml; the second tests, with higher counts, had a mean of 65 million/ml. There are also more people in the normal motility range, with an increase from 19% motility in the original tests to 62% motility in the second tests.

Table 6. Comparison of sperm counts in first and second tests at the Denver plant.

Case No.	First test, million/ml	Second test, million/ml	Difference
1	22	31	+9
2	13	15	+2
3	15	78	+63
4	0	0	0
5	0	20	+20
6	16	29	+13
7	47	45	-2
8	5	23	+18
9	19	54	+35
10	30	194	+164
11	31	56	+25
12	48	144	+96
13	9	47	+38
14	0	0	0
15	0	0	0
16	13	45	+32
17	11	73	+62
18	12	5	-7
19	28	143	+115
20	33	288	+255

ASSESSING TESTICULAR FUNCTION

We need to ask ourselves what we are trying to do. This is difficult to determine because we are not assessing fertility. Fertility implies a couple trying to have a child. We are

assessing testicular function. Dr. MacLeod stated many years ago that the germinal epithelium is exquisitely sensitive to a lot of the changes that take place in the environment. By going into these plants and speaking to the workers, we are trying to introduce them to the concept of "testicular function monitoring." This monitoring could serve as a sensitive indicator of the effects of exposures in their environment. The present testing has nothing to do with fertility since many of the people with low results in our evaluation may already have several children and may go on to have several more. This emphasizes the issue of what we are going to call "normal."

Semen Quality

Depending on the patient population that is selected to make up a study, data from reputable sources can be found to prove almost any point regarding semen quality. Unfortunately, most of the studies available today are prevasectomy studies, and it is very difficult to equate a group from Denver to a prevasectomy study in Iowa since they are different places with different socio-economic groups. Lack of knowledge about the abstinence periods in some of the reported studies creates a need for a group of controls from that area to enable us to make an accurate statement about testicular function in any given unit. The source of controls is another major problem. How do we determine whether a given group of men is different from another group of men? The control groups should be drawn from the same area as the study groups.

During emission, the sperm-containing fraction comes out first. If the specimen is collected improperly, an inaccurate assessment of testicular function is made pertaining to sperm production. If we rechecked these initial tests, we are bound to find some specimens collected improperly.

Sperm Motility

The lack of an accurate marker for testicular function is an intricate problem. We can look at sperm production, negative feedback from the testis on the pituitary, and testicular size, and then, taking all three factors into consideration, make an estimate of the semen quality. But we cannot base our opinion on one semen analysis; sperm density is only one part of a good semen analysis. Sperm movement, i.e., sperm motility, is just as, if not more, important as the sperm count. The information presented here concerning the Mobile and Denver workers is simply a preliminary evaluation of the problem since we have not yet considered sperm motility. The available data are very straight-

forward and demonstrate that we most likely have a problem, but the data, based merely on sperm density, is not complete enough to make a decision about the magnitude of the problem. I think that we have made a good start, but there are a lot of factors still to be considered.

Follicle-Stimulating Hormone (FSH)

I agree with Dr. Whorton that FSH can be an indicator of overwhelming testicular disease, but we have no guarantee that it will be foolproof. To test the effectiveness of FSH in indicating ranges, we tested a group of 26 oligospermic men. The results of this test (Figure 4) revealed that the oligospermic men had normal FSH levels. We then gave 13 men a pituitary extract, i.e., a gonadotrophic-releasing hormone (a synthetic deca-peptide). These 13 oligospermic men had a super-normal

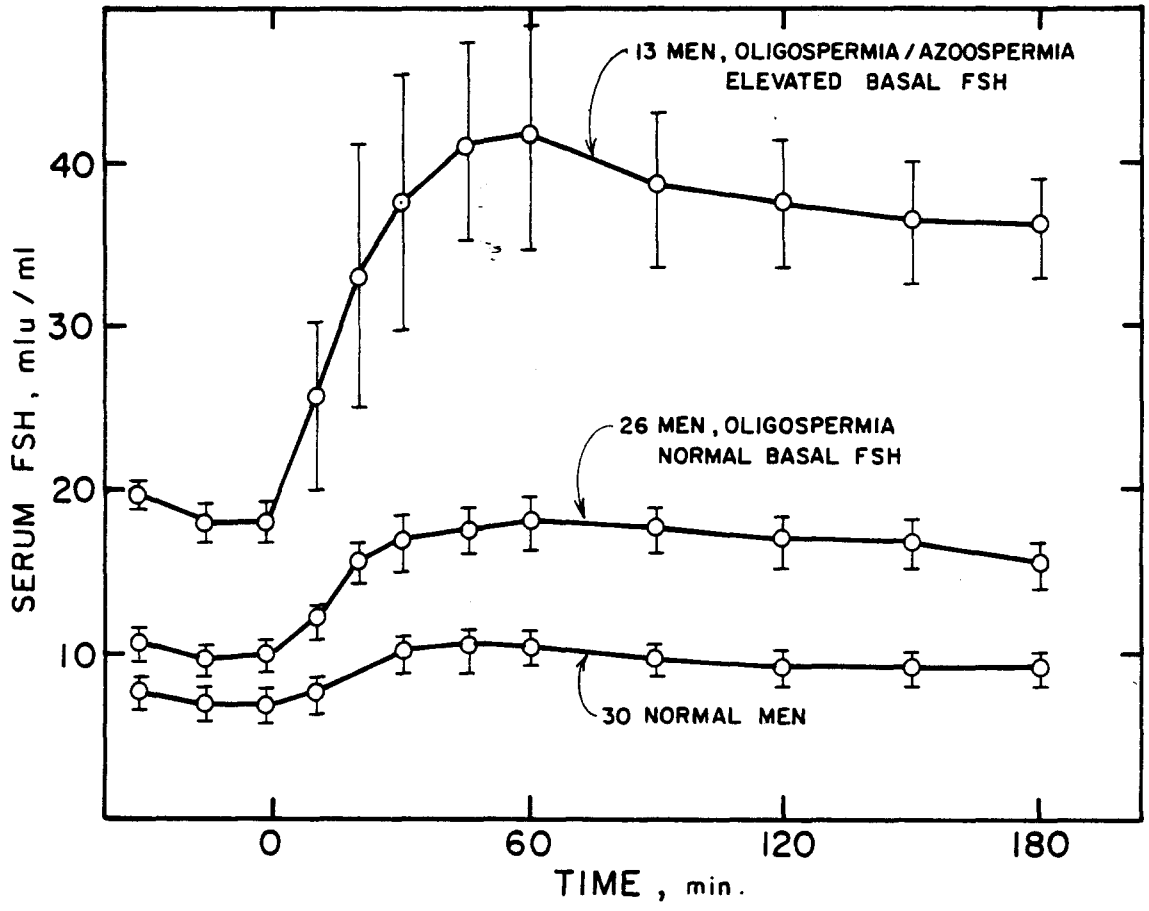

Figure 4. FSH levels for 26 oligospermic men and a control group of 30 normal men.

response--one that was statistically significant when compared with that of normal men. This does not give us any conclusive evidence. It could mean that we have unmasked a heretofore undefined abnormality of some part of the testis. It certainly reveals that a normal FSH level does not overrule the possiblilty of severe testicular disease. Persons severely oligospermic or azoospermic because of a primary testicular insult have a hyper response to gonadotropin releasing factor.

We now have fairly good laboratory evidence that the feedback product for FSH secretion is something that comes from the Sertoli cell, which Dr. Whorton (see The Occidental Chemical Company Experience, p. 3) referred to as the "nurse cell" in the testis. Physiologically, this may be the most important cell in the testis. In animals, it also produces a transport protein, "androgen binding" protein, that carries testosterone from the Leydig cells to the seminiferous tubules. Perhaps what we are seeing in our severly affected patients is a disease of the Sertoli cells. This seems possible looking at the increased or magnified FSH responses. This problem could result, perhaps, if there was not enough inhibin. I only show this now to emphasize that not only is there not a single marker for testicular function, but that the ones we have are not foolproof. The available tests can give some indication of testicular function as it relates to the pituitary gland and the hypothalamus, but they can't give the answer. The FSH tests do, however, serve as a good concomitant study with semen analyses and physical examination of the testis.

Testicular Size

The Dow experience showed that people who had severely impaired sperm production also had atrophy of the testis with an associated decrease in testicular consistency. This is logical because as cells are lost in the germinal layer of the semiferous tubule, the testis gets smaller. The question then arises, why did we not see testicular atrophy in the Occidental findings presented by Dr. Whorton? Did the testis appear normal? This is a very important question.

We do have some idea of normal testicular size (Table 7). Paulsen[3] demonstrated the normal length of the testes to be 4.6 cm. In a group of normal subjects that we looked at in 1975, we found the normal average to be 4.7 cm, a figure that is certainly very close to Paulsen's. When Dr. Charny[4] and Dr. Lubs[5] studied normal patients and those with Klinefelter syndrome, they found a similar figure of 5 cm in the normal population. So, if the length of a patient's testis is 4.5 cm, or certainly below 4 cm, there is very good presumptive evidence of some problem in

terms of intrinsic testicular function. Again, I want to emphasize that each of these tests is additive in terms of the information that they can supply.

Table 7. Testicular size in the unilaterally cryptorchid patient.

Normal testicular length (in cm):	
Charny[4] (1960)	5.0
Lubs[5] (1962)	5.0
Lipshultz and Snyder[6] (1975)	4.7
Percent normal testicular size of cryptorchid patients	
Guillon[7] (1966)	11
Nicole[8] (1966)	24
Lipshultz and Snyder[6] (1975)	21
Hand[9] (1956)	14

CANCER MARKERS

Markers for cancer of the testis also need further development. Initially, human chorionic gonadotropin (HCG) was a fairly good marker for testicular tumors, but we have progressed beyond that. We can now consider beta chains of HCG and alpha-feto-proteins; these are good markers for metastatic disease, i.e., microscopic metastatic disease from testicular tumors. Someday they may be used as routine screening tests, but right now they can only be used in a research capacitiy.

RECOMMENDATION

Now, we must assess the situation to determine where we go from here. The problem has been identified, but it must be defined more clearly. One of the basic issues is the need for good control groups at each location. The ideal situation would occur if we had semen samples on each individual before he began working. We could then come back and demonstrate a change. This would supply very clearcut information that some catastrophic event had happened to that individual that affected his testes. What we have now are men whose semen quality does not fall within the range that we would like to see. But, considering Dr. MacLeod's and other people's data, we can expect that 13 to 16 percent of persons in a normal control group have a sperm density of, at least, under 20 million. Can we then subtract this percentage from our patients and only look at those above this limit? This is a possibility; it could be

started by establishing control groups in several locations. The people in charge of these control groups could then pool their information. With the span of plants that we now have--California, Arkansas, Denver, and Mobile--we would have national data. If these data agreed, we could have a range of normal testicular function, although, again, not a range of fertility. This would be a very important step, but it has to begin at the local level so that it has meaning to the people in the plants that are being investigated.

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STANDARDS FOR HUMAN SEMEN QUALITY

John MacLeod*

Assuming the duct system (efferent, epididymal, and vasa deferentia, etc.) between the testes and the urethra to be intact and patent and the ejaculatory mechanism to be normal, the total number and quality of spermatozoa present in any given ejaculate should be a reasonable measure of the capacity of the germinal epithelium to deliver spermatozoa to the ejaculate following a known period of sexual continence (e.g., 3 days).

Until the late 1940's, in terms of the sperm count per se and the chance of a pregnancy occurring, there was considerable confusion as to what the sperm count figure should be. Until my laboratory published a series of papers in the early 1950's,[1-4] the generally accepted minimal figure was set at 60 million/ml. In our later and rather intensive analysis of large fertile and infertile populations, we were forced to conclude that a figure of 20 million/ml was more realistic and that the quality of sperm motility rather than the sperm count was the dominating factor in effecting conception.

I realize, however, that this audience is not as concerned about human semen quality in terms of potential fertility as in what they might expect concerning possible toxicity in the populations they are presently studying. Put another way, you wish to know which semen standards to use as a measure of possible toxic effects upon spermatogenesis.

As further background, the MacLeod and Gold (hereafter, MG) figures remained unchallenged until the 1970's when Nelson and Bunge[5] (NB) in a study of semen quality in 386 individuals in Iowa (presumably of known fertility) concluded from their sperm count data of this population that:

- -- the standards of fertility established by MG in 1951 no longer held true, and
- -- something had altered the fertile male population to depress the semen quality remarkably.

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These statements were based principally on the facts that their mean sperm count (48 million/ml) was less than half that of MG (107 million/ml) and that they found only 7% of the individual sperm counts >100 million/ml as compared with the 44% of the 1951 population. Several months later, in a similar study from New York on 1,300 pre-vasectomy patients[6], Rehan et al. (RSF) provided sperm count data that were radically different from those of NB and closer to those of 1951. Their mean sperm count was 79 million/ml, and the distribution was greater than 100 million/ml for 25% of the patients. They considered that their results generally agreed with those of MG.

More recently, Smith and Steinberger[7] (SS) furnished data on another large (N = 2,000) pre-vasectomy population derived from Philadelphia and Houston. Their conclusions led them to agree with NB that the MG standards of 1951 were too high in spite of the facts that their mean sperm count (70 million/ml) and their percent of counts above 100 million/ml were considerable higher than those of NB and closer to those of RSF. They suggested further that the obvious divergencies in the modern pre-vasectomy values derived from different locales in the United States may be explained by geographic factors, a point to be considered later in this discussion. But at this time, evidence accumulated in my laboratory over the years since our original data were published in 1951 does not support the contention that any substantial change in the numerical aspect of human spermatogenesis has occurred in the intervening years.[8] More specifically, the data supplied in the 1951-1956 series of MG on this subject probably are applicable today. Support for this statement is supplied to you now in tabular form as it will appear for publication in the near future.*[8] The data in it are derived from patients referred to my laboratory because of "infertile" (primary or secondary) marriage. They were appearing for their first semen examination. As a particular population, it can be considered at the present time as analogous to the "infertile" marriage group (N = 1,000) of MG in 1951--the one that demonstrated, in terms of sperm count per milliliter and the count frequency distribution, that the difference between the "fertile" and "infertile" groups were, with certain exceptions, not of great magnitude.

The patients were instructed to submit semen specimens obtained by masturbation after 3 days of continence. In Table 1, I have selected the years between 1966 and 1977 for analysis if only

*This manuscript has been rewritten and reedited by me (in August 1979) from the transcribed extemporaneous talks given nearly 2 years ago at the meeting on DBCP held at National Institute for Occupational Safety and Health in Cincinnati (October 1977). In doing so, it is inevitable that interim data appearing in the literature from any source must be discussed.

Table 1. Infertile marriage consultation, primary and secondary infertility, first semen examination anywhere--patients seen sequentially in groups of 1000 (1966-1977) (total, 9000).*

Period	Date	Mean volume, ml	Mean count, mil/ml	Median count, mil/ml	% of counts, mil/ml						Highest count/ ml	Total % of counts	
					<10	10.1-40	20.1-40	40.1-60	60.1-100	>100		<20 mil/ml	Azoospermia+
1	1/4/66-4/12/67	3.32	90.8	77	10.5	5.6	8.7	13.5	26.0	35.7	455	15.3	3.8
2	4/12/67-9/4/68	3.23	95.0	74	9.3	7.9	12.4	12.9	21.8	35.7	580	17.2	4.9
3	9/4/68-12/9/69	3.17	93.4	74	9.6	6.9	13.6	11.0	23.3	35.6	580	16.5	3.7
4	12/9/69-2/15/71	3.24	91.7	74	8.1	5.2	11.6	12.4	26.0	36.7	480	13.3	3.8
5	2/15/71-4/26/72	3.10	82.3	72	6.3	7.0	12.5	13.8	30.0	30.3	485	13.3	3.8
6	4/26/72-8/3/73	3.18	86.0	74	9.4	5.6	9.6	11.2	30.4	33.8	450	15.3	3.1
7	8/3/73-12/30/74	3.15	112.0	85	9.6	4.6	10.0	10.0	23.5	42.3	570	14.2	3.6
8	12/30/74-3/6/76	3.26	114.0	88	9.9	4.8	8.9	8.2	23.7	44.5	880	14.7	3.7
9	3/6/76-6/20/77	3.27	97.5	71	8.2	7.1	15.4	13.1	22.5	33.7	680	15.3	3.3
Overall values		3.21	95.7	76.5	9.0	6.1	11.4	11.8	25.2	36.5		15.0	3.7

*Reprinted with permission, Fertility and Sterility, 31:106, 1979.
+Azoospermia not included in sperm means or in frequency distributions.

because the modern studies referred to above are based on subjects evaluated for semen quality between 1969 and 1976. Intensive examination of the data therein is not required to determine:

-- that the means of ejaculate volume in each group of 1,000 men are constant,

-- that although the mean sperm counts for each group show minor variations over the years, the overall mean for 9,000 men is similar to the value for the 1,000 men in 1951, and

-- that the frequency distributions of the sperm counts not only are remarkably constant, but, too, are similar to those published in 1951.

An in-depth analysis of these modern data in relation to the findings of other modern observers is being performed by us for publication in Fertility and Sterility. A major conclusion will be, as already suggested, that there does not appear to have been a change, numerically, of any consequence in the capacity of the human testes to deliver spermatozoa to the ejaculate over a period of about 30 years. Does this statement mean that the modern figures in Table 1 can be accepted as standards to be met by any population you may wish to study? Not necessarily! I can only say at this time that they represent the best "infertile" population, in terms of semen quality, available for study in my laboratory over a 10-year period; that they probably are close to the standards to be expected of men of known fertility (the latter will be significantly higher but not to a major extent) at the present time; and barring an atomic calamity, that they are not likely to change in the forseeable future.

Lastly, in regard to the possibility that geographic factors within and without the United States may influence standards for semen quality remains highly debatable. At the time of this re-writing (nearly 2 years after the original meeting in 1977), a paper from Paris, France,[9] supplies data derived between 1973 and 1977 from a pre-vasectomy population in that area. Their sperm count data coincide almost exactly with the fertile population of MG in 1951 and, needless to say, differ considerably from and are much better than NB and SS's pre-vasectomy populations in the United States.

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DETERMINING INFERTILITY

Philip Troen* and Howard Nankin+

DR. PHILIP TROEN

In this very brief discussion of some aspects of seminal fluid, three fundamental points should be made in relation to the current discussion. The first concerns the techniques and the technology that are being used and should be used to study seminal fluid--techniques and technology that will give a representation of how the testis functions. The second is what seminal quality is adequate for fertility. The third question, which seems to bedevil most of the people present at this symposium, is what is normal. The three aspects, of course, overlap but each can be addressed separately.

TECHNIQUES AND TECHNOLOGY

Some very important aspects of technology should be stressed again, i.e., the collection of specimens and the period of abstinence. Data in terms of what represents a normal sperm count can vary significantly depending on the period of abstinence. The curve can shift one way or another by the period of continence or abstinence that may be present. Published studies report a wide range of abstinence periods ranging from 24 hours to more than 5 days. Standardization of the period is important for comparison. We use 48 to 72 hours for out patients.

By the same token, the number of specimens collected and analyzed becomes very important in trying to establish a baseline or a background for a person's normal seminal fluid. It has been clearly shown that, depending upon which indication of testicular function is used, one seminal fluid examination alone may not be adequate. If motility is being assessed, up to six counts may be needed to get a true indication of motility. To find the sperm

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density, as few as three counts may suffice. These are only broad, general remarks about technology and its importance; Dr. Lipshultz has pointed out some of the specifics in terms of the timing, training of the technicians, use of automated machinery for counting (particularly on specimens that have higher sperm density), etc.

Cytology studies provide one of the more stable indexes of seminal fluid analysis. I can only reemphasize what Dr. MacLeod has already stressed concerning this important predictor and the value of cytological determinations.

FERTILITY LEVEL

Establishing a fertility level for sperm count and seminal fluid content is the second problem. During the last decade, there has been an increased awareness that counts below 40 million/ml or even under 20 million can result in pregnancy, depending upon the statistical time period of exposure.

Indeed, in tests on some series of infertile couples, pregnancy rates as high as 18% to 35% have occurred with sperm density values under 20 million/ml. So this apparent inconsistency becomes a very important point and must be taken into consideration as the status of either patients or, in this case, subjects exposed to potential toxins is evaluated.

NORMALITY

The question of what is normal may be the most vital point being discussed. Clearly, what is normal depends on how the patients are selected, the demographic constituents of the population, various technological factors, etc. The most important point for the moment is that the range of sperm density is so great that it encompasses areas that would not otherwise have been considered normal. When trying to identify infertility, the word normal should be put within quotation marks.

Table 1, from an article by R. J. Sherins et al.,[1] indicates that there are a number of indices that should be used, including cytology (referred to here as the number or percentage of oval forms); motility; seminal fluid volume; and sperm density (listed here as sperm concentration).

These arbitrary designations demonstrate the difficulties of trying to assign titles to these groupings; good, equivocal, and poor are perhaps just as useful as normal/abnormal or fertile/infertile. These kinds of indexes can be used to group patients in terms of concentration (over 20, 10 to 20, or under 10 million/ml)

Table 1. Boundaries of semen parameters constructed from frequency distributions and fraction of all men in each category.*+

Category	Total sperm category, millions	Sperm conc., millions/ml	Volume, ml	Motility, %	Quality of motility, 0-4	Oval, %
Good	>60 42/119	>20 45/119	>2.0 77/119	>60 11/93	>3.0 22/93	>60 44/95
Equivocal	40-59.9 10/119	10-19.9 22/119	1-1.9 37/119	40-59.9 40/93	2.5-2.9 36/93	40-59.9 21/95
Poor	0-39.9 67/119	0-9.9 52/119	0-0.9 5/119	0-39.9 42/93	0-2.4 35/93	0-39.9 30/95

*Classification based on mean of all visits.
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to try to determine what the incidence might be of pregnancy or failure to become pregnant in a given population of patients. Table 2 shows the tremendous amount of overlap in these groups.

Table 2 demonstrates that when a sperm count of 40 million per total ejaculate or 10 million/ml is used as the upper limit of the "poor" category, only 58% of men who have been shown to be infertile over a long period of time fall into this category. Conversely, only 76% of men demonstrated to be fertile fall into a category having a sperm density over 20 million/ml. These figures alone, discounting all the other very important observations on cytology, motility, etc., show the enormous difficulty of extrapolating fertility in a given patient, as well as establishing norms for a wider population.

HOWARD NANKIN

I would like to review our experience over 8 years at the University of Pittsburgh using the endocrine evaluation of infertile men. We began doing detailed endocrine evaluations in 1969, including circulating levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, estrogens, and more recently, prolactin.

Table 2. Comparison of percent fertile and infertile men who fall within a specified boundary.*

Seminal fluid, parameter	Lower boundary, poor	Percent infertile men falling below lower boundary	Upper boundary, good	Percent fertile men falling above upper boundary
Density				
Total/ejaculate	<40 million	75%	>60 million	80%
Count/ml	<10 million	58	>20 million	76
Volume/ml	<1.0	5	>2.0	73
Motile, %	<40	58	>60	20
Quality, 0-4	<2.5	53	>3	43
Oval, %	<40	44	>60	80

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Infertility is quite common in the American population and around the world. Perhaps 10% to 15% of all married couples are infertile. About 85% of all couples conceive after 12 months, and within the next 12 months, perhaps another 4% or 5% will conceive without any medical intervention. The usual criterion for determining infertility is that a couple, without any medical advice, does not conceive after 24 months of trying. Practically speaking, if the couple is infertile after 1 year of trying, they probably will not conceive. The husband or the wife is about equally responsible for infertility, and in one-third of couples, both are responsible.

PHYSICAL EXAMINATION

Men are given a very detailed physical examination to determine reproductive status. Measuring the testicular size is quite important. Palpating for the epididymis is also important. Some men with azoospermia have either congenital absence of the epididymides or the vasa deferentia, which connect the testicles to the ejaculatory ducts. Some men have fibrosis or thickening of the epididymides.

A rectal examination should be performed, looking for prostatitis and inflammation of the seminal vesicles. Transient and almost complete interference with ejaculation of sperm can occur if there is inflammation of the seminal vesicles.

For evaluation, our patients were divided into several groups. One group consisted of men with structural defects, i.e., men who had something wrong with the apparatus connecting the testes to the ejaculatory ducts. The second group included subjects with various

atypical abnormalities of lymphocyte chromosomes. These men appeared to be normal in the physical examination parameters.

Another group was divided by the presence of varicoceles. The patients in whom we could find no abnormalities were put into an idiopathic group and subseparated into groups of men with sperm counts betweem 5 to 40 million/ml; with counts less than 5 million/ml; and totally azoospermic, i.e., men with idiopathic azoospermia.

RELATIONSHIP OF ENDOCRINE EVALUATORS TO SPERM LEVELS

Our data are not based on a single blood specimen. From each individual, we used three or four specimens, drawn at a particular time of day, that were then averaged. We tested normals throughout the control study to try to prevent minor differences in the technique that might occur from year to year.

Follicle Stimulating Hormone

I can only compliment earlier speakers who talked about the difficulty of using FSH as an indicator. We found that the average FSH in normal men (i.e., a sperm count over 40 million/ml) was about 178 nanograms/ml; in men who had counts between 5 and 40 million, there was only about a 35% increase in FSH levels. Between the normal and the men with less than 5 million sperm, there was a doubling of mean FSH with some overlap of the normal range of FSH levels. In men with a total absence of sperm, the average FSH level was three times the average found in normal men. Men with varicoceles in the scrotum had high FSH values (mean = 324 ng/ml, $p < 0.001$), and men with chromosomal abnormalities also had increased FSH (259 ng/ml, $p < 0.05$).[2]

Luteinizing Hormone

Luteinizing hormone (LH) was a difficult problem in that there was a tremendous overlap between the normal and the low sperm count population, except for the men with idiopathic azoospermia and men with varicoceles. With idiopathic azoospermia, the LH levels were significantly elevated (64 vs. 87 ng/ml, $p < 0.025$). Men with varicoceles also had high LH concentrations (79 ng/ml, $p < 0.05$).

Testosterone

Testosterone was even more complicated because although we could show a progressive decrease of mean testosterone corresponding to a reduction in sperm count, neither the men who had the mild lowering of sperm count, nor the men who had a moderate lowering of sperm

count, nor the men who had total absence of sperm were statistically lower than normal. In each of these groups, however, we could find men who were definitely subnormal in regard to testosterone, and there were probably more subgroups than these.

Prolactin

On screening frozen serum specimens from some 60 infertile men, three had elevated prolactin. One man who returned for a workup had a pituitary tumor, and surgery is planned. Treatment of high prolactin has resulted in conception in previously infertile couples.

Other Indicators

If you are in the process of planning this type of workup and are considering how to approach these patients, it is important that you try to identify other kinds of problems these patients might have. Exclude men with chromosome disorders, varicoceles, structural problems, and inflamed prostates or seminal vesicles and try to come up with a group that would only be related to the chemical in question. If you are going to screen for sperm count alone and not do these other evaluations, you may be skewing the pattern one way or the other. The best estimate of reproduction function would then include semen analysis and gonadotropin production. Perhaps a more sensitive indicator of gonadotropin production would be measuring excretions in the urine rather than a level in blood. Since 24-hour urine samples are complicated and tedious to collect, perhaps a first-morning specimen, where the excretion of gonadotropin can be related to the secretion of creatinine, may be a way to get around the tedious task of collecting 24-hour urine samples. This has been found to be helpful in evaluating youngsters who have delayed or abnormal sexual development. In boys and girls who have very low titers of gonadotropin before puberty, it is difficult to distinguish those who are abnormally low from those who are low normal. This problem was solved by collecting urine specimens; the discrimination is much easier and much better. You may find taking a urine specimen is a better screening technique than taking a blood sample.

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MUTAGENICITY OF DBCP

Arlene Blum*

BACKGROUND

Before addressing the mutagenicity of DBCP, I would like to tell you about the Ames test--a simple bacterial screening test for chemicals that cause mutations and are likely to cause cancer.

The Ames test ascertains whether a chemical causes mutations in bacterial DNA. If it does, the hypothesis is that it would also interact with DNA from other species--from animals and humans. There is a theory that chemicals that cause mutations also cause cancer. This theory has not been proven, but there is a fair amount of evidence and one of the convincing pieces is the Ames test itself. If 200 chemicals known to cause cancer in animals and humans are tested, about 90% of these will cause mutations in bacteria and about 10% won't. About 10% are false negatives. These 10% are in certain classes of compounds, like chlorinated organic molecules, that don't seem to work in the Ames test.

If, using the Ames test, several hundred chemicals that do not cause cancer are tested to see whether they cause mutations in bacteria, about 10% of these chemicals will be shown to cause mutations--or about 10% false positives. In several cases, this false positive result has turned out not to be a false positive because somebody did the cancer tests more carefully and determined that the chemical was, indeed, a carcinogen in animals.

The Ames test has been used to identify chemicals on which cancer tests were not done that should have been done--chemicals that were later found to cause cancer in animals. Examples of this are tris ((2,3-dibromo-propyl)phosphate)) and hair dyes. Tris, the flame retardant used in children's sleepwear, was shown first to be a mutagen in the Ames test and then, to be a carcinogen in animals. Hair dyes were shown to be mutagenic several years ago; recent results are showing that hair dye components are carcinogenic in animals.

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THE AMES TEST

An animal cancer test requires several years and several hundred thousand dollars. The Ames test requires about 2 days and several hundred dollars. It is a rapid, inexpensive way to get a preliminary answer.

The tests are done with a strain of salmonella bacteria that requires histidine to grow. In the absence of added histidine, they will not grow; a mutation in the gene of these bacteria requires histidine for their growth. If these bacteria are plated in a medium that does not contain histidine, a very few (perhaps 20 or 30) bacteria out of the many millions that are on the plate will have a spontaneous reversion--a spontaneous mutation--to the normal state so that these few bacteria can grow without added histidine in the medium.

If a mutagenic agent is added to the bacteria, there will be a great many more mutations that will allow the bacteria to grow without added histidine. Each bacterium that can grow will eventually form a colony. This colony can be seen on the plate, and by counting the number of colonies, you can estimate whether this particular chemical has caused an increase in revertants--whether it is a mutagen. Just adding a chemical to the bacteria gives a measure of the extent to which the chemical causes mutations.

For example, strain TA 100 will have about 120 spontaneous revertants. If a few micrograms of tris, the children's sleepwear additive, are added to the plate, there are at least a thousand revertant colonies. Based on this increase, tris can be considered a mutagen.

When I was studying tris, I became interested in DBCP because DBCP is an impurity in tris. They are fairly similar in that both chemicals are mutagens, both are animal carcinogens, and, at similar doses, both cause testicular atrophy in animals.

Figure 1 illustrates the dose response of the mutagenicity of tris and four impurities of tris, including DBCP. Tris can be seen to be a more potent mutagen than is DBCP. Along the abscissa is the number of micrograms of compound per plate; along the ordinant is the number of revertants per plate. When more chemical is added, there are more colonies of bacteria.

CARCINOGENIC POTENCY

In Bruce Ames' laboratory (where I work), scales of carcinogenic and mutagenic potency are being established. There is a very large range, a million-fold range, of carcinogenic potency. Aflatoxin

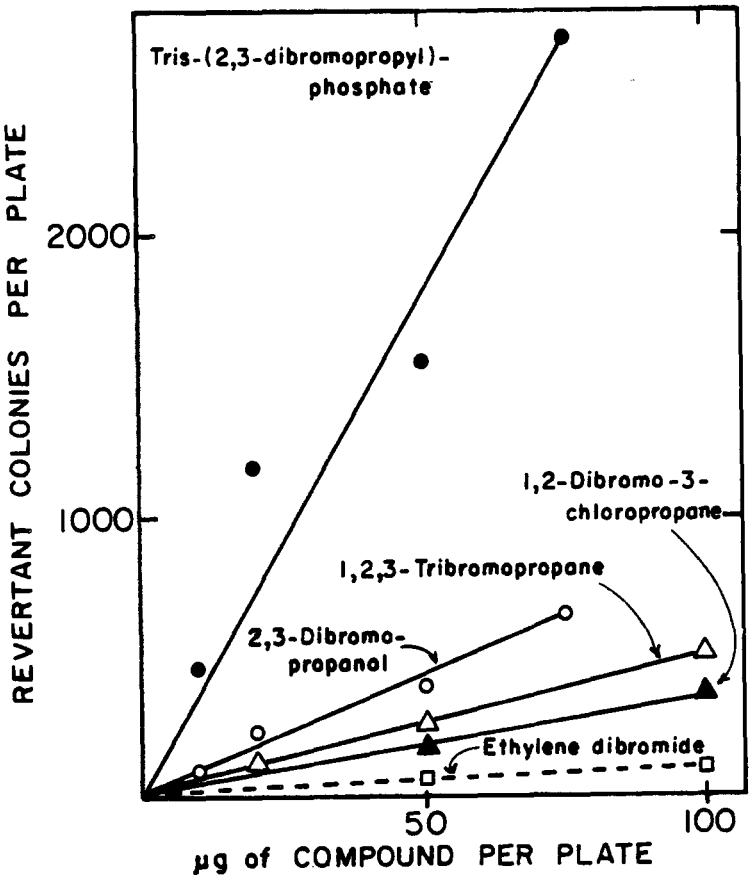

Figure 1. Dose response curves for mutagenicity of five compounds. (Reprinted by permission of Science, 195(4273):19, January 7, 1977.)

B-1, found in moldy peanuts, is one of the most potent known carcinogens. Saccharin and trichloroethylene are low on the potency scale. The relative carcinogenic potency of DBCP can be compared with some other chemicals.

For DBCP, a daily dose of about 1 mg will give half the animals cancer when administered over a lifetime.[1] This number was calculated based on extrapolation from the 1973 NCI study.[2]

COMPARATIVE CARCINOGENICITY

The life-time dose of DBCP that will give cancer to one half the animals can be roughly compared with the dose to which workers at the Occidental Chemical Company were being exposed. These workers were exposed to between 0.3 and 0.6 ppm in the air; it doesn't include skin exposure. Using 0.3 as the exposure level, it can be calculated that workers were exposed to about 0.4 mg/kg per working day.

Because they probably did not retain that amount, the dose they actually received was less than that. It is also possible that there was some additional exposure through skin absorption. Even with these very rough estimates, the amount workers were exposed to is in the same range as the dose that gave the animals cancer. I don't think, however, that more than that can be said.

RELATED CHEMICALS

The structure of a few, very closely related brominated chemicals should be of concern to us (Figure 2). The structure of tris(2,3-dibromopropyl)phosphate is similar to that of DBCP. Tris, the flame retardant that until recently was something like 5% to 10% of the actual weight of most children's sleepwear, was padded onto the fabric. It could be absorbed through the skin. The tris metabolite 2,3-dibromo proponal was found in the urine of children wearing tris-treated sleepwear--even wearing sleepwear that had been well washed. Tris and DBCP is now known to cause testicular atrophy in animals at similar doses.

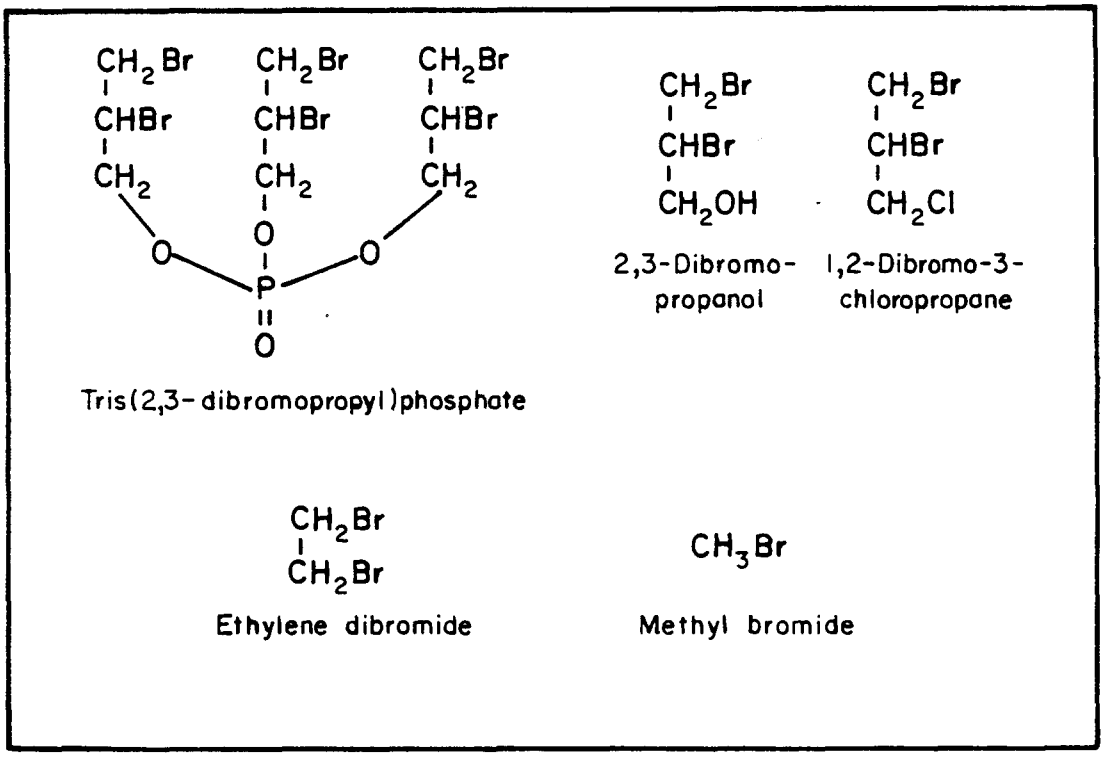

Figure 2. Chemical structure of some related brominated chemicals.

Ethylene dibromide, a fumigant, is another chemical (Figure 2) known to cause reproductive abnormalities. Brominated vegetable oils (vegetable oils where the double bonds have been brominated) are used as food additives in soft drinks. Brominated vegetable oils are also known to cause testicular atrophy in animals.

Methyl bromide, a widely used fumigant that has not been studied very much, is a mutagen. A cancer test has not yet been done on it, but one should be carried out.

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DBCP ENVIRONMENTAL MONITORING

Stephen Rappaport*

In January 1977, one of my colleagues at the University of California, Dr. Spear, and I were asked by a pesticide formulating company (Occidental Chemical Company) to help them establish an industrial hygiene program. As part of our consulting activities, we looked through their product line and picked several technical ingredients that we wanted to sample to determine exposure levels. Fortuitously, DBCP happened to be one of the ingredients we chose. Before the recent discoveries about DBCP were made, we had taken two samplings of the air concentrations in and around the area where the ingredients were being formulated.

The objective of a pesticide formulating operation is to take a chemical ingredient (in this case, DBCP) that is purchased from a manufacturer and mix it with other ingredients, such as emulsifiers, solvents, diluents, etc., to give the ultimate product the desired qualities. At the Occidental Chemical Company, the formulating occurred in a batch-type operation in a building that is actually semi-outdoors--open on all sides creating natural ventilation. DBCP was piped into a large tank, mostly in closed systems, the other ingredients were added, mixed, sampled for quality control, and then piped into a small adjacent area where the final product was metered into cans or drums. This was a relatively simple operation and only three or four people were involved: one actually did the formulating, that is, added the material to the big tank; and the others handled the drums, cans, or containers for the final product.

Because it was a batch-type operation with workers constantly moving in and around the area, it was difficult to get a true picture of what an integrated exposure, per se, would be in this facility. We used the method recommended by NIOSH for sampling solvent vapors in air, i.e., samples were drawn through small glass tubes containing 150 mg of activated charcoal, which absorbed the vapor from the air. The samples were then taken to the laboratory and placed in small glass vials and to which 2 ml portions of benzene were added. The benzene eluted the DBCP from the charcoal,

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and an aliquot of that was injected into a gas chromatograph equipped with an electron-capture detector.

Table 1 shows the results from the first day of sampling. On this day, three people were involved with the operation: a formulator and two people piping the material into the cans. The formulator was employed through most of the 8-hour shift in some capacity around the area. The other two people spent only a relatively short time in the area, and the exposure data on these two individuals reflect only that time.

Table 1. Air concentrations of DBCP in pesticide formulating plant facility on first date of testing (May 5, 1977).

Operator	Sample duration, hour	Sample volume, liter	Amount found,* µg	Air concentration (mg/m3)	Air concentration (ppm)	TWA, ppm
Formulator	1.08	6.62	16.2	2.4	0.25	0.35
	0.50	3.08	10.5	3.4	0.35	
	1.98	12.3	23.3	1.9	0.20	
	1.83	11.1	61.2	5.5	0.57	
Canner #1	1.50	9.27	23.6	2.5	0.26	0.38
	0.60	3.70	23.6	6.4	0.66	
	0.70	6.74	26.8	4.0	0.41	
Canner #2	1.42	11.4	14.0	1.2	0.13	0.43
	0.75	3.66	35.4	9.7	1.0	

*Incorporates desorption efficiency factors of 74% (0.4 to 20 µg) or 85% (>20 µg).

On this first sampling day, May 5, 1977, the time-weighted average (TWA) air concentrations were in the neighborhood of 0.3 to 0.4 ppm. The environmental conditions were relatively cool and windy; the temperature was 65 F at noon; and the wind velocity greater that 400 ft/min.

On the second sampling day, July 26, 1977, the atmospheric conditions were completely different: the temperature was 95 F at noon and the wind velocity was less than 100 ft/min. We suspected that because of the relatively low vapor pressure of DBCP we would find higher air concentrations on the second sampling date since both temperature and wind velocity would tend to favor more volatilization and residence of the vapor in the immediate area. The TWA concentrations for the three people employed on this date were, however, very similar to those on the the first date: about 0.3 to 0.4 ppm (Table 2). Because the

workers were wearing respiratory protection on this second day, concentrations are an indication of what the exposures would have been without respiratory protection and not what the individual was breathing.

Table 2. Air concentrations in pesticide formulating plant on the second day of testing (May 5, 1977).

Operator, location	Sample duration, hour	Sample volume, liter	Amount found,* µg	Air concentration (mg/m^3)	Air concentration (ppm)	TWA, ppm
Formulator	3.33	12.2	58.4	4.8	0.50	0.38
	1.20	4.45	7.83	1.8	0.18	
	2.38	4.99	14.3	2.9	0.30	
Canner #1	3.35	12.0	59.1	4.9	0.51	0.42
	1.45	5.40	12.1	2.2	0.23	
	2.33	4.65	19.2	4.1	0.43	
Canner #2	3.38	11.8	43.2	3.7	0.38	0.29
	1.52	5.28	6.70	1.3	0.13	
	2.33	4.38	10.5	2.4	0.25	

*Incorporates desorption efficiency factors of 74% (0.4 to 20 µg) or 85% (>20 µg).

We also collected several short-term (5-minute) samples around the area to get some idea of what the excursions above and below the TWA concentrations would be (Table 3). The highest concentration found at a 5-minute averaging time was about 3 ppm in samples collected in the breathing zone of the person at the console where the final product was being fed into cans.

The numbers in these tables incorporate desorption efficiency factors; this is explained more fully in "Evaluation of a Coconut-Shell--Charcoal Tube Method for 1,2-dibromochloropropane (DBCP) in Air" p. 77. Briefly, however, the DBCP is absorbed very strongly on the activated charcoal, and benzene does not completely elute the material. We, therefore, ran several static tests to determine how efficiently we could remove the material from the charcoal in our tubes and found efficiencies to be 74% to 85%, depending upon how much material was absorbed. These desorption efficiencies are higher than those measured by NIOSH, indicating that each batch of charcoal must be tested.

An electron-capture detector, which is specifically for use with electro-negative substances like halogens, provides a very sensitive

Table 3. Air concentrations of DBCP with a sample duration of 5 minutes and a sample volume of 4.75 liters.

Operator, location	Amount found,* µg	Air concentration mg/m^3	Air concentration ppm
Canning	142	30	3.1
	146	31	3.2
	16.9	3.6	0.37
	19.5	4.1	0.42
Formulating platform	32.5	6.8	0.71
	15.5	3.3	0.34
	26.9	5.7	0.59
Across room from canning	2.52	0.53	0.05
	1.45	0.30	0.03
At door	13.9	2.9	0.30
	3.14	0.66	0.07

*Incorporates desorption efficiency factors of 74% (0.4 to 20 µg) or 85% (>20 µg).

procedure for monitoring DBCP and related compounds in the workplace. We found that we could routinely quantitate as little as 10 picograms (pg) of DBCP (1 pg = 10^{-12} gram, or a thousandth of a nanogram (ng)), which was well above the detection limit. If we had a sampler capable of efficiently collecting very small amounts of DBCP, we could, with a 5-liter air sample (about the smallest amount one would ever collect in practice), have a quantitation limit for an air concentration of about 1/200 ppb.

EVALUATION OF A COCONUT-SHELL CHARCOAL TUBE METHOD FOR 1,2-DIBROMO-3-CHLOROPROPANE (DBCP) IN AIR*

Samuel P. Tucker+

INTRODUCTION

The purpose of the work was to develop a solid sorbent method for sampling and analyzing 1,2-dibromo-3-chloropropane (DBCP) in air at the OSHA standard.

The emergency temporary OSHA standard for DBCP was set at 10 ppb (0.097 mg/m^3) as an 8-hour time-weighted average with a ceiling concentration of 50 ppb (0.48 mg/m^3) during any 15-minute period. (See Federal Register, Vol. 42, No. 175, September 9, 1977, pp. 45536-45549.)

The proposed permanent OSHA standard was set at 1 ppb (0.0097 mg/m^3) as an 8-hour time-weighted average with a ceiling concentration of 10 ppb (0.097 mg/m^3) during any 15-minute period. (See Federal Register, Vol. 42, No. 210, November 1, 1977, pp. 57266-57283.)

The principle of the method evaluated was that air is sampled with a tube containing coconut-shell charcoal; the DBCP collected is desorbed with benzene or toluene; the sample is analyzed by gas chromatography using an electron-capture detector.

A solid sorbent tube for taking air samples was selected because it is convenient to handle and ship. Coconut-shell charcoal was selected as the first solid sorbent to be investigated in the laboratory because:

-- Various laboratories had been using coconut-shell charcoal as a solid sorbent for DBCP in air.

*Shortly after Dr. Tucker's original remarks were presented at the Conference, the results of the completed methodology study indicated poor recoveries of DBCP. This paper, therefore, updates his original presentation.

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-- Coconut-shell charcoal tubes are commercially available for wide distribution.
-- Coconut-shell charcoal is the most widely used charcoal for the collection of a variety of organic vapors. The vast majority of NIOSH methods involving charcoal tubes specify coconut-shell charcoal.

EXPERIMENTAL

Reagents and Equipment

1,2-Dibromo-3-chloropropane (ca. 97% pure by GC analysis) was obtained from Pfaltz and Bauer, Inc., and from Dow Chemical Company under a different name, Fumazone F. Benzene and toluene, "Distilled in Glass," were obtained from Burdick and Jackson Laboratories, Inc.

The 100-mg/50-mg, two-section charcoal tubes were Lot 106 organic vapor tubes obtained from SKC, Inc., Eighty Four, Pennsylvania. The charcoal used in the desorption efficiency experiments was taken from tubes of this type.

The gas chromatograph was a Hewlett-Packard Model 5710A equipped with a ^{63}Ni electron-capture detector. The 1.8-meter X 2-mm i.d. glass column was packed with 20% SP-2100/0.1% Carbowax 1500 on 100/120 Supelcoport. The analyses were run isothermally at 130°C with the nitrogen carrier gas flow set at 30 mL/min.

The controlled atmospheres of DBCP were based on the vapor pressure of DBCP and were generated by passing air over neat DBCP maintained at ca. 30°C. Excess DBCP condensing from the air stream inside a condenser indicated the effluent air was saturated with DBCP vapor. Dilution with additional air at this stage produced concentrations in the low parts-per-million range. An additional dilution stage produced concentrations in the low parts-per-billion range. Water vapor was introduced during the final dilution stage. The sampling manifold was a glass cylinder bearing five sampling ports in a row on the side and a sixth port at one end of the cylinder. The pressure of the atmospheres was maintained at 0.2 to 0.5 inch of water above atmospheric pressure.

Procedure

Analytical procedure tested--

-- The DBCP is desorbed from the charcoal samples by treatment of the samples with 10-mL quantities of either benzene or toluene in volumetric flasks for at least 1 hour with occasional agitation.

-- The solutions are analyzed by injecting 5-µL aliquots into the gas chromatograph to determine whether the concentrations are within the calibration range.
-- Those solutions with concentrations above the calibration range of the gas chromatograph are diluted to concentrations near 50 pg/5 µL.
-- The sample solutions are analyzed with external standards.
-- The quantities of DBCP per injection are measured by comparing peak heights of samples with those of the standards.

Determination of calibration curve--

The calibration curve was determined by using both benzene and toluene standards at concentrations ranging from less than 1 pg DBCP per 5-µL of solution to 200 pg DBCP per 5-µL of solution.

Desorption efficiency study--

-- Various quantities (48, 24, 5, 0.5, and 0.05 µg) of DBCP in hexane solution were added to 100-mg portions of charcoal. Six portions of charcoal were treated in this manner at each level.
-- Corresponding standards were prepared by adding the same quantities of DBCP to 10 mL of benzene.
-- The samples were stored for ca. 17 hours at room temperature in airtight vials to ensure complete adsorption onto the charcoal.
-- The DBCP was desorbed with 10-mL quantities of benzene. The contact time with the solvent was at least 1 hour.
-- The samples were analyzed with the standards in pairs. All solutions except those involving the 0.05-µg quantities required dilution to the calibration range of the gas chromatograph.
-- The desorption efficiency was calculated by dividing the quantity of DBCP in the sample solution by that quantity in the standard.
-- The study was repeated with toluene as the desorbing solvent at the 5- and 0.5-µg levels.

Storage study--

The storage study was similar to the desorption efficiency study except that additional storage time was allowed. Once the samples had been stored for ca. 17 hours at room temperature to ensure complete adsorption onto the charcoal, storage was continued for an additional 7 days at room temperature and also at -28°C. Only the 5- and 24-µg levels were examined in the storage study.

Breakthrough study--

The breakthrough study was performed to determine the capacity of the front section of the charcoal tube for DBCP at ca. 6 ppm at 80% relative humidity. The atmosphere of DBCP entered the charcoal tubes from which the back sections had been removed. The effluents from the charcoal tubes were monitored by a total hydrocarbon analyzer using flame ionization detection.

Air sampling experiments--

Air samples were taken with 2 to 6 charcoal tubes connected to the manifold. In most sets of experiments, a check on the air concentrations was made by taking samples with bubblers of toluene linked in series and analyzing the resulting solutions.

The limited number of sampling ports on the manifold precluded sampling with bubblers while six charcoal tubes were engaged. Thus, in earlier experiments, the sampling with bubblers was begun generally within 10 minutes after completion of sampling by charcoal tubes. In later experiments, fewer charcoal tubes were used at a time and bubbler and charcoal tube samples were taken simultaneously as a closer check on the air concentrations. The relative humidity was 28% to 30% in one set of experiments and was 80% in all other experiments. Two sampling rates were employed: 1 and 0.2 L/min; critical orifices were placed in line behind the charcoal tubes and trains of bubblers to control the flow.

For each of two storage studies, the limited number of sampling ports on the manifold required the design of experiments in which randomly selected charcoal samples stored at -28° for 7 days could be compared with replicate samples analyzed immediately. In each experiment, 18 samples were taken during these sampling periods with 6 samples in a set per period. Two samples were selected randomly from each set and analyzed immediately. Other charcoal samples were stored at -28°C for later analysis. These experiments were performed in this manner to eliminate the possibility of apparent losses of DBCP during storage due to slight variations in air concentrations from period to period. The two experiments were performed at different concentrations.

RESULTS

Determination of Calibration Curve

Figure 1 presents a calibration curve for a series of toluene solutions in the range of 5 to 200 pg of DBCP per 5 µL of solution. Under the gas chromatographic conditions employed, the

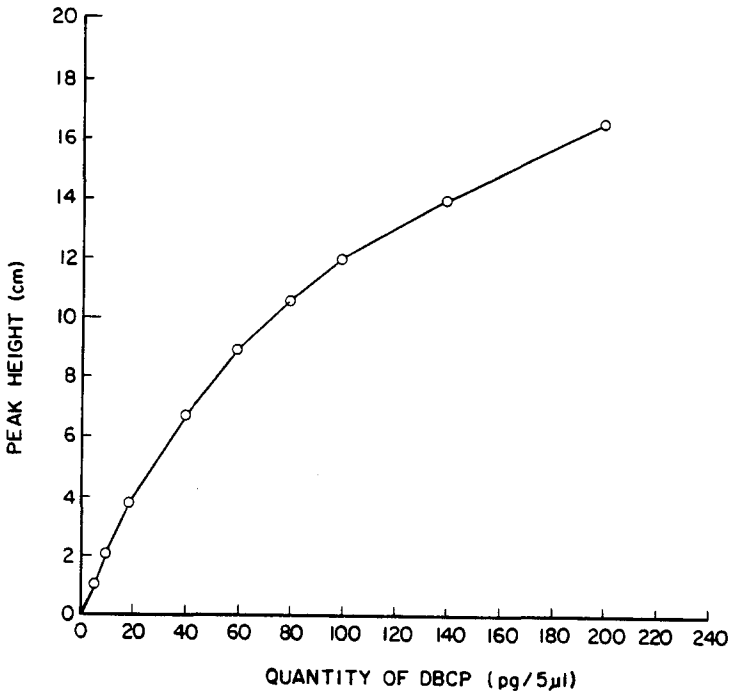

Figure 1. Calibration curve for toluene solution.

retention time of DBCP was ca. 3.8 minutes. The detection limit for DBCP was ca. 0.25 pg. The relative standard deviation of measurement of DBCP was 0.054, 0.038, and 0.01 at the 1-, 5-, and 10-pg levels, respectively.

Desorption Efficiency Study

The desorption efficiency (DE) study results are given in Table 1. Each DE value is a mean of six values. The relative standard deviation of measurement ranged from 0.030 to 0.067 at these levels.

Table 1. Desorption efficiency study.

Level, µg	DE Benzene	DE Toluene
48	0.908	----
24	0.929	----
5	0.843	0.878
0.5	0.788	0.789
0.05	0.591	----

Storage Study

Storage study results at the 5- and 24-µg levels are given in Figure 2. Each value is a mean of six values, and 95% confidence limits are indicated for each level.

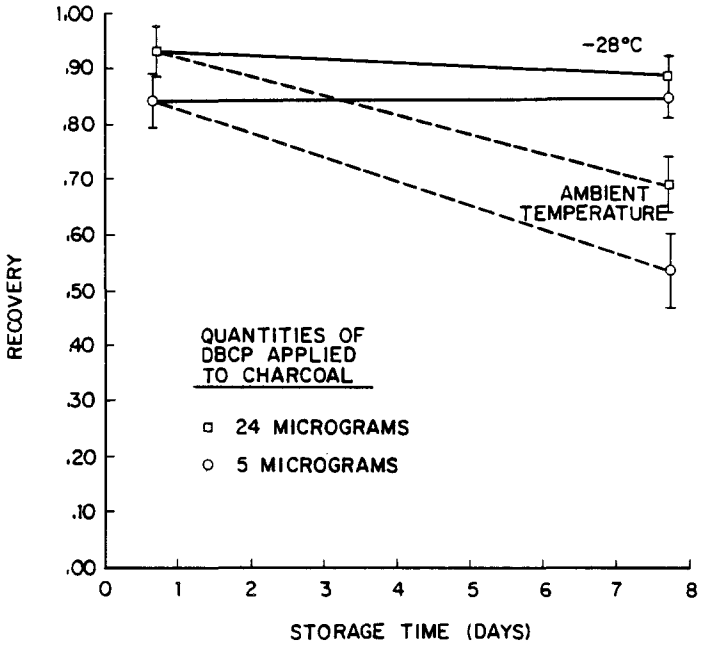

Figure 2. Results of storage study.

Breakthrough Study

Breakthrough (Table 2) occurred only after more than 359 liters of air had passed through the tube. Thus, the capacity of the 100-mg section of charcoal at ca. 6 ppm of DBCP at 80% relative humidity was greater than 21 mg.

Table 2. Breakthrough study.

Tube no.	Flow rates, mL/min	Sample volumes, liters	Break-through detected
1	208	62.4	No
2	909	359	No
3	909	975	Yes

Air Sampling Experiments

Results of air sampling experiments are given in Table 3. The sampling rate in most experiments was 1 L/min, but in later experiments it was reduced to 0.2 L/min. The reduction in the rate decreased the amount of turbulence in the bubblers of toluene and substantially reduced the possibility of washover from one bubbler to another in a series. Even with the reduction in sampling rate, however, DBCP generally was found in each bubbler in a series. The back sections of more than 25 charcoal tubes were analyzed. Generally, the DBCP found, if any, was less than 0.02 µg. In one case in which a large interfering peak obscured a possible peak due to DBCP, reanalysis was not attempted. This interfering peak was a late eluter from a previous injection.

Table 3. Air Sampling Experiments.[a]

Experiment	Sampling method	Sample volume, liters	Mean quantity of DBCP found, µg[b]	Mean concentration of DBCP, ppb[b]	n[c]	RSD[d]
1A[e]	charcoal	220	6.27	2.95	6	0.401
1B[e]	charcoal	220	4.15	1.95	6	0.431
2A[e]	charcoal	220	47.4	22.3	6	0.0885
2B[f]	bubblers	5	4.84	100	1	-----
2C[e]	charcoal	220	46.1	21.6	6	0.0834
3A	charcoal	200	1.76	0.91	6	0.316
3B[g]	bubblers	8	1.98	25.7	3	1.05
4A	charcoal	200	1.25	0.65	6	0.172
4B[g]	bubblers	8	1.27	16.5	3	0.188
5A	charcoal	25	1.12	4.65	6	0.141
5B[g]	bubblers	8	1.10	14.2	3	0.408
6A[h]	charcoal	78	0.42	0.56	2	1.21
6B[h]	charcoal	20	<0.14	<0.71	3	>0.955
6C[h]	charcoal	20	0.90	4.67	3	0.243
6D[h]	bubblers	12	2.09	18.1	3	0.364
7A[i,j]	charcoal	0.6	4.10	707	2	0.0340
7B[i,j]	bubblers	0.6	0.15	25.7	1	-----
8A[i]	charcoal	25	5.30	22.0	2	0.0419
8B[i]	bubblers	25	4.25	17.6	2	0.297

a. The sampling rate in experiments 1 through 5 and 6C was 1 L/min;in all other experiments, it was 0.2 L/min. The relative humidity in all experiments was 80% except in experiments 3A and 3B when it was 28% to 30%.
b. The quantities and concentrations of DBCP determined by the charcoal tube method are uncorrected for desorption efficiency.
c. The symbol n refers to the number of air samples taken simultaneously within an experiment. In the case of the bubblers of toluene, n refers to the number of trains of bubblers, each train consisting of three bubblers.
d. RSD is the relative standard deviation of the mean concentration of DBCP.
e. These experiments were the storage experiments described in the Air Sampling Experiment section of Procedure. The charcoal samples in experiments 1B and 2C were stored at -28°C for 7 days before analysis.
f. Sampling with bubblers in experiment 2B began before sampling by all of the charcoal tubes was completed. (Because of slightly different sampling rates, sampling times for different charcoal tubes varied slightly, and one of the first sampling ports that became available was connected to the train of bubblers.)
g. The initial times of sampling by these bubblers were within 10 minutes after sampling periods with charcoal tubes were complete.
h. Sampling with charcoal tubes in experiment 6A took place over a 6.5-hour period. Within this period, sampling for experiments 6B, 6C, and 6D was performed in separate intervals.
i. Bubbler and charcoal tube samples were taken simultaneously in these experiments. The bubbler trains and the charcoal tubes were connected to alternate sampling ports on the manifold.
j. The actual concentration of DBCP was intended to be near 1000 ppb as the additional dilution stage had been omitted from the generation system.

DISCUSSION

The results of all experiments before the air sampling experiments suggested the feasibility of a method for determining DBCP in air in the low parts-per-billion range using the coconut-shell charcoal tube. These results indicated that such a method would have two limitations:

-- storage times greater than 1 day would require refrigeration of the samples, and

-- rather long sampling times would be required. The quantity of DBCP collected must be large enough to permit a satisfactory desorption efficiency, i.e., at least 80%. Based on the desorption efficiency study alone, this quantity would be ca. 1 µg or more. At the 1-ppb level, for example, sampling for 4 hours at 1 L/min would mean the collection of 2.3 µg of DBCP.

On the basis of generally poor precision and low recoveries, however, the results of the air sampling experiments indicated that the charcoal tube method involving coconut-shell charcoal is unreliable for determining DBCP at low parts-per-billion levels, at least when toluene is the solvent used for desorbing the charcoal samples.

In most charcoal tube experiments listed in Table 3, the precision of measurement was poor; the relative standard deviation in most cases was greater than 0.14. Comparison of the mean concentrations found in experiments 1A and 1B suggested a loss of DBCP during storage. Application of the pooled t test at the 95% confidence level indicated, however, the two concentrations were not significantly different.

The concentrations of DBCP determined by the charcoal tube method usually were much lower than the concentrations determined by the method involving bubblers of toluene. Since DBCP was generally found in all three bubblers in a series, it is assumed that some DBCP passing into the third bubbler was not trapped and the calculated concentrations based on the bubbler method were lower than the true concentrations. Thus, the generally low results based on the charcoal tube method appear to be real. The reasonable agreement between the calculated concentrations based on the charcoal tube and bubbler methods in experiments 8A and 8B (22.0 and 17.6 ppb, respectively) is not representative of the majority of the results of air sampling. No explanation is offered for the anomalously low result of 25.7 ppb from the bubbler method in experiment 7B.

Three experiments involving air samples failed to improve noticeably the total recovery of DBCP from charcoal. In one experiment, most of the 10 mL of toluene used for desorption of DBCP from one charcoal sample in experiment 2C was decanted and replaced with acetone for a second desorption attempt.

In a similar experiment, isopropanol was used. Although there was no evidence that either acetone or isopropanol would be superior to toluene in desorbing DBCP, desorption attempts with these solvents appeared worthwhile because these solvents are miscible with water. Air sampling in the humid atmosphere caused many of the charcoal particles to cling to the glass surfaces of the volumetric

flasks when toluene was present. In a third experiment, two charcoal samples were treated with toluene in an ultrasonic bath.

In spite of the poor precision frequently encountered in measurements involving both charcoal tubes and bubblers, the generally poor recoveries of DBCP from the charcoal in the air sampling experiments reflect two possibilities:

-- reaction of a portion of the DBCP with one or more agents such as oxygen and the charcoal surface, and
-- low desorption efficiencies when toluene is used as the desorbing solvent.

In any case, it appears that the recoveries of DBCP from air samples involving coconut-shell charcoal were generally lower than those recoveries determined as a result of applying the same or similar quantities of DBCP in solutions of hexane to the charcoal.

CONCLUSION

The results of all work done before the extensive air sampling experiments suggested the feasibility of a method for DBCP in air in the low parts-per-billion range using the coconut-shell charcoal tube. The results of air sampling experiments with controlled atmospheres, however, showed that:

-- the precision of measurement at low concentrations was generally poor, and
-- the concentrations of DBCP determined by the charcoal tube method usually were much lower than the concentrations determined by the method involving bubblers of toluene.

The results indicate that the coconut-shell--charcoal-tube method for determining DBCP at low levels is unreliable, at least when toluene is the solvent used for desorbing the charcoal samples.

DBCP RESPIRATORY PROTECTION

Gene Kennedy*

One of the main responsibilities of the Protective Equipment Section of NIOSH is to evaluate respiratory protection equipment and to present recommendations for standards to the Department of Labor. In this case, the use of respirators will probably be one of the major control measures for worker protection against DBCP since its production is being phased out in the United States.

Warning properties are one of the major considerations when evaluating protection for DBCP and a number of other compounds. The joint NIOSH/OSHA Standards Completion Program Respirator Decision Logic[1] summarizes this problem as follows:

> Warning properties relying upon human senses are not fool-proof. However, they provide some indication to the employee of possible sorbent exhaustion or of poor facepiece fit or other respirator malfunction. Warning properties include odor, eye irritation and respiratory irritation.
>
> Adequate warning properties can be assumed when the substance odor, taste or irritation effects are detectable and persistent at concentrations 'at' or 'below' the permissible exposure limit.
>
> If the odor or irritation threshold of a substance is many times greater than the permissible exposure, this substance should be considered to have poor warning properties.
>
> If the substance odor or irritation threshold is somewhat above the permissible exposure limit (not in excess of three times the limit) and there is no ceiling limit, consideration is given as to whether or not undetected exposure in this concentration range could cause serious or irreversible health effects. If not, the substance is considered to have adequate warning properties.

I emphasize that the effects must be "persistent" because some compounds, such as hydrogen sulfide, generate olfactory fatigue and are not detectable after a certain exposure.

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Table 1 shows the procedure for deciding on respiratory protection for DBCP. First, you must assemble all the information that is available. The permissible exposure limit is 10 parts per billion (ppb). The warning properties must be considered poor because the odor, taste, and irritation effects occur at much greater levels than 10 ppb. The odor level is about 1.7 ppm; therefore, DBCP is not detectable by human senses below the permissible exposure limit.

Table 1. Respirator decision logic for exposure to DBCP.

Property/hazard	Measurement	Effect	Use of respirators
Property:			
Permissible exposure limit	10 ppb		
Vapor pressure	1 mm @ 21 C*		
Vapor concentration	1 ppm		
Physical state	vapor		
Hazard:			
Warning properties		Poor	Do not recommend use of air purifying type.
Eye irritation		Yes	Use full facepiece only.
Flammable limit		NA+	
IDLH†		NA	If IDLH established, use positive-pressure SCBA~ and combination positive-pressure SCBA and supplied air respirator above this level.
Sorbent efficiency		Good	
Skin absorption		Yes	Use supplied-air suit.

*About 1000 ppm in saturated vapor.
+Not available.
†Immediately dangerous to life and health.
~Self-contained breathing apparatus.

Next, we wanted to determine the allowed respirators by their use and type and the necessary protection factor. Protection factor refers to the multiple of the permissible exposure limit that the respirator is recommended for, with 10,000+ being considered the maximum protection factor available from many of the respiratory protectors on the market today.

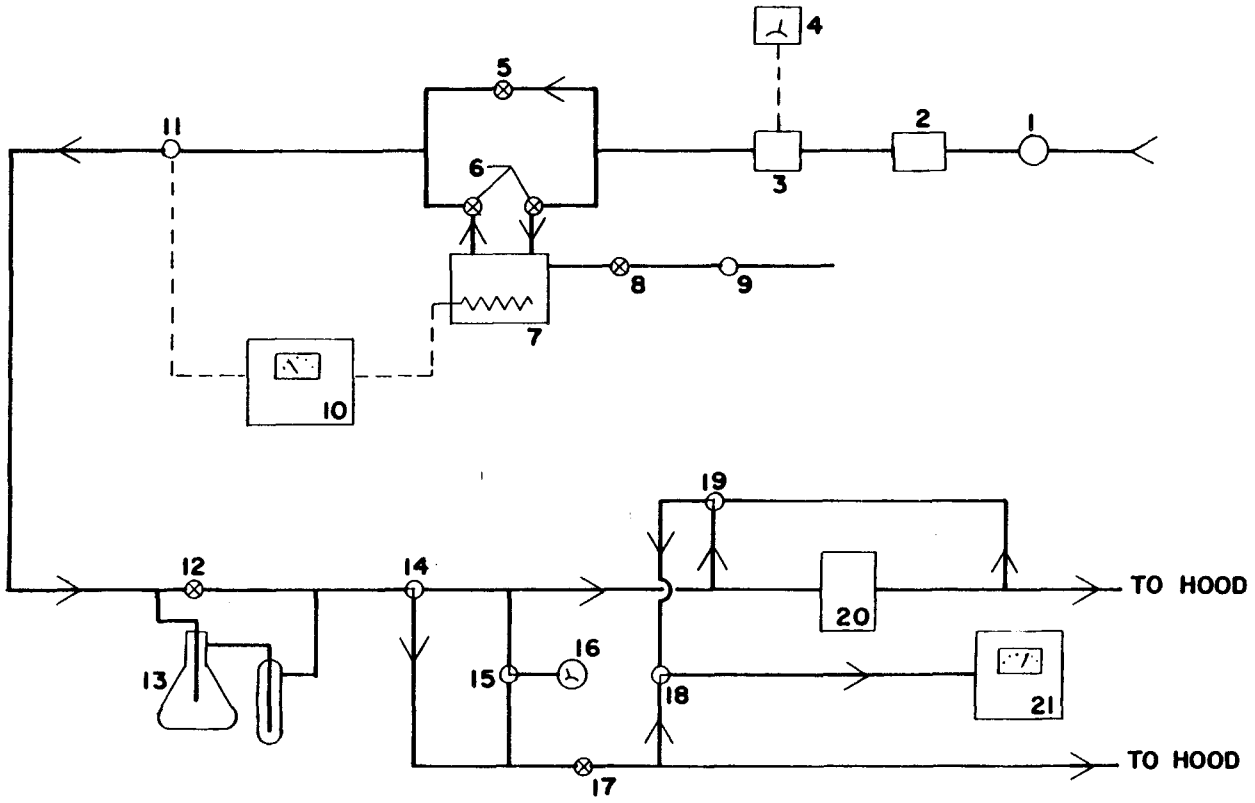
For entry and escape at unknown concentrations, a maximum protection factor is required. The only respirators that can be recommended for this use are (a) positive-pressure, self-contained breathing apparatuses (SCBA) and (b) combination positive-pressure, supplied-air respirators (SAR). This second type, referred to as airline respirators, requires the user to carry an egress bottle that permits breathing for approximately 5 to 10 minutes after disconnecting the normal air line.

For fire-fighting, the necessary maximum protection factor, again 10,000+, is only afforded by positive-pressure SCBA. For escape, any SCBA or gas mask is sufficient. The use of the gas mask is dependent on sorbent efficiency, and in this case, the sorbent efficiency is quite good. Nevertheless, gas masks should only be used for escape purposes.

The half-mask chemical cartridge respirators must be eliminated from consideration because of poor warning properties, the possibility of eye irritation, and the fact that effectiveness would depend upon administrative control, i.e., requirements to change respirators at set times. Full-facepiece chemical cartridge respirators would be eliminated for the same reasons.

Combining all these data creates the recommended respirator table (Table 2). Respirators that are allowed in higher concentrations can be used at lower concentrations.

We also conducted research on respirator cartridges, using those approved by NIOSH for pesticide use. Figure 1 is a schematic drawing of the apparatus for these tests. The air is brought in through a regulator (1), metered (3,4), and then sent through a humidification system kept at 50% or 80% humidity (5-11). Next, the air is metered by a valve (12) and bubbled through a flask (using a fritted gas bubbler) containing DBCP (13). The vapor-carrying air is then taken out of the flask and passed through a trap filled with glass-wool to remove any large droplets. The trap and flask are contained within a constant temperature bath. The vapor saturated air is then taken down to a three-way valve (14) where the flow can be diverted to a bypass line and up to the hood or downstream to the cartridge and then exhausted into the hood. The relative concentration was monitored by a flame ionization detector (21). We can monitor the relative concentration of either by-pass line, upstream or downstream from the cartridge.



1. Regulator
2. Charcoal canister
3. Mass flow meter
4. Mass flow meter
5. Airflow valve
6. Humidifier airflow valves
7. Humidifier (heater and water level switch)
8. Water inlet solanoid valve
9. Water pressure switch
10. Humidity sensor/controller
11. Humidity sensor/controller
12. Vapor generation valve
13. Vapor generation flask and trap
14. Three-way test/bypass valve
15. Three-way valve
16. Magnehelic
17. Back pressure regulation valve
18. Three-way valve
19. Three-way valve
20. Cartridge holder
21. Flame ionization detector

Figure 1. Schematic of test apparatus.

Table 2. Respirator recommendations for DBCP.

Concentration	Permissible respiratory protection
Up to 50 times the TLV*	Any supplied-air respirator (SAR) with a full facepiece, helmet, or hood (30 CFR 11.110(A)); or any self-contained breathing apparatus (SCBA) with a full facepiece (30 CFR 11.70 (A)).
50-2000 times the TLV	A Type-C SAR with a full facepiece operated in pressure-demand or other positive-pressure mode with a full facepiece, hood, or helmet operated in continuous-flow mode (30 CFR 11.110 (A).
50-10,000 times the TLV	SCBA with a full facepiece operated in pressure demand or other positive-pressure mode (30 CFR 11.70 (A)); or a combination respirator which includes a Type-C SAR with a full facepiece operated in pressure-demand or other positive-pressure or continuous-flow mode and an auxiliary SCBA operated in pressure-demand or positive-pressure mode (30 CFR 11.70 (B)).
Escape	Any SCBA(30 CFR 11.70 (A)); or any gas mask providing protection against organic vapors (30 CFR 11.90 (B)).

*Threshold limit value; used here interchangably with permissible exposure limit.

Table 3 presents the results of the work to date. These data are very sketchy now since it is not a complete study. We did not have all the duplication that we would have preferred for these cases, but the concentrations were very, very high--much higher than normally used. This occurred because we couldn't see breakthrough at lower concentrations. Also, because the workday is 8 hours, we ran fairly close to the end of the working day.

We were interested in a 10% breakthrough area. This is the area where the respirator cartridge should be thrown away and respirator use ceased. In the first case, the test was ended at 290 minutes and a 1% breakthrough had not occured.

Table 3. Test results of studies on respirator cartridges, using a flow rate of 32 l/min.

Cartridge	Charcoal weights, gram	Relative humidity, %	Concentration, ppm	Breakthrough, minutes 1%	5%	10%	Wheeler prediction minutes
Willson	46.5	80	360	290*	---	---	473
MSA 412		40.5	80	360	243	259	272
American Optical	39.0	80	370	237	257	266	385
American Optical	39.0	80	380	278	296	309	375
Willson	46.5	80	440	257	287	300	384
MSA	40.5	80	550	198	215	225	265
Norton	32.5	50	600	187	206+	---	195
American Optical	39.0	50	500	215	232	242	282
Willson	46.5	50	400	290	315	325	424
MSA	40.5	50	343	262	276	287	433
Willson	46.5	50	320	220†	---	---	535
Norton	32.5	50	60	133~	---	---	2244

*Test terminated at 290 minutes.
+Test terminated at 5% breakthrough.
†Test terminated at 220 minutes.
~Test terminated at 133 minutes.

The respirator sorbent efficiency was quite good for this compound. If the data were extrapolated down towards the permissible exposure limit, the life of the cartridge could possibly be extended weeks or even months. This is not recommended, however, because changes may occur within the cartridge, e.g., over a period of time while not in use, the vapor can distribute itself throughout the entire cartridge and establish an equilibrium situation. When the cartridge is used the second time, the respirator wearer could be exposed to DBCP on the first breath. There is some correlation between the weight of the charcoal and the breakthrough time, but all the cartridges apparently worked well. Two more cartridges are going to be tested: a Pulmosan cartridge and an MSA canister.

REFERENCE

1. Pritchard, J.A. 1976. A guide to industrial respiratory protection. DHEW (NIOSH) Publication No. 76-189. National Institute for Occupational Safety and Health, Cincinnati, Ohio. pp. 137-148.

DISCUSSION

Question (Dr. Meyer, NIOSH): We have heard that we can measure DBCP in the environment and can protect workers with relatively good removal efficiency in terms of respiratory protection against DBCP, even with very substantial air concentrations. Many problems, however, still exist with the medical monitoring. Obviously, there are varied opinions. Our situation in the field is often a great deal different than that experienced in a laboratory setting.

The first question is addressed to Dr. MacLeod. What do you suggest we do in a situation where semen needs to be analyzed for motility, but because of logistical problems such as transport delays and time involved, a motility study cannot be done? How do we get the best possible data in these circumstances?

Answer (Dr. MacLeod, Cornell Medical College): I faced that problem about 15 years ago when studying the effects of certain antispermatogenic compounds upon semen quality, and eventually upon the testes, in volunteer prison populations located in widely separated regions of the United States.* The motility readings preferably should be made within 90 minutes after ejaculation but can be reasonably reliable for up to 3 hours. The problem was solved in part during the control phase of the experiments (the examination of three semen specimens before the first ingestion or injection of the drug to be tested) by my personal examination of the motility at the respective prisons for a period of about 10 days. This phase also involved the screening of the volunteers in terms of semen quality before admittance to the various studies. In certain studies, up to 60 prisoners actually were used. Their semen quality had to be good in all important parameters (volume, count, motility, and morphology). Simultaneously during this control phase, I trained the prison hospital technicians, most of whom were long-term prisoners themselves and already competent workers (mostly in hematology), to perform sperm counts and adequate motility readings. They also were instructed in the preparation of seminal smears for later study by me in New York. During the course of several of these studies, each of which

*MacLeod, J. 1965. Human seminal cytology following the administration of certain antispermatogenic compounds. In: Biological Council Symposium on Agents Affecting Fertility. J. & A. Churchill Ltd., London. pp. 93-122.

extended perhaps over the period of 1 year or more, I made periodic visits to the prisons to assess the progress in person, particularly when the reports on motility and my own observations of the morphology indicated a critical phase of the study. In this fashion, I was able to check on the accuracy of the technicians.

I realize that these controlled procedures will be difficult to follow in the present and future assessment of the effects of DBCP on the ejaculate and particularly on sperm motility. The only suggestion I can make is that in any present studies of DBCP in widely scattered parts of the United States rough estimates of sperm motility always should be made and, however crude, be accepted.

A real problem does not exist in regard to the sperm morphology. Seminal smears made at the time of the semen examination can be stored, unfixed and unstained, for extended periods and can be shipped thereafter to central laboratories for the appropriate staining procedures and experienced analysis of the sperm morphology. The latter stage actually is the most sensitive in terms of the possible effect of DBCP on spermatogenesis.

Lastly, in terms of sperm morphology, the entire semen specimen can be stored indefinitely in the freezer compartments of regular refrigerators without disturbing the sperm morphology pattern.

Question (Dr. Troen, Montefiore Hospital): Perhaps today's discussion can be summarized by four questions:

What does one do to evaluate testicular function, including fertility or infertility, for a given patient? The answer is very clear; the literature is replete with techniques to follow, the standards are available, and the medical-biological knowledge is available. This is not a problem for the doctors who are seeing and assessing these patients.

The second, more difficult, question is, How does one follow a group of patients? One has to use the standard epidemiologic techniques and statistical methodologies and be aware of the limitations. In answer to Dr. Meyer's question about field studies, I think Dr. MacLeod pointed out that since you can preserve a specimen for cytology and since the epidemiologic information you would want is more important initially than the detailed information on a specific patient, you would be very well advised not to worry at that point about the absence of motility studies but to make certain all the other factors that are available are also present.

The third question is, How do you assess the cause and effect relationship of a given toxin in a given patient? I don't believe that anyone can answer that question categorically; one can only

make a presumption on the basis of both the animal and clinical data that are available.

The fourth question is, What does society plan to do about these agents in terms of allowing their use to be continued, and how are standards to be set, given the information on the obvious toxicity of these agents that has been presented today and previously?

Comment (Dr. Howards, University of Virginia in Charlottesville): I am a urologist and reproductive physiologist and have had a long interest in male infertility and male reproductive biology. I would like to reinforce some of the points Dr. Troen made.

First, semen analysis does not test fertility. To test fertility, animal scientists and veterinarians take a bull and put him with 10 cows, or take his semen and inseminate 10 cows, to see how many get pregnant. Obviously, we can't do that in men so we do not have a test for fertility in man. I think this is a very important concept that all of the people concerned with this problem should take away from this meeting.

Second, the only way statistically valid conclusions can be drawn when comparing two populations or groups (e.g., men who have been exposed to a certain chemical, or men who have a varicocele, or the men who live in Texas) with other groups is to have the semen tested in the same laboratory by the same people in a blind fashion. If one population tested by one group with one set of methods is compared with a population tested with another set of methods, accurate conclusions cannot be drawn, except in the extreme case of men with azoospermia; that is abnormal, as we all agree.

As far as evaluating the individual, I would like to reemphasize what Dr. Troen has pointed out. The only way to know for sure that any given thing has caused a change in testicular function in that individual is to have pre- and post-exposure evaluations of that individual. If there are going to be continued exposures, the people will have to be monitored before and after exposure, with more than one semen analysis.

There is a social or philosophical problem associated with monitoring single, unmarried men. If we find that a single man has a low sperm count, which may or may not imply infertility, what are we going to tell him? Because there are differences of opinion--many people believe it is not appropriate to inform a young unmarried man that he may be infertile--this is something we will have to think about.

Someone alluded to studying patients 90 days after exposure to a toxin because studies show that it takes approximately 74 days for

spermatogenesis to be complete and 10 days to 2 weeks for the sperm to move from the seminiferous tubule out, through the epididymis, vas deferens, and urethra. I will add a word of caution that I am sure almost everybody is aware of, i.e., if there is an injury by any toxin to the Sertoli cell, which is the most likely site of injury, it might take a month or a week or a year for the Sertoli cell to recover. It would have to be 60, 70, 80, or 90 days after recovery from the injury, not after the insult.

A final word about semen analysis is that, as Dr. MacLeod has emphasized, motility is probably the most important single parameter, although many parameters are important. Unfortunately, it is also the most variable parameter, as demonstrated by Dick Sherins in his longitudinal studies. It is very difficult (tricky) to evaluate motility on one or even two analyses. Motility is definitely affected dramatically by the abstinence period.

Concerning reversibility, the data are not complete. Fortunately, however, if one looks at other things, such as radiation and various known drugs, that affect the seminiferous epithelium in many of the patients, the lesions are reversible--although not in all. At some point you reach the point of no return. If this is analogous to other lesions seen in infertile men, some of these should be reversible. Dr. Whorton's biopsy specimen is most encouraging because at least that man had no fibrosis or permanent changes; hopefully, his lesion is reversible.

We can also be encouraged that up to now there are no documented reports of abnormal children as offspring of men who had various insults to their seminiferous epithelium. There is worry and concern but no documentation that incidence of congenital abnormalities in their children is any greater than that in the children of men who have not had a insult.

Finally, if I could be presumptuous enough to try to answer Dr. MacLeod's question about bone marrow. I suspect DBCP does affect the bone marrow, but the reason we don't see it is that the bone marrow has much more reserve than the testis. Thus, if the testis of an average man is impaired 50%, signs of that will be seen in the semen. If the bone marrow is impaired 50%, it has tremendous reserve and can still keep the circulating blood count normal.

Comment (Dr. Whorton, University of California at Berkeley): I would like to make one comment about the biopsies. Because we put some in glutaraldehyde and are going to look at them under the electron microscope, those 20 biopsies are going to be looked at and discussed further. In the original group of 27, we looked at motility and morphology. We didn't have to worry about those with sperm counts of zero. We found that those with sperm counts of 1 million/ml had both a decrease in motility and increased altered

morphology. The two individuals with counts between 10 and 30 million varied: one had a decrease in motility and the other showed an increase in abnormal morphology pattern. All those above 40 million had both motility and normal morphology.

One of the reasons that Dr. Meyers asked Dr. MacLeod about the practicality of such testing is because we had a logistical problem of trying to collect the semen in central California and then take it to the laboratory 80 miles away (making sure to collect it early enough to get it to the laboratory), plus all the problems inherent in using large numbers. Studying the individual patient is easy; when you start taking 20 to 30 specimens a day, it becomes more difficult. It was not feasible to take the laboratory technicians with us. In the future, I think we will try to do the morphology or cytology assays and sperm counts; we will also save our smears.

Question (Dr. Zavon, Hooker Chemical and Plastics Corporation): I am concerned that there is some confusion in purpose. DBCP has been in production for some 20 years as a pesticide, and as a pesticide, it was evaluated for possible dangers along with all other pesticides with which we were concerned. We had no trouble with DBCP; it was not a material that caused acute poisonings or resulted in problems among users.

Now we are looking at it from a different point of view, and I am curious as to what the logic was in making the decisions concerning respiratory protection. I wonder how many other compounds are pursued in the same way and with the same logic and what their biological impact is that causes this logic to be used. A series of logical steps were given to determine what should be allowed or what type of respiratory protection should be recommended or required and the degree of protection that was ultimately available. Can you give me examples of two or three other compounds where you are requiring or recommending that degree of respiratory protection? What are the biological determinants for the level of protection? You said that other changes can occur if the cartridge is set aside. In terms of the country as a whole, this becomes a very expensive process. Do we really know the life expectancy of the cartridge under these circumstances, with DBCP at the present permissible levels? I am not sure I know where we stand at this point.

Secondly, we have an immediate concern as doctors for the people affected. How can we maintain surveillance? What is a reasonable method of surveillance? I am very skeptical about the ability to determine if the testes diminish in size or not by palpating, unless it is really atrophied. In view of blind studies that have been done on reading chest films and on other sorts of things, I could be even more skeptical about our ability to judge testicular size on the basis of palpation.

Answer (Dr. Kennedy, NIOSH): The whole basis for the respiratory decision logic utilizes the permissible exposure limit. All respiratory protection is based on multiples of the permissible exposure limit to which the worker will be exposed. In the case of escape or entry into unknown concentrations, you want the maximum protection that is available.

In this case, the self-contained breathing apparatus (SCBA) or combination supplied-air respirator (SAR) and SCBA offer the maximum protection. The projection factors are based on studies that have been done over the years and are based mainly on face-piece leakage.

Question (Dr. Zavon): I accept that explanation, but are these recommendations based on the presumption that 10 ppb or 1 ppb is the threshold limit value (TLV), when this limit has been proposed without any knowledge as to what is a reasonably safe level?

Answer (Dr. Kennedy): The TLV or the permissible exposure has not been decided by the respiratory protective people, but is based on epidemiological studies and the data that have been presented from animal studies and studies of that order.

Comment (Dr. Zavon): No, not in this case. What epidemiological studies could support 1 ppb or 10 ppb? We have no data to support it; it is an ex cathedra statement by EPA, OSHA, or NIOSH. It has no data to support it.

Comment (Dr. Meyer): Perhaps it was determined the same way as 1 ppm was decided on originally.

Comment (Dr. Zavon): The TLV was decided on a reasonable basis. The slope of the pharmacological curve in the Torkelson and Hines studies between the effect of 12 ppm and the effects of 5 ppm is a very steep slope. They extrapolated these data, and recommended, using normal, acceptable pharmacological reasoning, that with that kind of slope, it is likely that there will be no problem at 1 ppm. This is the basis we have had to use in the absence of specific data for many years, and we have used them mainly with good results.

Now we run into an instance in which the exception proves the rule. Perhaps there are other chemicals that we aren't aware of yet. But the point is, don't ignore that the slope shown in that work is a very steep slope and that there was a reason that Torkelson recommended 1 ppm. Perry Gehring, in California last week, said he still felt safe with 1 ppm inhalation. Whether he is right or wrong, I can't say; but the point remains that there are no data to substantiate the parts per billion limit that has been proposed by OSHA, EPA, and others. We are talking about a dataless base.

Comment (Dr. Meyer): There are no data except those from Occidental Chemical Company and from elsewhere that the environmental levels are indeed less than 1 ppm. I don't think there is any argument that there are effects. Is that not correct?

Question (Dr. Zavon): That is correct, but skin absorption and one other factor must be considered: the possibility that surges well over 1 ppm have occurred and that these may be critical in this particular situation. I understand that the data from Pittsburg, California, indicated that they had levels showing 0.02 ppm in the air, and supposedly this had no effect on sperm in the people they have monitored to date. Dr. Whorton, do you have any specifics on this?

Answer (Dr. Whorton): I don't have specifics on air levels except that I was told by Dr. Gerlack, the physician for Dow's Pittsburg, California, plant, that he didn't know the levels. He did say that they used DBCP very sparingly. I am uncertain how to evaluate these data if the amount of exposure was really very insignificant.

Comment (Dr. Zavon): I think, though, that we really don't have the data on which to base any sound decision. We have a very intriguing problem, and I would like to urge this group not to foreclose on it. We don't even know that it is DBCP without epichlorohydrin that causes these problems. As far as I am aware, all the material we are talking about contained 1% epichlorohydrin.

Comment (Mr. Davido, EPA): I want to clarify the fact that EPA has no responsibility in the area of setting standards--that is the responsibility of NIOSH and OSHA.

Comment (Mr. Moure, Oil, Chemical and Atomic Workers International Union): I am an industrial hygienist for OCAW and would like to address the comments Dr. Zavon made about the limit of 10 ppb being proposed by OSHA. It is known that we asked OSHA for an Emergency Temporary Standard on August 23, 1977, after we received information about the exposures of people at the Occidental Chemical Company and their vendors. We requested a level, a time-weighted average, of 1 ppb. I can explain the rationale for our requesting that level although I cannot talk about the rationale for OSHA's choosing 10 ppb. Our rationale was that the toxicological information that we were aware of--specifically, animal experiments run by the National Cancer Institute (NCI) and DBCP experiments that were sponsored by Dow Chemical Company concerning ingestion--showed definite evidence of induction of cancer. Since our obligation is to represent workers that handle these chemicals, we believe we'd be remiss if we allowed workers to be exposed in any way, at any level, to carcinogens. So we proposed that the lowest possible limit that could be measured in air should be the standard because the

toxicological evidence shows that a carcinogen, on any level, could produce some effects. Because NCI has stated that there is no way to determine a safe level for a carcinogen, we decided to request the least possible measurable level.

Dr. Gary, from Dow Chemical Company, recognized that fact during the inquiry in California. I am quoting from his testimony: "Even though the NCI studies are of little value for assessing the rates of cancer from low-level exposure to DBCP, the high incidence in the case, indicates to me, that cancer, in particular stomach cancer, may be induced by ingestion of DBCP. This conclusion has been rendered more valid by interim results of a study being conducted by Hazelton Laboratories, as sponsored by Dow."

I am sure that tomorrow we will hear about the rationale from OSHA for establishing the level of 10 ppb.

Question (Dr. Lucier, National Institute for Environmental Health Sciences): Is it possible that toxicological symptoms aren't really related to the inhalation exposure or the levels in the air, but to spillage on the hands and so forth because of the inability or failure to wear protective clothing?

Answer (Dr. Meyer): I think everybody will agree that it is possible. Dr. Whorton?

Answer (Dr. Whorton): If you talk with the exposed workers, especially the applicators, they will tell you that they try very hard not to get DBCP on the skin because it burns. I have heard some people claim that they have literally worked up to their elbows in DBCP, splashing it all over themselves, etc. I doubt if the latter has been true in the past few years. I think that there may be some skin absorption, but certainly DBCP is not being splashed on except for infrequent occurrences. My understanding for the past 3 years at Occidental Chemical Company is that, for the most part, people have been very careful about not getting it all over themselves. The work situation and environment at Occidental Chemical in the last 3 years has been relatively good in that respect. I think the levels that Dr. Rappaport reported have probably been true for the last few years.

Comment (Dr. Tanaka, NIOSH): I have an impression that palpation of testes is going to be very important, at least in industrial screening examinations. Because no one has proposed any standardized method, we would be dealing with inconsistent evaluations. In this respect, I think ophthalmologist are much ahead of urologists in this technology. I suggest that urologists develop a tonometer (e.g., Schiotz' tonometer) or some modification thereof for practical use for standardized testing. They could establish some numerical value on the consistency of the testicle

that may be helpful in preemployment examinations. A sperm examination or biopsy wouldn't be necessary.

Comment (Dr. Nankin, University of South Carolina): I am intrigued with that approach, and perhaps somebody can develop such a system. For about 10 years, there have been ovoid models, called orchidometers, that are quite precise and give volume in the nearest milliliter or cubic centimeter. The only way to get experience in determining normal and abnormal consistency is to get experience by palpating testicles. I don't know any standards for consistency.

One point I do want to make about Dr. Whorton's data on gonadotropin titers is that where there is testicular damage, the hypothalamus and pituitary sense that there is something missing and put out more signals for the testicles--for both sperm production and testosterone production. The magnitude of the elevations that he found in his patients was severalfold greater than we saw in our infertility studies, even in men who had total lack of sperm, apparently on an idiopathic basis. We can infer from his data that we are dealing with a more devastating problem. The kind of defect that the hypothalamus and pituitary sense in that population is much greater than we see in our population of infertile men.

Comment (Dr. Whorton): Dr. Lanham told me of his belief that he felt a different turgor of the testes. He then talked with Dr. Marshall, a urologist, who also examined 10 of the people, some of them very severely affected. Dr. Wilcox examined a fair number of the people we examined. We would all agree that we did not find abnormality in the testes themselves, as far as consistency is concerned, whether normal or not. Usually, we didn't know sperm counts before we started checking. So maybe we were unobservant.

Comment (Dr. Lamm, Tabershaw Occupational Association): I think a system for measuring testicles does exist. When I was a pediatric resident, working in clinics, we used the silastic models from Dow. The usual procedure was to measure both the size and consistency of the testicles using a pocket test, i.e., we would hold the silastic models in a pocket with one hand while the other hand would be on the gonad being examined. We would compare what we felt with the two hands, and when we determined that both hands were feeling the same size and consistency, we had found the appropriate grading. We found that these models worked very consistently from examiner to examiner. Earlier discussion indicated measurement of testicular size based on measuring the size of the normal testicle in people with a cryptorchid testes. I would suggest, though I have no basis in fact, that if there is a question that one of the testicles is abnormal (hidden and small) that there might be a compensatory hypertrophy of the descended testicle, and this might not be the appropriate standard for a comparison.

Question (Dr. Whorton): I would like to ask Dr. Krauss two questions. The FSH levels that we consider abnormal are very different from the levels that Bioscience uses. Can you talk about specificity of androgens? Could you also discuss testosterone production by DBCP in in vitro sections of rats at the levels found in your laboratory?

Answer (Dr. Krauss, Alta Bates Hospital): The FSH anti-sera we used was highly specific. Our normal range, which is based on our unexposed workers, corresponds well with published results for normal ranges in the past and with those of a number of other institutions using highly specific anti-sera. The range is about 3 to 5 mIu/ml of serum. It is important that the most specific anti-sera be used and that this sort of procedure be standardized as much as possible.

I am not familiar with the source of the Bioscience anti-sera. I wonder whether it came from the National Institute of Health's National Pituitary Agency (NPA). I would urge anyone doing studies on exposed workers to make sure that the anti-sera involved is standardized against that of NPA or that of other reputable laboratories using monospecific anti-sera.

Testosterone production has been of interest because we would like to know the specificity of DBCP toxicity. Everything we have seen to date indicates that DBCP is a primary spermatogonia toxin, or a primary spermatocyte toxin, and possibly causes some effect on the Sertoli cell (although we weren't able to document that morphologically). The question is, particularly in view of our results indicating an increase in LH, could there also be some influence on testosterone production? We are still looking at our clinical data in this regard. Dr. Gerry Connell, one of my colleagues at the University of California at Berkeley, has developed a very simple screening test using a system of isolated slices of rat testes in an incubation medium. He has found that adding DBCP in femtogram concentrations was sufficient to supress production of testosterone in in vitro situations. This is, of course, entirely nonphysiological, but it does give some indication that, at least in the rat, there may be more effects than those involving seminiferous tubules. His studies also use concentrations for possible toxicity that are incredibly small and make us wonder whether some of the criteria established for low-exposure monitoring might even be of too high an order of magnitude. I strongly urge people conducting experiments in animal systems to take their low dose exposure down to the lowest possible exposure.

Question (Mr. Phillips, JRB Associates): I am an industrial hygienist and my question is addressed to Dr. Rappaport. Was there local exhaust ventilation or other engineering controls in the areas that you sampled? In doing the survey, did you make measurements in

areas outside the formulating area to determine background concentration? Do you have information that could answer the question of risk to clerical employees in adjacent buildings? If the background concentrations were on the order of 10 ppb and risk were defined as the exposure limit finally adopted in the permanent standard, would clerical employees in adjacent buildings be at risk?

Answer (Dr. Rappaport, University of California at Berkeley): To answer the first question, there was no exhaust ventilation system in the facility at Occidental Chemical where the material was being formulated. The building was semi-enclosed and I think the original design intent was to make the building as much out-of-doors as possible to use natural dilution ventilation to the fullest extent possible. This is not unusual in similar facilities. They are currently installing an exhaust ventilation system in that facility and have had plans to do so for quite some time.

Concerning the second question, we were only able to make measurements on two different occasions. Had we known the obvious importance of the work, I am sure that these would have been made more thoroughly and more quickly. The only short-term exposure data we had were from the immediate formulating area. The measurements varied from about 3 ppm at the highest exposure point--an open part of an essentially closed system where they pour DBCP into the drums--to the lowest concentration in an area across the room in the middle of an open doorway where the concentration was about 50 ppb. I would suspect, just on the basis of those data, that we would probably find a gradient down to 10 ppb in areas immediately surrounding the entire formulating area, depending on what the end conditions were, how many spills of material there had been, etc.

Question (Dr. Blum, University of California at Berkeley): I have several questions that I hope might generate discussion about the action mechanism of DBCP. We have shown that chemicals that cause mutation also cause cancer in many cases. The case of DBCP suggests that some chemicals that cause mutations also cause sterility. Possibly they might also cause genetic birth defects at lower exposure levels.

With the use of an animal test for mutagenicity, called the sperm abnormality test, it as been found that a large percentage of chemicals that cause cancer also cause a high incidence of abnormal sperm. I am interested in knowing if anybody is doing experiments looking at the F_1 generation in animals that have been fed a low level of DBCP. For example, if you feed male rats a low level of DBCP, would their offspring have a higher level of genetic birth defects? Have careful epidemiological studies been done on the families of workers exposed to DBCP to see if there are higher levels of miscarriages and other problems? Someone said there were no known birth defects; I'm not sure how well documented that was.

Answer (Dr. Meyer): Is anyone doing or does anyone know of experimentation being done along these lines? I am not aware of any.

Answer (a speaker): I think there are some teratology studies planned at NIEHS.

Comment (Dr. Blum): Teratology is really a different thing from genetic birth defects.

Comment (Dr. Meyer): In terms of specific epidemiological studies, we have not become involved. Considering that we discovered this DBCP situation the first part of July, that in about 3 months we have been able to put this amount of data together, and that we have enlisted the cooperation of all the people who have contributed to this conference, as well as other sharing of data, much has been accomplished. Unfortunately, there is only a certain amount of manpower and resources that can be devoted to this kind of research, but I think that it will be provided soon. I hope to discuss our current and future plans tommorow, and Dr. Blair Smith, from NIOSH's industry-wide studies, can give us some detail as to the scope of things that we are planning as follow-up studies.

Comment (Dr. Blum): I think the potential insult to the human genetics--the chronic effect in addition to the acute effect--is something that should be considered.

Question (Dr. Meyer): I am going to pose a question that may be very difficult for our panel of semen analysis experts to answer. If you were screening a population of workers under the most adverse circumstance, with data collection less than optimal, at what sperm count level do we begin to become concerned that a toxic substance is interfering with testicular function?

Answer (Dr. MacLeod): The sperm count per se, unless it is very low (less than 20 million/ml), need not be the answer. If, however, you are examining a population with a substantial N value (more than 50) exposed to DBCP and you find 40% to 50% of your group has sperm counts per milliliter under 30 million, you would have reason to suspect that the quantitative aspect of spermatogenesis had been diminished in the group under study as a result of DBCP exposure. Thus, the frequency distribution of sperm counts per milliliter does have considerable value (see Table 1, p. 60).

But, as I have answered in a previous reply to a question of Dr. Meyer's, if the men under study were still being exposed to DBCP, the seminal cytology (sperm morphology) almost certainly would be the most sensitive indicator. Unfortunately, most of the studies reported at this conference are retrospective, i.e., the semen is being examined many months, or perhaps years, after the last exposure to DBCP. In these cases, unless spermatogenesis had been

wiped out completely (no spermatogonia remaining for regeneration), enough recovery in sperm count and sperm morphology could have occurred to mask the earlier effects of the DBCP exposure. I have published evidence along these lines in regard to the recovery of spermatogenesis following almost complete suppression by X-irradiation or by certain drugs.* Such recoveries certainly require many months or even years, but when they do occur, the sperm morphology pattern is restored to the original control level.

I should emphasize that these experiments were performed under conditions that were as carefully controlled as we could make them. The subjects were all long-term prisoners, adapted to their environment, living under the same dietary and ambient conditions, and subject to essentially the same emotional pressures. Their health was carefully supervised. They were willing to supply semen specimens at regular intervals and testicular biopsies when necessary. In most cases, at least six control semen specimens were analyzed before any experimental procedure and at least weekly thereafter.

Dr. Meyer has asked me to suggest a protocol for DBCP experimentation in man. I already have done so in the previous paragraphs but I am reasonably certain, in terms of DBCP or any drug, all experimental work of this sort, particularly in prison populations, has been banned.

However, in all my experience of determining the effects in the ejaculate of a variety of drugs under the controlled conditions described by me earlier in this conference, I believe I can state with reasonable certainty that if a drug is toxic to the testes, the initial effects will be seen in the sperm morphology and not necessarily in the sperm count. Or to put it another way, subtle changes will appear in the sperm morphology and other cellular contents of the ejaculate considerably before an obvious reduction in the sperm count. These damages and their kinetics already have been described by me in the literature and are readily detected by the experienced eye, particularly if control semen analyses on the individual are available. Unfortunately, they are not available in the DBCP studies under discussion. Unless high doses of X or other irradiation (above 200 r) applied directly to the testes comprise the "toxic element," the initial effect on spermatogenesis as seen in the ejaculate will be found at the late spermatid (precaudal) level of spermiogenesis. These cells, prematurely exfoliated, may be seen as early as 21 days after the intial ingestion or injection of the drugs I have studied. We should emphasize, however, that if

*MacLeod, J. 1965. Human seminal cytology following the administration of certain antispermatogenic compounds. In: Biological Council Symposium on Agents Affecting Fertility. J. & A. Churchill Ltd., London. pp. 93-122.

any compound does affect the testis in this manner immediately after the first ingestion or other application, the cellular effect in the ejaculate cannot be seen for at least 15 days if only because it may take that long for the "normal" cells already present in the entire duct system distal to the testes (epididymis, vasa deferentia, etc.) to have been eliminated by ejaculation.

Answer (Dr. Troen): Let me try to answer your question in a different fashion, Dr. Meyer. Unless one accepts the premise that the agent is capable of damaging the testis, a clear answer can't be given to your question. We must start from the premise that this particular substance is known to damage the seminiferous tubule. You use different end points for what you are trying to do. If you are trying to determine whether a material is indeed toxic, you use one end point; if you are trying to find out for a given patient whether he will become fertile or infertile, you use a different end point. The answer depends on what you are concerned with.

Your question reflects the concern: Do clinicians really know how to evaluate someone for testicular function and infertility? The answer is yes, we know how to do it, but you must tell us what you are looking for.

Comment (Dr. Meyers): You still didn't give me the count.

Answer (Dr. Troen): If it is zero, one is always concerned.

Question (Dr. Tucker, NIOSH): Today I presented the feasibility for a charcoal tube method for DBCP at 10 ppb. The charcoal tube samples must be refrigerated for a fairly long storage. I wonder how practical this method is for the worker in the field who takes air samples? How convenient is it for the worker in the field to obtain dry ice for low-temperature storage? Perhaps DBCP would be more stable on another solid adsorbent at room temperature. An attractive feature of a charcoal tube method is that the charcoal tube is commercially available. (Dr. Tucker's original paper has been replaced by a newer paper that indicates the charcoal tube method is unreliable for the determination of DBCP in air at low parts-per-billion levels, at least when toluene is the solvent used for desorption.)

Answer (Mr. Kusnetz, Shell Chemical Company): As a working industrial hygienist, I, too, am concerned with trying to transport samples at -28°C once I have taken them. I would be happy to make available the Shell method for sampling DBCP in which we use Florosil, a known sorbent in GLC techniques. We use hexane to elute the material. For example, spiking at 20 nanograms with 10 observations gave us a mean recovery of 20 nanograms with a standard deviation of 1 nanogram. Storage tests both at -20°C and 25°C up to 15 days gave the worst recovery, but still left 88% of the

DBCP remaining on the tubes. This is fairly good, particularly when talking about field applications.

We have a fair amount of data on other kinds of sampling conditions. The use of hexane as the eluent and the ability to handle, store, and ship at ambient temperatures speaks well for the method. Although it is not commercially available, the technique for preparing the tubes is available and we would like to see it commercialized.

ETHYLENE DIBROMIDE

J. Gordon Burdick* and Jonathan Jacoby+

DR. BURDICK

Ethylene dibromide (EDB) has been used since 1925 as an anti-knock additive in gasoline. In addition to its use in gasoline, EDB has important uses as a soil fumigant and as a fumigant in milling machinery. It has been used extensively in federal, state, and international quarantine treatments since the early 1950's. EDB serves as a basis of treatment to allow the import and export of many fruits and vegetables between the United States and foreign countries. In particular, some of our citrus fruits exported to Japan are fumigated with EDB.

EDB STUDIES

Problems associated with exposure to DBCP in the work environment have caused many of us to wonder about other brominated hydrocarbons--especially EDB since it is a product that is manufactured in substantial volume. Support for this questioning lies in other studies that indicate EDB can affect reproduction in certain animals.

Two recent epidemiological reports, one from Dow Chemical Company[1] and one from Associated OCTEL[2] in England, are being prepared for submission to OSHA and EPA. These reports don't pertain primarily to spermatogenesis; rather they concern about 450 workers with EDB exposures, some dating back to the 1920's. The cancer rate for those employees thought to have only EDB-type exposures is less than the cancer rate for the population at large. This establishes a basis for confidence that EDB does not cause cancer in humans at the levels encountered in a workplace.

In other studies previously reported,[3,4] it was noted that in hens EDB was found to cause a decrease in egg size and egg fertility and cessation of egg laying. In male chicks, the sperm counts were not affected and body and testes weights remained normal.

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In large doses, a reversible effect on spermatogenesis has been demonstrated in rats and bulls.[5,6] We believe there is an adequate safety factor between the exposures producing these reversible effects in bulls and the exposures experienced by most, if not all, workers.

EDB PLANT, MAGNOLIA, ARKANSAS

Although EDB has been used as a major ingredient of anti-knock compounds since 1925, the Ethyl Corporation did not actually manufacture EDB until the last few years. From 1925 until about 1970, Ethyl purchased EDB from a plant at Freeport, Texas. Our manufacturing facility, near Magnolia, Arkansas, has been in operation since 1969. In the early years, another company operated the Magnolia plant for us; we have, however, retained a substantial number of employees who have been with that plant since 1969.

At first, in addition to the manufacture of EDB, this plant also stripped bromine from brine pumped from wells located beneath the plant and beneath adjacent properties. Through time, other processes have been added including the production of vinyl bromide and, more recently, production of some other chemicals. Other brominated hydrocarbons are also involved in the workplace, so that today an individual employee receives mixed exposures--not just exposure to EDB.

We believe that all employees at the plant have had some exposure to EDB. To help clarify our situation, Jonathan Jacoby, who has been surveying the plant for us, will describe the processes carried out at the plant and the types of exposures encountered there.

MR. JACOBY

Ethylene is reacted with bromine to form EDB, which is used primarily as a lead scavenger in lead anti-knock fuels. The production of EDB at the Magnolia Plant has been monitored since 1975. During this time, ninety-five, 8-hour, time-weighted average samples have been collected with levels ranging from nondetectable to 4.5 ppm.

Samples obtained at other locations that blend the EDB into tetraethyllead indicate average EDB exposures of nondetectable to 1.5 ppm. Since the inception of personnel monitoring, exposure levels have decreased by installing engineering controls and improving housekeeping.

Exposures found during blending were less than those found during production of EDB. It should be noted that ambient air levels at gasoline stations near busy roads and at their refineries are approximately 100,000 times less than the levels to which workers are safely exposed during the production of EDB.

DBCP and trimethylene chlorobromide (TMCB, which is also called 1-bromo-3-chloropropane) is made when hydrogen bromide is added across a double bond of allyl chloride. The TMCB serves as an intermediate in the prodcution of chlorobutyronitrile (CBN).

DBCP, in concentrations up to 0.6 percent, is formed as a trace impurity in the intermediate. It is worth noting that this is a completely enclosed system. The only opportunity for exposure is during maintenance or process sampling.

We calculated DBCP work exposure from the following data: the mole fraction of the DBCP in TMCB with the use of Raoult's law and the highest TMCB exposures found from monitoring our employees. The results indicated nondetectable levels. Our highest exposure to TMCB (3 ppm) would result in an exposure to DBCP of approximately 1 ppb, one-tenth of the present emergency temporary standard.

In the past, our average TMCB exposure would result in a DBCP exposure of 0.4 ppb, which is one twenty-fifth of the present temporary DBCP standard. Based on analysis of five, 8-hour, time-weighted, personnel monitoring samples per job classification, for the back-end operator of the CBN process, TMCB exposure averaged 0.75 ppm; for the front end operator, 1.4 ppm.

To provide additional safety, protective clothing, i.e., impervious clothing, is being used to prevent skin contact; sources of exposure, including quality control sampling points and sewers, are being closed or covered to further reduce employee exposure; and an internal Ethyl standard of 0.5 ppm has been recommended to control TMCB. This standard is based on animal testing in the USSR, which indicated a statistically significant reduction in sperm count in chronically exposed rats.[7] In general, recommended standards in the USSR are more conservative than in the United States. We belive that a conservative level of 0.5 ppm will ensure the health of our employees.

After well over a month of additional animal toxicity studies to define the effects of exposure to TMCB, our preliminary information is very encouraging--we have found no reduction in sperm counts in animals exposed to TMCB.

DR. BURDICK

FERTILITY STUDY OF EDB WORKERS

When we first heard of the problems at the Occidental Chemical Company and the problems thought to be related to DBCP, we attempted to assess the fertility of our male employees at the Magnolia Plant, all of whom have had some EDB exposure. The men selected for the study were married, were under age 50 (assuming that beyond age 50 they might have little desire for children), had wives under age 40, and had worked at the plant 12 months before the birth of a child. Of the approximately 106 men, 52 met these criteria. Of these 52, 15 had presumably fathered children; of these 15, 4 had fathered 2 children.

These data were easier to gather than were the semen analysis data. Magnolia, Arkanas, is a small, rural town--the home town of many of our supervisory people. We first talked with Dr. Joe Rushton, a local general practioner, and with the plant manager describing our need for sperm counts on these men. Dr. Rushton agreed to examine all 59 men, obtain medical histories, check prostates, measure testicle size on a subjective basis, and obtain sperm counts and testosterone levels. (Measuring testosterone levels was later dropped.) Tests were not made for follicle-stimulating hormone (FSH) or luteinizing hormone (LH). Of these men, Dr. Rushton believed that five had slightly enlarged prostates, two had sets of testicles adjudged small, and two had testicles adjudged large. The two men with small testicles had sperm counts of 79 and 104 million. The two with large testicles had sperm counts of 12 and 80 million. The five men with enlarged prostates had counts ranging from 31 to 122 million. Except for the noted difference from testicle normality, no correlation could be made among these nine men.

For the semen examination, Dr. Rushton provided each man with a nonspermocidal condom to be used at home, generally in the morning. The condom was to be tied at the top, kept warm, and be brought to the hospital within 2 hours. At the hospital, it was to be examined immediately upon receipt. Because Magnolia is a small town, the sample was probably presented to the hospital for analysis within an hour of collection. Enzymatic action had probably liquified the specimen so it was reasonably homogeneous.

Fifty-nine sperm samples were received, and the count distribution ranged from over 200 million/ml to zero; the median count was 61.4. I, too, found that different literature references indicated different distributions of count normality; I chose the breakdown used in Tables 1, 2, and 3.

Table 1. Sperm counts of 59 employees.

Number of men	Sperm count, million/ml	Percent of total
14	> 100	23.7
29	40 - 100	49.1
9	20 - 40	15.3
7	0 - 20	11.9

Table 2. Sperm count of 59 men by exposure.

Sperm group/number of men	Sperm count, million/ml	Percent of total
<0.5 ppm/ 40 men	> 100	26
	40 - 100	54
	20 - 40	10
	0 - 20	10
0.5 to 5.0 ppm/19 men	> 100	21
	40 - 100	37
	20 - 40	26
	0 - 20	16

Included in these figures is one man whose sperm count was zero. He, his wife (to whom he had been married for 4 years), and his ex-wife agreed that he had been sterile for as long as they had been aware. We don't, of course, have previous sperm counts for him.

Because this is a small group of workers, it is difficult to draw any conclusions. Overall, however, the maintenance workers had a little lower distribution than did the laboratory workers, who we believe had somewhat equal exposures. The workers in the CBN area of the plant are the ones most likely to have exposure to TMCB.

When I asked the plant manager to identiy those people who he thought had had only bromine and EDB exposures, he could identify only five such people. Forty percent of those had sperm counts of over 100 million; the others had counts between 60 and 100 million.

Table 3. Sperm count of 43 workers by work area.

Work group	Number of men	Sperm count, million/ml	Percent of total
Maintenance	5	> 100	26.3
	5	40 - 100	26.3
	5	20 - 40	26.3
	4	0 - 20	21.0
Laboratory	1	> 100	12.5
	5	40 - 100	62.5
	1	20 - 40	12.5
	1	0 - 20	12.5
CBN	3	> 100	27.3
	5	40 - 100	45.5
	1	20 - 40	9.0
	2	0 - 20	18.2
EDB (principally)	2	> 100	40.0
	3	60 - 100	60.0

We then asked Mr. Jacoby to try to identify, using work histories without looking at sperm counts, those men exposed to less than 0.5 ppm EDB and a second (smaller) group of men thought to have had exposures to between 0.5 and 5 ppm. We found a higher percentage of people in the low than in the high exposure group, but I am not sure that that is really a significant difference.

CONCLUSIONS

What does all this mean? First, I think it tells us that the problem of these EDB workers is not anything like that seen in some of the DBCP workers. For one thing, this plant is currently, continuously operating. Everyone has had continuous exposures and, for a variety of reasons, have had an exceptionally high amount of overtime. Many of these men, particularly maintenance workers, have worked much longer than 40 hours a week. The sperm count findings for this group, despite the continuous exposure, are not much different from that of the general population.

Second, since this plant has not been in operation long, I believe that we must continue to check our people and check them better next time. Because we learn from meetings such as this, we will want to check hormone levels and we may change our semen collecting protocol.

Third, and almost immediately, we will again instruct our people and management to reduce worker exposure to EDB to an absolute minimum. In every way possible, our management is doing what they can to provide less exposure and additional safety.

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DISCUSSION

Comment (Dr. Lanham, Dow Chemical Company): After doing the analysis and reviewing the fertility data of a plant that had been manufacturing TMCB for a number of years, I found that the fertility of the men was at least as great as would be predicted, based on U.S. male fertility rates.

For several reasons, I question your type of analysis. Because the birth rates have been falling quite markedly over the last 15 years, the exposure years you are talking about makes a difference, and obviously, the expected fertility of a married couple depends on the age of the couple at that time. With these two factors, you can quite well ferret out what your predicted and expected fertility would be for comparison.

Reply (Dr. Burdick): I believe that at least some of the other manufacturers of EDB have, primarily, taken this approach. We have been pressing them to do some semen analysis. We don't have those data, but we appreciate your help.

Question (Dr. Nankin, University of South Carolina): Since you are now screening all of these couples, are any of the couples experiencing difficulty in conception? To me, this would be as (if not more) important as doing just sperm counts.

Answer (Dr. Burdick): I don't believe so. I haven't specifically asked Dr. Rushton if he has asked that question of anybody. Our plant is very close to the Dow plant where they have had substantial problems, and I believe we would be aware if they had problems. We haven't, however, specifically questioned that. It is a good point.

EFFECT OF ETHYLENE DIBROMIDE ON WORKERS PRODUCING FUEL ADDITIVES

Jeffery A. Lybarger*

The National Institute for Occupational Safety and Health (NIOSH) conducted this evaluation at the request of the Oil, Chemical and Atomic Workers International Union (OCAW) as a health hazard evaluation. The request to evaluate worker exposure to ethylene dibromide (EDB) was prompted by the toxic effect resulting in infertility that was brought to attention by the DBCP problem, the close similarities between the chemical structure of DBCP and EDB, and some past work indicating possible sterility in bulls caused by EDB.

The plant is involved with EDB in the production of fuel additives. To my knowledge, the plant is not involved in pesticide formulation or production, and no chemicals, other than EDB, known to affect sterility of animals are used.

The protocol involved in the study was to try to evaluate employees working in the EDB area of the plant for at least 3 months within the last 12 months. This time was choosen from Dr. Whorton's study, which indicated that workers in his group that had had less than 3 months' contact with the DBCP seemed to be little affected. We immediately eliminated all people with vasectomies and all people that had known causes of sterility before working in the EDB area.

There was some concern about men who had worked around an old EDB distillation column. The company constructed a new distillation column approximately 1 year ago. Five men who had worked in the old area, but not in the new, wanted to be studied. Three of these five men had had vasectomies or a known reason for sterility before working in that area, so only two were studied. (They are not included, however, on Table 1.)

The medical protocol, again, came from Dr. Whorton. The preliminary data from his first 41 workers (already available to us

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at the time of our evaluation) showed that there was no need to perform complete blood counts or general biochemical-clinical screens (SMA 12); therefore, the workup consisted of luteninizing hormone (LH), follicle-stimulating hormone (FSH) and testosterone assays, and a sperm count. The laboratory data were processed through National Diagnostic Laboratories, which has a branch laboratory in the town. The delay between the time the workers brought the sperm specimens to the company and the time they were received by the laboratory was very short. I used sperm count, not sperm motilities, because I was working with an unfamiliar laboratory in a different part of the country and didn't know how good their technicians were; the sperm count was something I could do and could rely on the accuracy of the results.

The physical examination consisted of measuring testicular size and consistency. I palpated the testes of all the workers myself by grasping the testes on the longitudinal and vertical axis between my fingers and measuring them with a centimeter ruler. Gynecomastia was measured by palpation, and an indication of the male hair distribution was noted. The history form not only had demographic data but included, as far as medical history was concerned, possible causes of reduced sperm count, e.g., prostatitis, mumps, forms of orchitis, forms of veneral disease, or other major illnesses.

When the workers came to see me during their shift, I spent some time describing the study and explained to them what we wanted. I gave them a urine cup to take home with them, asking them to abstain from any ejaculation until they produced a specimen the next day before they returned to work. I asked for masturbatory samples. For those who indicated a dislike for that method, I allowed coitus interruptus. The shortest time period for return of samples was about 24 hours; it depended on whether the worker came to work the next day or waited several days.

On physical examination, I found no worker with gynecomastia, no worker with an abnormal hair distribution, and no worker with any testicular atrophy or abnormal consistency. The history of illnesses detected some illness of varying effect on reproductive potential.

The company was requested to search through their staff for office workers who had had no exposure to EDB; on my first trip to the plant, however, we had only three volunteers. On our second trip, we would like to expand greatly the number of controls.

On Table 1, those workers with a sperm count of <30 million/ml that might be explained by their medical history are indicated with a $^{+}$. Five people who initially indicated they would participate and produce a sperm sample did not supply one; these are indicated on the table by NA. Two workers with reduced sperm counts had other

Table 1. Hormonal assay and sperm count data for workers exposed to EDB and for three controls.

Worker number	Years exposed	Age	Last child	Sperm count, X 10^6/ml	FSH, mIu/ml	LH, mIu/ml	Testo-sterone, ng/dl
1	5-10		1973	NA*	11.5	31	485
2	>10		1966	40	7.2	15.9	608
3	>10		1964	1.2+	37	47	765
4	5-10		1971	217	17.5	9	648
5	>10		1964	33	22	27	465
6	>10		1962	60	31	52	300
7	<5		1976	56	12	165	400
8	<5		1959	23+	13.8	26	600
9	<5		1972	NA	18	39	613
10	<5		1972	107	21	31	300
11	>10		NA	60	13.5	20	335
12	<5		1962	NA	8.4	19	195
13	5-10		1969	98	7.7	200 †	495
14	5-10		1974	6.8	7.3	20	380
15	<5		1976	77	17	21	543
16	5-10		1975	NA	10	15	500
17	<5		1976	52	9.5	23	1035
18	<5		1976	61	8.3	13	753
19	5-10		1966	40	13	19	rerun
20	5-10		1975	64	8.6	15	583
21	5-10		1975	NA	10	18	340
22	<5		1966	8.8	13	16	QNS~
Range	0.75-16	26-46		1.2-217	7.2-37	9-52	195-1035
Mean	6.31	35.32		59.11	14.42	23.50	517.15
S.D.	4.72	6.54		50.30	7.72	11.10	169.20
CONTROLS							
23	0		1956	79	20	16	600
24	0		1958	102	8	11.2	420
25	0		1969	79	13	11.2	520
Range	0	35-49		779-102	8-20	11.2-16	420-600
Mean	0	42.3		86.67	13.67	12.8	513.33
S.D.	0	7.02		13.27	6.03	2.77	90.18

* Not available.
+ Sperm count might be explained by past medical history.
† Questionable.
~ Insufficient quantity of serum.

explanations in their medical histories that could account for the reduced count. One LH value is questionable, one worker's testosterone assay is being repeated, and one worker had an insufficient quantity of serum.

Because there were only three controls, any comparison between the two groups should be interpreted with caution. The mean ages of the two groups were similar, 35 and 42. The sperm count values were 60 million/ml as compared with 86 million/ml; this simply indicates that the control group must be significantly expanded. If there were an adequate number of controls, these figures would be more meaningful. The FSH results were not very different, although the LH results were--23 mIu/ml as compared with 12. The testosterone results showed no difference (517 ng/dl as compared with 513).

The major conclusion that I have drawn from these figures is that we are not seeing the great reductions in sperm count that the people working with DBCP displayed. No one had a zero count, and only four people had reduced sperm counts.

DISCUSSION

Question (Mr. Davido, EPA): Did you record the abstaining times?

Answer (Dr. Lybarger, NIOSH): No.

Question (Dr. Lipschultz, University of Texas Medical School): When a patient brings in a specimen, is the jar labelled with his name?

Answer (Dr. Lybarger): Each worker was assigned a number.

Comment (Dr. Lipschultz): We have found it helpful to put a blank label for the worker to write in the time of collection and the date of last ejaculation. The information is then available for the records.

Comment (Dr. Lybarger): I am going to recontact the workers. Letters have already been written to those who had counts under 30 million/ml asking their further cooperation in the study and asking them to estimate the amount of time between their last ejaculation and production of the specimen. I would like to see as many of that group as I can again. In the letter, I indicated I wanted a second specimen from them, with a more controlled abstience period, preferably 72 hours.

Comment (Dr. Lipschultz): Although people have been saying, "Well, the testosteronea are usually normal," I believe testosterone is important in terms of its effect on LH. A high LH with a normal testosterone level could be very important because it is telling you that for the Leydig cells to produce a good level of testosterone, you have to have more LH. Testosterone level alone is not nearly as important as how it reflects the LH level; these two things have to be viewed as one system and taken into account that way rather than as isolated values.

Question (Dr. Lybarger): Can LH and testosterone be run into a simple correlation?

Answer (Dr. Lipschultz): Yes, as far as LH and testosterone are concerned the system is pretty reliable. FSH, however, is much less well understood.

Comment (Dr. Lybarger): I was somewhat concerned with the difference in LH between the controls and the workers. This wasn't

what had been found in other studies. I was surprised that the LH and not the FSH was elevated.

Comment (Dr. Krauss, University of California at Berkeley): I want to remind us again that interpreting the FSH and the LH levels in different studies depends heavily on getting comparable antisera. Again, I think the interpretation of the results has to be suspended until we get some comparable data.

Question (Dr. Zavon, Hooker Chemical Company): Dr. Lybarger, were any other brominated compounds, other than EDB, produced in the plant? My understanding is that a tri-brominated compound is produced in that plant. One reason we were interested in the matrix being developed is because a mono-brominated compound is produced in the plant that Dr. Burdick reported on.

Answer: The industrial hygienist (Gary White) that took the environmental samples at Occidential Chemical Company didn't indicate any other brominated compounds there.

Answer (Dr. Lybarger): I can only say that the workers I asked to participate in the study were those specifically involved with EDB production or use. Whether they had another exposure, I can't say.

Answer (Dr. Calandra, Northwestern University): The exposures in question started back in 1962, and the new plant started up a year ago. The EDB levels that I have been told about are in the low parts-per-billion range. To my knowledge there have been no tribromo compounds prepared there.

Question (Dr. Meyer, NIOSH): Dr. Troen, in light of the data presented yesterday, can you comment on the data presented this morning and give us some indication about differences between DBCP and EDB, if, indeed, you can draw any?

Answer (Dr. Troen, Montefiore Hospital): If I adequately understood the data, it appears that there is not the same kind of clear-cut time-dose relationship demonstrated this morning as we were shown so very nicely yesterday. If that is the case, then the question of degree of toxicity and degree of pathogenicity remains to be established. I am not certain I could say much more than that considering the limited numbers and limited information concerning time-weighted exposure that we were given today.

Question (Dr. Meyer): But you do agree that there was not the same obvious problem in today's data as in that presented yesterday?

Answer (Dr. Troen): Yes, assuming there was the same degree of exposure. When the exposure information (which was not as complete

as yesterday's) and the fewer numbers of workers are considered, there seems to be less general toxicity.

Indeed, my initial impression of the material presented today is that the distribution, as Dr. Burdick pointed out, is very close to what might be expected from a population that had not been at risk to a known amount of toxins.

Comment (Dr. Burdick, Ethyl Corporation): I believe these EDB exposures were for as long as the DBCP exposures. This is not well quantitated, but certainly a large number of our workers have been there since 1969. I don't believe there are many whose DBCP exposure is like that.

Comment (Dr. Troen): I wasn't certain that the quantitation of the sperm counts in relation to the exposure of individuals had the same kind of correlation that was shown to us yesterday.

Question (Dr. Meyer): Dr. Whorton, would you be willing to discuss the graded pathology from the testicular biopsy specimens taken in California?

Answer (Dr. Whorton, University of California at Berkeley): The first slide (see Figure 9, p. 25) illustrated normal appearing testicular tissue from a man exposed for 3 months. Figure 11 (p. 27) showed tissue containing almost only Sertoli cells within the tubules with a minimal amount of fibrosis around the tubules and no other information. This man had been exposed for about 10 years. Figure 12 (p. 28) showed tissue from a person (exposed for 1 year) who had a moderate loss of spermatogonia and spermatogenesis in general. There were a few spermatogonia in some of the tubules from the tissue of some azoospermic men. Some, who had been exposed for a couple of years, had foci of apparently normal spermatogonia and then huge areas lacking any spermatogonia. From this, the pathologists were actually able to grade the tissue they saw: this person appeared best, second best, third best, etc. I was able to say, this man was exposed this long--this man was exposed that long. It was a fairly good gradation with time so that the histology we saw was confirmed.

Question (Dr. Troen): Were all these slides of the same type of toxicity? When histology specimens from infertile men, or oligospermic men, are reviewed, arrest at different levels of development may be seen, or some may have sloughing in the tubular lumen. Were none of these things present? Was there only a single type of defect, just quantitatively different?

Answer (Dr. Whorton): A few biopsy specimens indicated arrest at different levels of development, but the main thing was the quantitative type. Dr. MacLeod reviewed all the slides and can comment on this.

Answer (Dr. MacLeod, Cornell University Medical College): First, I must express my gratitude to Dr. Whorton for the privilege of viewing his testicular biopsy material obtained from 10 subjects exposed to DBCP for varying and, in most cases, extended periods. At the time of my review, it was my understanding that these subjects either had very low sperm counts in their ejaculates or were azoospermic.

With the exception of the last three subjects in Dr. Whorton's table, my overall impression of the germinal epithelium was one of marked denudation or devastation back to the level of the spermatogonium and, in an occasional case, even the spermatogonia were absent or when present, appeared abnormal. I will add at this point that I found little evidence of peritubular fibrosis in any of the biopsies, which suggested to me that the effects of DBCP were imposed directly upon the germinal epithelium or upon the hormonal support necessary for normal maintainence of spermatogenesis.

Earlier in these proceedings (p. 93), I described, in my experiences in prison populations, the effects of certain antispermatogenic drugs on the testes and on the cellular aspects of the ejaculate. These observations are pertinent to the present discussion of DBCP and the possible kinetics of the action of the compound on the testes; as such, I believe they deserve reemphasis at this point. Perhaps the most illustrative experiments are those that concerned a compound (N, n'-bis dichloroacetyl-1,8-octane diamine),* one of a class synthesized at the Sterling-Winthrop Research Institute as a highly effective amoebicide, given orally in lower animals (rats, rabbits, etc.). In toxicologic studies over extended periods in these species, it was found to be nontoxic with an important exception--namely, that it was highly antispermatogenic.

When these studies were transferred to the human in the form of volunteer prison populations, I was invited to participate by performing all the semen analyses, before and following the daily oral ingestion of this compound at various dose levels. Several semen specimens from each participant in the study (selected for good semen quality--high sperm count, usually above 80 million/ml; good motility; and excellent sperm morphology, more than 70% normal oval form--were seen over a period of 30 days before the first ingestion and twice weekly thereafter. Control testicular biopsies were obtained and repeated at obvious critical periods in the ensuing sperm count depression. Obvious effects on the sperm morphology were apparent. The participants were under careful

*MacLeod, J. 1965. Human seminal cytology following the administration of certain antispermatogenic compounds. In: Biological Council Symposium on Agents Affecting Fertility. J. & A. Churchill Ltd., London. pp. 93-122.

medical supervision including CBC's, liver function tests, etc., throughout. Obvious effects, other than those of the testes and the ejaculate, were not found. A summary of the principal effects in terms of the ejaculate and the testes are as follows:

1. The first effect of the drug may be seen in the seminal cytology within 30 days after the first ingestion and may precede a depression in the sperm count or obvious effect upon the sperm motility.
2. These changes in the seminal cytology normally are manifest in the appearance in the ejaculate of immature germinal cells (late spermatids in the precaudal stage).
3. During the stages in the sperm count depression that may not be seen until 40-50 days, the cephalic sperm morphology may degenerate (appearance in the ejaculate of "tapering" and amorphous forms) and be accompanied by an increased exfoliation of the immature form (spermatids).
4. The above cytologic damage becomes more obvious as azoospermia is approached; the latter stages, in terms of the drug under study, may be reached about 80 days after the first ingestion.
5. At or close to azoospermia, a testicular biopsy usually shows the germinal epithelium damage to be composed of the middle and late stages of spermiogenesis with only minor, if any, disturbances in the premeiotic phases of spermatogenesis. These biopsies show obvious premature exfoliation of spermatids into the lumen of the seminiferous tubules.
6. All of the above effects were completely reversible within 100 to 150 days after cessation of the drug intake, with spermatozoa first reappearing in the ejaculate within 50 to 60 days.

The points in the above summary are applicable to the effects of other drugs (e.g., certain of the synthetic sex steroids, certain acute allergic reactions, and viral diseases) on the human testis, both in terms of the rapidity of testicular response and the kinetics of testicular depression and recovery as seen in the ejaculate.

Before proceeding to an analysis of the above results and their relationship to Dr. Whorton's observations on the effects of DBCP, I should cite the effects of direct and measured doses of X-irradiation on the testes and on seminal cytology in a limited number of subjects.* I was invited to examine only the seminal cytologies of these men before and following the irradiation (the sperm counts and testicular biopsy readings were performed by the

*MacLeod, J. 1974. Effects of environmental factors and of antispermatogenic compounds on the human testis as reflected in the seminal cytology. In: Male Fertility and Sterility. Edited by H.E. Mancini and L. Martini. Academic Press, New York. pp. 123-148.

experimenters and the results transmitted to me). Two of these cases receiving different doses of radiation deserve brief mention because their seminal sperm morphologies reflect the levels of spermatogenesis affected by radiation in terms of dose and because they are examples that recovery of normal spermatogenesis is possible after sterility is produced by radiation.

The first case received 235 r directly upon the testes. His control sperm count (a mean total of 715 million in 10 specimens) was high but, fortunately, in an experiment of this type, his control sperm morphology was anomalous in that between 40% to 50% of the spermatozoa present were of the microcephalic variety, and most of the remainder were the normal oval forms. No immature forms (spermatids) were present. Thirteen days after irradiation, the sperm count and sperm morphology remained unchanged or higher, as would be expected since these cells were already in the duct system before the radiation. However, on post-irradiation day 40, a sharp reduction in the total sperm count was obvious without a hint of any disturbance in the sperm morphology patterns. At day 96, only a very occasional spermatozoon remained in the ejaculate but enough, after intensive coverage of the stained smear, to allow a reading of the sperm morphology pattern. It was unchanged!

Thereafter, and for a period of 13 months, regular semen examinations showed the ejaculate was devoid of spermatozoa except for the inexplicable and very sporadic identification of an occasional mature spermatozoon in the stained smear. I use the term "inexplicable" because I had been assured by my colleagues that at least two testicular biopsies obtained from this subject during the 13-month period of apparent azoospermia showed inhibition of spermatogenesis back to the early spermatogonium level. Thus, the new generation of spermatozoa (low in total number) appearing in the ejaculate after the 13-month span of sterility had to be derived from the spermatogonia surviving the effects of the radiation. My morphology readings on these cells showed the original control morphology pattern (high percentage of microcephalic) spermatozoa to be reproduced in precisely the same ratios as those found before the irradiation. The latter finding was most significant to me because it appeared to confirm for the first time, and in experimental fashion, the thought long held by me--namely, that anomalous patterns of sperm morphology so consistently found as a "steady state" in certain individuals are genetic in origin, imprinted in the spermatogonia, and not acquired in the later stages of spermatogenesis.

A further footnote to this case, and again in relation to Dr. Whorton's testicular biopsy findings, is that although obvious recovery of "normal" spermatogenesis did not occur for at least 13 months after irradiation, a return to the control total sperm count production in the ejaculate was reached slowly and not attained for

nearly 3 years. Thus, one can offer a modicum of hope for eventual recovery to those subjects of Dr. Whorton and Dr. Scharnweber who apparently were either sterilized or brought close to that level by prolonged exposure to DBCP, provided that enough spermatogonia remain for regeneration. Further evidence for this assurance has been provided in a paper by us in a long-term study of subjects exposed to atomic radiation.* For further details on the X-irradiation case discussed here and in another case exposed to 600 r directly to the testes, the original data should be consulted.*+

Comment (Dr. Whorton): To amplify on the 10 men we biopsied:

No. of men	Sperm count, million/ml	Exposure
3	azoospermic†	>4 years
1	1	3 years
1	10	1 year
1	vasectomy	3-1/2 years
1	vasectomy	1-1/2 years
1	50	3 months
1	23	1 hour/day, 7 years
1	100	3 years exposed/ 3 years not exposed

†Sertoli cell only.

The last three were the most normal appearing. The man who had 3 exposed and 3 nonexposed years still had an overall appearance of decrease in absolute number of spermatogonia and of functioning spermatogenesis, but he obviously had enough to make a reasonable sperm count. With the two vasectomized men, we saw what you often see in a vasectomy--granulomas. We could even pick that up on the pathology.

Question (Dr. Krauss): Do you have any information from long-term followup with your radiation subjects? Can you follow up for possible carcinogenesis.?

Answer (Dr. MacLeod): The subjects were not mine. I saw only the seminal smears for reading the sperm morphology and am not aware

*MacLeod, J. 1974. Effects of environmental factors and of antispermatogenic compounds on the human testis as reflected in the seminal cytology. In: Male Fertility and Sterility. Edited by H.E. Mancini and L. Martini. Academic Press, New York. pp. 123-148.

+MacLeod, J., R.S. Hotchkiss, and B.W. Sitterson. 1964. Recovery of male fertility after sterilization by nuclear radiation. J. Am. Med. Assoc. 187:637-641.

at this time (1979) of any long-term followup on their general physical condition, particularly possible carcinogenic effects.

Question (Dr. Whorton): I think the question is: We have seen people who have been irradiated develop, among other things, thyroid cancer many years later (this has been shown especially in the Hiroshima-Nagasaki followup). If DBCP acts like radiation, are we going to see something in 30 years?

Answer (Dr. MacLeod): I am afraid that none of us is in a positon to speculate unduly on the long-term effects of DBCP in terms of carcinogenicity or in the possible similarity of the effects of DBCP and irradiation of any sort.

Comment (Dr. Vernon, Colorado State Health Department): There are at least two areas about which I am greatly concerned: one is standardization of techniques, the other is controls. We have had many different studies with many different collection methods. Dr. Krauss expressed concern about the way in which the FSH studies were done, which laboratory was used, and which agents were used.

The Denver example of the first round of sperm counts was unhappy not only from the point of view of the company and from those epidemiologists who are looking at this, but certainly for those particular individuals who happened to be screened by an inadequate technique in that first round. So we must talk more specifically about techniques; we must be doing them well, and they must be reproducible and reliable.

Perhaps the issue of controls is even more important. Adequate studies cannot be done without adequate control groups. I don't believe the individual is an adequate control for himself; certainly not in the situation we are dealing with here. The vagaries of geography, time, socio-economic background, ethnic group, etc., are most important.

Answer (Dr. Meyer): Your comments are well taken. When we began planning this symposium, we had no hope that we would solve all the problems and answer all the questions that would be generated in this 2-day session. My primary objective was to make those questions made known to everybody, so that during an appropriate followup period, we can solve these particular problems that you address, as well as some other concerns that other members of the audience have expressed.

PRELIMINARY EPIDEMIOLOGY STUDIES OF COHORTS OF DBCP- AND EDB-EXPOSED WORKERS[1]

Frank L. Davido,* S. Hope Sandifer,+ and Roger Glass†

FRANK DAVIDO

The Human Effects Monitoring Branch of the Environmental Protection Agency's (EPA) Office of Pesticide Programs was given the responsibility of developing a cohort of workers and applicators who used and/or were exposed to DBCP and EDB in the field.

Based on a pesticide usage survey conducted by the Human Effects Monitoring Branch, five projects from our Epidemiologic Studies Program (ESP) (in California, South Carolina, Texas, Mississippi, and New Jersey) were assigned this work in appropriate areas of the country where these chemicals have been most widely used. The ESP projects are EPA contracts with State health departments or university medical schools. These contractors have worked jointly on previous studies and maintain a laboratory quality control program. All projects utilized the same protocol for this study. Our studies are still on-going, and to date, approximately 165 people have been examined. Of this number, nine have been exposed only to EDB; the others have been exposed primarily to DBCP.

The information Dr. S. Hope Sandifer, the Center Director of EPA's South Carolina project, will present is only our most preliminary data.

S. HOPE SANDIFER

THE EVALUATION

Our evaluation of workers using DBCP and EDB includes sperm counts and motility; morphology; FSH, LH, and testosterone; exposure history;

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complete physical examination; and SMA-12. The eight-page form used to collect background data on these people reports on such information as the hours since they last ejaculated; their exposure to these compounds (in the last 3 months, 6 months, year, lifetime); how many and the birth dates of the children they have; whether or not they want to have more children (we found only one person who wanted to have more children), etc.

At the present time, sperm counts are being done (one technician is doing them all); motility checks were done at the time of the physical examination; for the morphology data, Dr. MacLeod is going to examine the smears that were made); FSH and LH are being done (some of the first 14 FSH's look high by our standards); testosterones are within the normal range although no correlations have been done; and SMA-12's were done because we wanted to make sure that we didn't have diabetics or people with liver disease that we didn't know about.

RESULTS

The use survey that we did in 1974 indicated that in that year about 10 million pounds of DBCP were used: about 5 million pounds in California, 3 million in South Carolina, and the rest was split up, mainly in the Southeast.

A preliminary listing of 54 workers using DBCP is given in Table 1. We arbitrarily divided the sperm count at 20 million/ml. We found four custom applicators; these men probably use the compound as much as 5 days a week, 15 weeks a year, mainly building new golf courses. One of these men has had no exposure for 2 years; his count was low. (Incidentally, in the South Carolina phase, we found nobody with zero sperm.) In the group of farmers, mainly from Arkansas and Tennessee, three had low counts. Of these, one had a moderate varicocele; one had an enlarged liver (but his liver

Table 1. Preliminary sperm counts of 54 workers using DBCP.

Exposure	No.	Vascetomy	No sample	Sperm count >20M	Sperm count <20M
Mixers	10	0	1	3	6
Custom applicators	4	2	0	0	2
Farmers	19	2	2	12	3
Sales	9	3	0	6	0
Research	12	0	1	11	0
Total	54	7	4	32	11

function studies by SMA-12 were normal); and the third one, age 58, gave a small volume, about 0.5 cc. This last man is probably not an adequate person to study. The research people came from agricultural colleges in South Carolina and Arkansas; they were all within the normal range.

The sperm counts of 44 of these 54 workers are given in Table 2. The count (million/ml) for the mixers ranged from 162 to 0.6; for the custom applicators, from 4.8 to 2.2; for the farmers, from 222 to 1.8; for sales, from 162 to 54; and for research workers, from 179 to 34 million/ml. Some of the workers were, for various reasons, unable to produce specimens. All of these men said they would have a count done by their doctors, but because the quality control wouldn't be the same, they will not be included in our group.

Table 2. Sperm counts from 44 of 54 workers using DBCP.

Exposure	No.	Mean age	Sperm, millions/ml				
			Mean	S.D.	Highest	Lowest	<20M
Mixers	9	28.9	32.0	51.0	162.0	0.6	6
Custom applicators	2	34.5	3.5	---	4.8	2.2	2
Farmers	15	38.9	51.2	55.7	222.0	1.8	3
Sales	7	35.7	97.5	42.1	162.0	54.0	0
Research	11	43.4	87.2	59.0	179.0	34.1	0
Total	44						11

Figure 1 illustrates the cumulative frequency distribution of 56 workers using DBCP in South Carolina. The count is from less than 10 to over 100 million/ml. The frequency distribution of these 56 workers is about that of the 9,000 people included in MacLeod's data.[2]

The preliminary data gathered by the other EPA projects are summarized in Table 3. In the California study, two applicators and one farm worker had zero counts. One, however, was a coding error--the man had had a vasectomy. Another man had a history of infertility.

We have not uncovered any fertility problem in the people we have seen. The motivation of these people who work with DBCP is to save a chemical compound that they believe is valuable to agriculture; it is not because of any concern about their health. These people think this compound is safe; they have no concern about their health; they are not scared by the publicity that has come out.

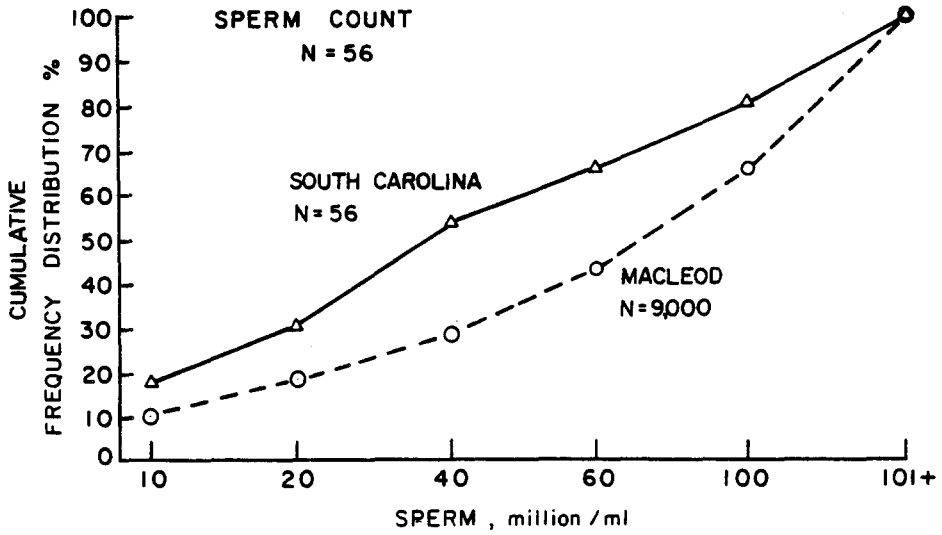

Figure 1. Cumulative frequency distribution of 56 workers using DBCP in South Carolina (——) compared with that from MacLeod (- - -) (Reference 2).

Table 3. Prelminary data of workers using DBCP and EDB in Texas, New Jersey, and California.

Exposure	No.	Sperm count, millions/ml Mean	High	Low
		DBCP		
Texas				
Farmer	8	53.1	110.3	16.6
Irrigation worker	4	53.7	53.0	12.6
New Jersey				
Farmer	4	66.2	105.0	38.0
California				
Applicator	60	57.3	239	0(2)*
Farm worker	13	98.9	465	0(1)
		EDB		
Texas				
Inspectors	8	77.1	153.3	8.7
Florida				
Fruit fumigators	16	---	---	---

*The zero count represents one person who had had a vasectomy and one with a history of infertility.

Is there a health problem from the use of this compound by the people who use it? My current thinking (and it may change because these findings are, admittedly, preliminary) is that I don't think so. For the people who manufacture and mix DBCP, I am personally convinced that there is a problem.

FRANK DAVIDO

As Dr. Sandifer has mentioned, EPA has other studies going on. In Michigan, Texas, and California, we have a good possibility of developing a cohort of EDB-exposed people. We will be continuing the one in Florida.

EPA is also looking into DBCP and EDB soil and air exposures. In Maryland, plots in strawberry fields have been treated with DBCP, and soil and air samples have been collected. In Mississippi, soil samples have been taken from DBCP-treated soybean fields, and in Florida, air and soil samples have been taken after turf application of DBCP.

In Maryland, soil and air samples have been taken on EDB-treated plots, and in Florida, air samples around EDB citrus fumigation chambers will be taken.

At this time, the EPA has taken the following regulatory action. On September 8, 1977, the Administrator issued a notice of intent to suspend DBCP. This is an interim action. DBCP is described as an imminent hazard, and its distribution, sale, and use are prohibited. Shortly after the notice for suspension, or notice of intent, the Office of Special Pesticides Review issued what is called an "RPAR," a Rebuttable Presumption Against Registration. The animal test data developed by the National Cancer Institute indicated that DBCP in animals is carcinogenic and triggered this issuance. The next process, if the Agency finds it necessary, would be a suspension order and then an intent to cancel registration.

Dr. Roger Glass, who has worked with the California project in collecting information, is with us. Would you comment on that project, Dr. Glass?

ROGER GLASS

The California study,[3] which was done by the California Department of Health with help from the California Department of Food and Agriculture, had several distinguishing features. First, we felt that it was critical to have an appropriate control group.

There are no normal values for the distribution of sperm counts in a healthy population and no acceptable cutoff point below which a man is uniformly infertile. Dr. MacLeod's data are based on his experience with men being evaluated for infertility, and other studies have examined men prior to vasectomy--neither of these can be considered a normal population. Men in our control group were chosen in the same fashion as men in the exposed group except for their history of work with DBCP. Many men worked in hot temperatures, which we know will affect the sperm count, and some were subjected to the vibration of tractors 10 hours a day. Furthermore, great variability in sperm count can be introduced in the field work (e.g., days of abstinence before giving a specimen), handling of specimens (e.g., time and temperatures maintained between collection and analysis), and counting (e.g., adequacy of mixing prior to counting).

Secondly, in California, we have tried to use pesticide-use reports as an objective way to select the pesticide users and applicators to be included in this study. This prevents the bias of having men who are worried about their fertility selecting themselves into or out of their designated group.

Finally, because we are looking at smaller, possibly subclinical effects on sperm-count depression, the problems of sperm-count variability will be much more important since we had no one with a zero sperm count from their exposure.

ADDENDUM

The final report on DBCP is contained in "Spermatogenesis in Agricultural Workers Potentially Exposed to 1,2-Dibromo-3-chloropropane (DBCP)" by the Epidemiologic Studies Program, Human Effects Monitoring Branch, Technical Services Division, OPP, OTS, EPA, March 10, 1978.

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1. To be published as: Spermatogenesis in agricultural workers exposed to dibromochloropropane (DBCP). S.H. Sandifer, R.T. Wilkins, C.B. Loadholt, L.G. Lane, and J.C. Eldridge. Bulletin of Environmental Contamination and Toxicology. December 1979.

2. MacLeod, J., and Y. Wang. 1979. Male fertility potential in terms of semen quality: a review of the past, a study of the present. Fertil. Steril. 31:103-116.

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THE PROPOSED PERMANENT STANDARD

Eula Bingham* and William Demery+

EULA BINGHAM

The proposed final standard for DBCP is near completion.† Because we have worked in close cooperation with at least two of the industries involved in the manufacture of this pesticide, it has been possible for us to get out the emergency temporary standard (ETS) in 3 weeks, a record for the Agency.

With this particular standard,, there was intensive collaboration with the Environmental Protection Agency (EPA) and communication with the Food and Drug Administration (FDA). As some of you are aware, there is a question of jurisdiction of workers in the area of pesticides between OSHA and EPA. For this particular material, there was total cooperation--cooperation that will make us more effective, as well as efficient, in controlling substances such as this one.

Mr. Demery will comment on some points in the emergency temporary standard.

WILLIAM DEMERY

I would like to comment on our future plans with respect to the change from the ETS to the proposed permanent standard and also on the problems that a regulatory agency such as OSHA has because it is not involved directly in the scientific research that serves as the background for these standards.

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†The final standard on occupational exposure to DBCP was published in the Federal Register March 17, 1978. This standard limits worker exposure to 1 ppb averaged over an 8-hour workday and prohibits eye and skin contact. Reprints of this Federal Register notice are available from the OSHA publications office.

As an agency, we are interested in ranking the potency of carcinogens and other chemical substances (as presented by Dr. Blum yesterday). Eventually, we hope to be able to rank-order chemical and carcinogenic substances in a system that could be used to set priorities for inspections. One of the difficulties of this task is exemplified by the fact that there is a list of approximately 25,000 substances listed in the Registry of Toxic Effects of Chemical Substances (published by NIOSH[1]), including about 40,000 substances listed by chemical trade names. Trying to find all of the information on all these chemicals is very difficult. OSHA has standards for about 420 of these substances right now. For those substances that we know we should be aware of, we would like to establish priorities and use a systematic approach to their control, or to the inspection for their control. Approximately 10,000 substances are used in industry in the United States in excess of a ton per year. We hope to concern ourselves with those substances that are used in large quantities, have a large number of workers exposed, and have a high toxic rating.

Dr. Bingham has made the decision that OSHA will eliminate those standards that do not directly affect safety and health.* We will try to simplify the standards so they are more easily understood.

The ETS for DBCP was published on September 9, 1977, and the permanent standard will be published shortly in the Federal Register. Before I discuss some of the differences in the proposed standard from the temporary standard, I would like to discuss some of the problems facing us when determining standards.

DETERMINING STANDARDS

Some of the evidence considered for establishing the ETS is included in the preamble of the standard, including that sterility had been found in employees in several plants where exposure to DBCP was in some cases brief and, in most cases, low level. When this was coupled with the evidence of animal carcinogenicity, the Agency

*On October 24, 1978, OSHA published a final rule in the Federal Register revoking 928 provisions of its general industry safety standards deemed unrelated or no longer necessary to job safety or health.

+A new permanent lead standard was published by OSHA in the Federal Register November 14, 1978, with the main provisions of that standard going into effect March 1, 1979. Engineering controls and work practice provisions of the standard have been stayed pending judicial review. The standard lowers permissible worker exposure levels to 50 µg lead/m^3 of air averaged over an 8-hour workday. A review of the hearing records on the noise standard still is under way.

was faced with the question of what to do when a regulatory agency must translate scientific knowledge concerning health effects of chemicals into regulatory action for protection of workers.

We go through some very vigorous work to try to find the proper approach and the proper standard. As evidence of the difficulty that we have in the standards promulgation process, consider the records on lead and noise.+ We have over 15,000 typewritten pages of testimony on the lead standard and over 10,000 pages of testimony on the noise standard. Standard promulgation shouldn't be an easy task; it has to be a difficult task to determine standards. If it were easy, I think that government agencies, which have a reputation of over-regulating, would do just that; and we are attempting not to over-regulate.

The problem is not whether you should regulate, but how much and where you should regulate. We operate on the frontiers of the scientific, technological society, and it is not unusual, in the standards hearing, to hear strident pleas concerning over-regulation. OSHA is working hard to get rid of the stigma that we are creating regulations for industry that are unfair.

CHANGES IN THE STANDARD

The temporary standard is for an 8-hour time-weighted average of 10 parts per billion (ppb), and the proposed standard is for 1 ppb. This change is due, in part, to the fact that there is two-specie, two-target-organ evidence of carcinogenicity for DBCP and known human gonadotoxic effects. It is also because we have demonstrated achievable levels in the area of bis-chloromethyl ether of 1 ppb and less.

The section on methods of compliance has also been changed. There was not time to develop engineering controls to the point where they could be applied in the temporary standard, but the permanent standard will address the issue and will require that engineering controls be implemented.

The decision logic for the respirator table has not changed a great deal, but it has changed slightly because we are considering a lower standard.

There will be a section on what should be done in cases of emergency and what is required of a company in case of emergency spills.

The section on medical surveillance has also been changed. We anticipate that the requirement concerning testosterone will be deleted; that the requirement for the SMA-12 will be changed to

include a complete blood analysis as well as a differential count; and that a complete urinalysis, including a microscopic analysis, will be required.

The recordkeeping requirements will be, of course, for 20 years.* The present requirement was only for the duration of the ETS. These are the major changes that I am aware of.

REFERENCE

1. National Institute for Occupational Safety and Health. Registry of toxic effects of chemical substances. NIOSH, Cincinnati, Ohio. 1978.

DISCUSSION

Question (Mr. Estep, OSHA): Do we have some information on the ceiling?

Answer (Mr. Demery): The ceiling has been changed from 50 ppb to 10 ppb for a 15-minute sampling period.+ The due date for written statements and comments is December 1, and at that time, you should also let us know about your intention to appear at the hearing.

Question (Dr. Lipschlutz, University of Texas Medical School): I would like to know the rationale for dropping the testosterone and retaining the T-3 and the T-4, the thyroid studies.

Answer (Mr. Demery): As stated in the preamble to the final standard, the requirement for serum testosterone has been eliminated on the basis of evidence that serum testosterone levels do not correlate with DBCP-induced toxicity. Thyroid studies are also not required in the final standard.

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*Under the new standard's recordkeeping requirements, an employee's exposure and medical records must be kept for 40 years or the duration of employment plus 20 years, whichever is longer.
+The new permanent standard for worker exposure to DBCP has no ceiling limit.

OCAW INVOLVEMENT IN THE DBCP INVESTIGATIONS

Rafael Moure,* Tom Neel,+ and Jeffrey Chapman+

RAFAEL MOURE

The interest of NIOSH, as I understand, is to evaluate scientific information in order to make scientific judgments in two specific fields: the need for medical surveillance to prevent potential delayed health effects of DBCP exposure and the steps necessary to prevent a future tragedy of similar proportions.

MEDICAL SURVEILLANCE

In addressing the first point, I understand that the possibility of putting together a future registry of DBCP workers is seriously being considered by the federal government. We endorse this idea and propose that such a registry be expanded from a simple record-keeping of future disease experience in this group of workers to a continuing preventive medicine program that will monitor the health effects of DBCP for their lifetime.

Such a program should include routine screening tests in this population to identify any precancerous condition in these workers. I believe that the in-vitro evidence of mutagenic effects of DBCP, as well as the in-vivo animal evidence of carcinogenic effects of DBCP, defines this worker population as a high-risk group for the future development of cancer.

Yesterday we heard that Dow Chemical Company has reported one case of embryonal testicular cancer in a DBCP formulator at Magnolia, Arkansas. Although there is no proven cause-and-effect relation between the worker's DBCP exposure and the testicular cancer, the fact that very low DBCP air concentrations have produced a very high gonadotoxic effect points to the need for considering DBCP, by itself or in conjunction with EDB (the other exposure that this worker had), a potential causative agent of this worker's condition.

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+Members of Oil, Chemical and Atomic Workers International Union and Shell Chemical Company employees.

OCAW would like to suggest as part of our proposed "lifetime preventive medicine program" for DBCP workers that appropriate medical screening tests, especially tumor marker tests, be performed twice a year, in addition to the medical tests suggested in OSHA's emergency temporary standard.

In my literature search of tests that are tumor markers, with emphasis on the sites that we could expect cancers to appear through the animal experiments, I found four that I would like to present to you for discussion.

The first is the measure of estradiol levels, i.e., HCG hormone in serum of workers exposed to DBCP. This is, of course, in conjunction with the other hormone tests that have been proposed before.

The second are the tests that measure the level of specific modified purines and pyrimidines that are end products of RNA catabolism in urine of people. This type of test could provide good information about cancer for the purpose of prevention.

For the third, we could consider periodic examinations of the feces of workers involved with DBCP, and the fourth would be studies on blood cell cultures for chromosome damage, cystochromatid exchange, and DNA repair.

These suggested screening tests are not invasive and could be performed in conjunction with the biological samples to be collected as the result of the proposed medical surveillance section in the OSHA emergency temporary standard.

We recognize that some of these tests are new, experimental, and not fully developed as screening tools. We believe, however, that their experimental use in this case is justified by the urgent need to address the problem of early cancer detection in populations exposed to DBCP.

OCAW also suggests that whatever costs are involved in this preventive medicine program should be covered by the corporations involved in DBCP production and formulation.

The success of any medical surveillance program depends on employee participation. Such participation has been hampered by worker fear that the results of medical examinations could be used to impair his or her ability to make a living. Future OSHA regulations must provide two guarantees to the worker to obtain their participation: first, a guarantee of full confidentiality of medical results from all sources, including the employer; and second, a guarantee that any change in the worker's classification as a result of a medical examination will maintain the worker's rate of pay, seniority, and rights for future promotion.

PREVENTION

The second and most important scientific task for federal research and for the regulatory agencies is to take steps to prevent further occupational tragedies of this magnitude. A gap exists between the content of toxicological studies and the information about these substances supplied to the chemical operators and formulators at the point of production. Warnings of the need for medical followup recommended in the Torkelson paper,[1] in the Shell preliminary paper,2, and in those from the years before (1957 and 1958) were not heeded. The medical surveillance recommended in light of the specific toxic effect in the reproductive systems of exposed animals (i.e., testicular atrophy and abnormal sperm production) is the reason to recommend the tests mentioned above.

The only toxicological information available to managers of the Occidental Chemical Company in California and the Shell Chemical Company at Denver were the general warnings on product labels--"use protective clothing"--"avoid breathing the vapor and fumes"--"keep out of the reach of children." Because this type of information does not inform anybody of the risks involved, OCAW suggests that the federal government regulate and monitor this process of transmitting toxicological information.

With respect to workers, we suggest that a fact sheet, summarizing the known toxic effects in lay language, be given to every operator handling the substance.

OCAW INVOLVEMENT

Direct worker involvement, applying the art of "workers' health screening" uncovered the infertility cases of employees involved in manufacturing and formulating DBCP in California. OCAW's direct intervention in June 1977 uncovered the relationship between handling DBCP and infertility. The decision to medically document workers' complaints of infertility through medically supervised sperm counts was conceived, planned, and carried out by OCAW workers at the Occidental Chemical Company plant. One worker collected the sperm samples from the first seven operators examined. These seven sperm tests submitted to Dr. Whorton were the first medical evidence of this problem. On July 21, 1977, OCAW requested the NIOSH health hazard evaluation that involved Dr. Meyer and Dr. Whorton. On August 23, we requested the emergency temporary standard from OSHA. This was followed by a similar health hazard evaluation request to NIOSH for our Denver plant as well as a request for involvement from the Colorado Department of Health.

Dow Chemical Company (in testimony presented October 13th in the California inquiry on DBCP and expressed through Dr. Perry Gehring,

their Director of Toxicological Research) recommended in 1961 that exposure levels for DBCP be below 1 ppm in the work environment. Dr. Gehring expressed his belief that those levels are unlikely to produce adverse effects if skin contamination is avoided. Today we know that those 1961 recommendations did not protect Dow Chemical workers.

Shell Chemical company declared in the California hearings that Shell observed adequate operating procedures recommended by the 1961 report. The reports of 95 infertile and possibly permanently sterile workers, to date, point out the deficiencies of these work practices. Accounts of workers at the Shell Denver plant as well as that from the Shell plant manager point out the unavailability of toxicological information. The reason that more than 3,000 DBCP workers in the United States are not exposed today is the diligence of an OCAW local union leader.

CONCLUSIONS

A proper scientific question we should objectively examine is where traditional toxicology, traditional epidemiology, as well as traditional medicine have failed the American worker. We should critically study the "how's" and the "why's" corporations have failed in their responsibility to provide a workplace free of hazards to DBCP workers.

The OCAW hopes for meaningful and substantial changes in governmental regulations in three areas:

-- The transmission of meaningful toxicological information to workers from employers;

-- The assurance of worker participation in medical screening tests through rate retention guarantees;

-- The establishment of corporate responsibility (by at least a medical program to be provided for the worker's lifetime) for the actual and future health effects of DBCP-exposed workers.

TOM NEEL

I am the chairman for the Workmen's Committee at Shell's Denver plant. We no longer manufacture DBCP, but we urge a standard to help others still involved. We urge evaluation of all other chemicals we work with for we want a safe workplace.

OSHA began in 1970. In March 1971, we formed a voluntary safety committee; in 1973, the "health and safety" clause came into our contract. Although we have a cleaner, better-smelling plant since OSHA and our health and safety clause, there is still room for improvement. We believe a permanent standard is needed to upgrade past mistakes. Please help us improve our conditions so that another group of people down the road will not suffer the problems faced by the alleged victims of DBCP.

JEFF CHAPMAN

I work at Shell's Denver plant, and I was a DBCP operator in 1974 and 1975. We who worked with DBCP were given no information on the possible effects as far as sterility. We were told "the stuff is poisonous; don't breathe it too much. Avoid it. If you get it spilled on you, wash it off." We weren't given impervious clothing for everyday wear. Rubber suits were availabile, but no emphasis was given us to wear this clothing.

There are lots of protective devices at the plant. I think, since I have been there, that they have provided us very well with respiratory equipment and protective clothing.

Because it is very annoying to work in hot heavy equipment, men generally wear their safety equipment when they know there is an immediate danger such as working with caustics. The long-term effects are not pointed out to us very well, if at all, and men don't consider what they are taking home in their tissues. If I had been informed I would become sterile with high exposures to DBCP, I would have worn more respiratory equipment. For example, whenever I had to open the bottom of the reactor because it was plugged, to let DBCP pour all over the floor, and be down there with my wrenches in a puddle of it, I would have had something on. I didn't. I did my work as quickly as I could. I let my eyes tear, and I got out. If I got it on my body or on my coveralls, I washed up. But I had no idea what this stuff could do to me. Another standard procedure used at the Shell plant (it is gone now) after the finished product was filtered and packaged was to change the dirty filters. The worker put on rubber gloves, opened the canister, took the used filters from the canister, and put them into an open drum that was not under a hood. There were heavy fumes--enough so that you couldn't wait to get out of there.

The standards, which you people have been studying, are all well and good, but they don't relate very well to plant reality--not unless people are put into pressurized rubber suits and complete protective equipment whenever they have to be at the workplace. Men

don't want to do that; it is just too much trouble. Management might get more cooperation, however, if we knew what these things could do to us.

Although DBCP is now gone from the Denver plant, we have many other chemicals there. A lot of men suspect trimethyl phosphate, which is in widespread use at our plant, is causing sterility problems. We don't know; we haven't been given information on it. If this material has any effect like DBCP, the men don't use the necessary protection. We need studies done on every material that is used in the chemical industry; and we need the information. If we get straight information, if we know how dangerous these materials are, what they can do in the short- and long-range, I think the men will be much more cooperative with management about wearing the safety equipment.

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2. Shell Chemical Corporation, Agricultural Chemical Sales Division, New York, N.Y. Summary of basic data for Nemagon soil fumigant. Sept. 24, 1976. (Exhibit #17, hearing, Department of Industrial Relations, State of California, San Francisco, California, October 13, 1977).

THE FOLLOWUP

Donald Whorton,* Robert Spirtas,+
Channing Meyer,† and Alexander B. Smith~

DONALD WHORTON

EXTENT OF THE PROBLEM

Where does our medical surveillance go from here? I don't think we know the extent of the problem. Examinations are going on or have been completed at five plants (one each in Arkansas, Alabama, Michigan, Colorado, and California). Many people still haven't been examined although we intend to try to examine some of these exposed people, e.g., at least five or six DBCP formulators in California.

The presented data have been mainly from manufacturing or formulating companies. Some, as yet inconclusive, data concern the applicators. So, at this point, we really have no idea how many patients we are talking about.

At the Occidental Chemical Company plant, 15 men--applicators, set-up men, and truck drivers--were examined. Fourteen of the fifteen gave sperm samples. Of these 14, 2 were azoospermic; 1 had a count of between 1 and 9 million; 2 between 10 and 19 million; 2 between 20 and 29 million; 2 between 30 and 39 million; and 5 above 40 million/ml (actually they were above 70). I think these are very different from the data that some of you have been seeing. It indicates that there is a problem among applicators, at least in California where we have examined the most workers.

It was difficult to assess how much these men were really exposed, for it depended on where they lived in California and how

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much DBCP they used. In some parts of California, DBCP was used the year around; in other parts, 2 or 3 months a year. One of the azoospermic men was a tractor driver who apparently specialized in DBCP; with the other men, the exposure varied. This does show that there is an effect and that the effect extends beyond the plant.

REVERSIBILITY

The question of reversibility versus permanence of testicular injury needs answering. This can be done by following people over time.

What kinds of tests ought we to use: cytologies, motilities, etc.? Whatever kinds, they must be relatively uniform so we can establish comparable figures. We don't, however, have enough data to answer that question yet.

A second question is, For those who are reversible, i.e., those who father children, what is the best sign of reversibility? Will their children be normal? Pregnancies must be followed--families must be considered and involved--it is more than just the workers.

A third question concerns the relative risk for cancer in these individuals. Again, the only way to answer that is to find and follow the people over time. Of the people we have talked about, one individual has testicular cancer. Now, if the incidence of testicular cancer is 3 in 100,000 and seminomas are half of them (this particular one is not a seminoma), we already have a bias. We must also ask, Are we going to see cancer not only of the testes, but cancer of the thyroid, or of some other organ, 10 to 15 years from now? We don't know; the only way to know is through a followup. If we are going to talk about followup, these questions need to be addressed. Unfortunately, we can't give people answers right away.

ROBERT SPIRTAS

A case registry, as we're considering the term here, is a listing of people exposed to a work hazard. The list is used to measure the magnitude of the problem and to keep track of the people as efficiently
as possible. To develop a registry for a particular exposure, we try to collect baseline information: name and address, social security number, date of birth, race, sex if it is appropriate, and some measure of exposure, which is most easily obtained from work histories.

NIOSH has started to maintain registries--an angiosarcoma case registry and a registry for Kepone and Mirex workers. Now we have the question, Should there be a registry of workers exposed to DBCP?

Because NIOSH began its work on Kepone/Mirex after several other groups had been working on the problem, it has been very difficult for us to get all the data we need. We were able to get the work histories for our registry from most of the manufacturers, especially from the large manufacturers, of these chemicals. Because the formulating companies are smaller, often not as well organized with varying degrees of expertise in matters of health, with varying degrees of interest in cooperation, and with fewer employees, it's been more difficult to get the information we need. It is an even more difficult story when we get to the applicators.

Several people have expressed the need to have more information--on fetal outcome, on repeated measurements, on other types of health outcomes. Where do we draw the line on how much information to collect? I suggest that an economic principle is involved. We need a baseline of information on all workers. After that, certain tests could be given to or records collected for certain workers. The greater degree of testing or record collection would be done on the workers at highest risk; a smaller sample would be taken of the other workers so that we have an estimate of the overall problem. For the purposes of estimating the dose-response relationship, we have techniques available that will allow us to stratify the population and to spend a certain amount of money in a way that will give us the maximum amount of information. This is for the purposes of scientific information. The consideration of the social consequences and the fact that the workers have asked for a certain procedure are additional issues.

Beyond the need to standardize protocol, the laboratory procedures, and the testing procedures, we also need a standard baseline of information on each worker so that we have some idea of the total population of exposed workers and their exposure history. We need this information as quickly as possible before we begin any program of medical testing or medical surveillance.

To collect this baseline of information, we need the cooperation of industry and labor so that we can measure the magnitude of the problem and keep track of it as efficiently as possible.

CHANNING MEYER

I think it is important to look at two parameters: potential reversibility of testicular malfunction resulting from exposure to

DBCP and the possibility that DBCP may be a human carcinogen in addition to being an animal carcinogen.

A DBCP case regsitry would allow us to keep track of these exposed workers, especially those with the greatest amount of dysfunction as a result of exposure. Although it would be good to evaluate everybody and every chemical, it is not feasible with our resources. By operating in a stratified manner, we will be able to watch most closely those people who have been severely affected and, then, to enlarge the study as the results of that surveillance may dictate.

We know that DBCP is a problem, and we know that there are many other chemicals in the environment. What are we going to do about some of the other ones?

There are a number of theories at this point about the actual mechanism of the toxicity of DBCP. When that mechanism is worked out, we can take other chemicals, similar in structure to DBCP, to see if it is the chemical itself, or a metabolic byproduct, or whatever, that is toxic. Until then, we will look at a variety of exposures in an industry-wide study that is currently being approved.

BLAIR SMITH

Our interest in certain types of pesticides stems from work that we have been doing on certain chlorinated hydrocarbon compounds as determinants for cardiovascular disease. In planning those studies, it became apparent with the emergence of the DBCP problem that, as one part of the study, we would be looking at basically the same types of populations that would be examined to study the problem of sterility caused by certain halogenated hydrocarbons.

We need to obtain certain information in a standardized, uniform way, so that we can make comparisons between compounds, between geographical areas, and between sites. We are searching for some epidemiologic leads to this and other problems.

We plan to look at those chemicals that we, from our review of the literature, have reason to suspect might cause these problems to occur. At the outset, we are going to concentrate on chlorinated hydrocarbon pesticides.

Our medical protocol concerning the infertility problem will follow, in large part, Dr. Whorton's recommendations. We will also do some other medical examinations.

DISCUSSION

Question (Dr. Zavon, Hooker Chemical Company): Mr. Chapman, I think you have made some of us realize again that there are concerned workers in the plant and that this isn't an academic situation. My question is: If we have not been able to get people to stop smoking cigarettes, where the data are reasonably good concerning the potential for lung cancer and other diseases, can you make any specific suggestions as to how we can be more persuasive in getting workers who are exposed to chemicals, with either known or unknown potential hazard, to observe precautions in the workplace?

Answer (Mr. Chapman, Oil, Chemical, and Atomic Workers): A man has a choice with cigarettes; a man has a choice with chemicals if he knows the danger of the chemical. We didn't know the danger of the chemical other than it would irritate the skin. Employees knew nothing of sterility problems, nothing of carcinogenic problems. Knowing these things, a man can protect himself. You can't guarantee the man will use his safety equipment, you can't supervise him 8 hours a day, but you can at least tell him what he is up against.

Question (Dr. Zavon): Recognizing the validity of what you are saying about informing him, how can we motivate him--any more than we can motivate him to stop smoking?

Answer (Mr. Chapman): Perhaps if OSHA came out with very strict control rules on letting a man be exposed, management and supervision could tell him "We are going to be coming in and out of here, and we are going to be watching how you work. If you are not using your equipment, you will lose your job." Management also needs to be monitored to make sure they are requiring people to use their safety equipment. In our plant, a foreman might tell a worker to put on an airline mask. The man might put on an airline mask until the foreman walks away, or he might keep it on, caring enough about his body to not want to absorb these things. But between labor and management, I don't think you can do it--you have to have government in there making sure that both sides are obeying the rules that need to be made.

Comment (Dr. Craft, NIOSH): The best way to solve the problem is with engineering control. It eliminates the problem of trying to convince the man to do something. I believe we surely have the technology to do that now.

Question (Mr. Mike Wright, United Steelworkers of America): Dr. Zavon, one of the problems we have is to motivate management to put in the engineering controls. We would appreciate hearing any suggestions you might make along those lines.

Answer (Dr. Zavon): As federal laws are enacted, whether by OSHA or other regulatory agencies, that all industry must comply with, industry won't be moving from a state that has strict rules to a state that has less strict rules. But if these federal rules are much stricter than rules elsewhere in the world so that our industry cannot compete with industry elsewhere, we have to face the fact that we are going to lose jobs here and be prepared to accept and in some way cushion it. I think management can be motivated--I haven't run into anyone in management who deliberately wants to hurt anyone.

Comment (Mr. Kusnetz, Shell Oil Company): I want to thank Jeff Chapman and Tom Neel for saying what I think really had to be said. If there is one message that we take away from here--and certainly we at Shell are more sensitive to their comments because they are our fellow employees--it is that the avenues of communication have to be broadened, made two-way, and be very open. I would also like to set the record straight concerning the hearings in San Francisco last week that Mr. Moure referred to. I was the only Shell spokesman at those hearings. The Shell Denver Manager was not at the hearings and, consequently, made no statement concerning what information had or had not been passed to him.

Comment (Mr. Moure, Oil, Chemical, and Atomic Workers): The statement of Mr. Knaus, Manager of the Denver plant, about this information came out of the meetings Mr. Knaus had on September 20 in Denver with the Colorado Department of Health and representatives of OCAW and the Shell managers at Denver. In that meeting, Mr. Knaus stated that he didn't know about this information until July 1977.

Question (Dr. Troen, Montefiore Hospital): My question relates to standards that are to be set. I gather they represent a level of DBCP in the air above which exposure is unacceptable. Is there to be a time limit put on this exposure? We have been told and given evidence that this material is gonadotoxic--that it probably acts on the spermatogonia. This means there is a very long lead-time between the time toxicity takes place and the time that any usual monitoring methods, such as sperm counts, will show any change. It may not be enough to look for a level below so many parts per billion; we also need to know how long an exposure. What methods should be used to minimize exposure? Has any thought been given to rotating workers or giving a "cooling-off" period for whatever toxicity may be present?

Answer (Dr. Bingham, OSHA): First, I want to comment on rotating workers. When you have a material such as this (for which we have some very good animal data in two species that say it is a

carcinogen), I get very nervous because I don't want to spread that risk around too far. We will, of course, be talking about exposure limits in terms of what will be allowed in hours.

I would like to make a plea to NIOSH, to the people who are planning these studies, and to you in the audience. When you do these studies (and I'm not just talking about DBCP), talk with people in the regulatory agencies (not just OSHA, but with EPA, and others, depending on the material) and get their perspective as to what is required to come up with the regulation that will protect workers, the ambient environment, or the general population. This might help you have a better insight as to how useful the data you collect are going to be.

How are we going to translate these data you collect into standards? You should start thinking about this at the very beginning of your studies, not when we are at the public hearings and people say, "Well, this is wrong with the study, and that is wrong with the study, and why didn't you take this into account?" It might even be good to talk about what constitutes evidence because eventually we do come to that basic question.

I appreciated the remarks of Mr. Chapman and Mr. Moure and would like to direct questions to them. How much do you know about the substances with which you work? What kind of labels do you have? What do you think you should have? And to Mr. Moure--When you talk of confidentiality of records, do you mean so confidential that the worker is not told of the results? Or confidential as far as the rest of the--

Answer (Mr. Moure): The world.

Answer (Mr. Chapman): We know the materials we work with at the Shell Plant (and there are a lot of them) are dangerous. We know, of course, they are chemicals. We know that there are acids--caustics that will cause immediate harm. If you get them in your eyes, you will go blind; if you get them on your skin, you will be scarred for life. We know that the end-products--such as the DBCP that was being made there and, now, other products--are poisons. We don't want to eat them for lunch; we don't want them absorbed through our skin. We are not chemists. We know poisons to a certain extent, so we are careful. But we don't know with any assurance that a material is a carcinogen or that it can cause sterility. We don't have the information on these materials.

We know the short-term effects of some things that are immediately dangerous. We know very little about long-term effects, especially of the end-products of the things that the plant actually manufactures.

Comment (Dr. Meyer, NIOSH): I have participated, either in terms of directly conducting the study or assisting in conducting the study,

in approximately 40 or 50 health hazard evaluations. My conservative estimate of the people who have not the faintest idea of what they are working with or its potential dangers is in the range of 75 percent. Worker education really must have a high priority--not only for government agencies, but certainly for corporations and unions. It is time that labor begins to ask these questions and begins to insist that labor and management know about these hazards, because in a few cases management has not even known.

Comment (Mr. Moure): In my research in different plants and in finding different ways to pass on information, I have found that in a great number of plants there is a material safety data sheet for every substance. Normally, there is a copy of this in an office. The type of warning given to workers is "Don't breathe the fumes." My suggestion is that the specific effects should be provided to these workers--a leaflet, written in lay terms, giving the results of toxicological experiments and what could be expected.

In the production of any chemical, the operator making the chemical is given the standard operating procedures. This type of information could be included in this standard operating procedure so that the operator and the people handling the chemical could read it while they work with the chemical.

Question (Dr. Vernon, Colorado Department of Health): We have found that the results of conveying information to vaccine recipients with the so-called informed consent forms are dismal. But that in no way relieves us of the responsibility for such conveyance. It reminds me of a comment made yesterday concerning whether or not a young man who happened to have a low sperm count might not be told of the situation. I think we are well beyond the era when a physician should fail to communicate results of that sort.

Dr. Smith, could you tell us about the studies that are underway? Who is involved? Will you study reversibility? Carcinogenicity?

Answer (Dr. Smith, NIOSH): At this time, the study is envisioned as being primarily cross-sectional. We are working with the University of Illinois School of Public Health, which will be doing a retrospective mortality study of the pesticide formulators. The provision to do some work prospectively is in the planning stages. Input is needed from concerned parties to help us define what people outside our organization believe is necessary in these areas. The studies could very well be used as the basis for a prospective followup of the people involved.

Comment (Dr. Glass, CDC): The questions of variability brought up throughout this meeting all point in the same direction--there

is a lot to be done to standardize some of the studies and, as Dr. Whorton said, to determine the extent of the problem.

Future studies should be done in a well-controlled fashion with large numbers of exposed and unexposed workers or with multiple specimens taken from smaller numbers of workers. A control group is particularly important since there are no reliable data on the distribution of sperm counts in a normal (i.e., neither infertile or prevasectomy) population and because specimen handling and counting can lead to great variability of results as well.

Comment (Mr. Eller, International Chemical Worker's Union): For the last 2 days, we have very microscopically examined what I believe may turn out to be only the tip of an iceberg. We have looked very closely at the events and the effects of one particular toxic substance and perhaps some of the effects of related compounds. We have also seen cooperation in terms of the federal government and industry trying to evaluate the events that led to what we are, perhaps, going to label the "DBCP disaster." I am somewhat hesitant in applauding this kind of cooperation because I think that the history that has been laid out here indicates that the producers of DBCP knew that workers exposed to the substance might suffer from the potential carcinogenic and gonadotoxic effects.

I have to wonder how many additional reports, such as the Dow and Shell animal studies, exist in corporate medical files. Only history will indicate whether or not we have made any progress here or whether or not we are going to repeat the same events. One of the things set forth at the start of the conference was the possibility of determining how we might avert future disasters. I think one of the ways is through a complete disclosure of studies. There will have to be a different relationship to animal data. We will also have to make corporations financially responsible for the effects of their own production. One way this might be done is to have the federal government ask that producers be responsible for the financial burdens that are going to come out of the the exposure to DBCP.

Comment (Mr. Wright): In discussing where to go from here, I want to raise two issues. One is an issue for OSHA. The Steelworkers' top priority for standard-setting is a comprehensive labelling standard--a standard that would include not only labelling, but posting and giving information to workers about the toxic substances to which they are exposed. I am sure that in 6 months or a year, we're going to be talking about some other chemical, and the sooner that people know what they are exposed to, the sooner we can begin to diminsh the frequency with which we have to meet about some other crisis.

The other issue concerns NIOSH. We are in favor of a case registry for DBCP and for similar substances. Unfortunately, there

are some questions that have to be addressed about confidentiality of records. In the recently concluded beryllium hearings, we had an experience concerning death certificates. The certificates, supplied by the states to NIOSH under what I understood were signed agreements that they be kept confidential, were given to one of the companies involved. That company then used that information to hire a private detective agency to do what they called smoking histories on workers who had died--by visiting relatives and families. The potential for harassment in that kind of situation is very high. There is also a case registry for beryllium, and as far as we can tell, representatives of the companies had very open access to that case registry. Now, I don't think that information was misused, but again, the potential was certainly there. I think that until we can discuss in detail some procedures that will assure us that the information cannot be used against individuals, we would be hesitant to ask our members to supply personal information to NIOSH or any other agency. I think before a DBCP registry can be set up, we want to have that kind of discussion.

Question (Dr. Meyer): NIOSH, to my knowledge, wasn't responsible primarily for the beryllium registry. Is that right?

Answer (Mr. Wright): As far as I know, NIOSH supplied the funding.

Comment (Dr. Meyer): In terms of release of information, that may well have happened elsewhere. The point about death certificates is irrelevant because a death certificate is a matter of public record.

Comment (Mr. Wright): The fact remains that NIOSH signed agreements with states not to release the information and then disregarded them. So we are afraid that you will sign an agreement with somebody else and ignore it.

Comment (Dr. Smith): I would like to address the point of confidentiality of information that we obtain in the course of our studies. Specifically, you are referring to the confidentiality of death certificate information. This is part of a broader issue, namely of medical information as it pertains the deceased. Regardless of any agreement that NIOSH may have signed with a state, it is the decision of the General Counsel Office of DHEW that deceased people do not have a right of privacy. This issue has come up a number of times with respect to data that we hold within our Branch. We have fought vigorously against the disclosure of medical data on deceased individuals, and we have been able to reach agreements with these people requesting such information. I don't believe we have released any medical data.

The death certificates, however, are a public record, and as such, we cannot withhold them if someone requests them. As for medical information on living people, this is subject to the Privacy Act. We cannot release this information, and legally, we are on very

firm ground here. Generally, we cannot, will not, and will never release confidential information on living people without their signed consent.

Comment (Mr. Demery, OSHA): To return to the issue of high priorities for labelling, I would like to comment that Dr. Bingham also has that under very high priority.

Comment (Dr. Ligo, NIOSH): In light of informing the working man about what he is working with, I would like to tell you about the Standards Completion Program (a joint OSHA-NIOSH program) in which we have prepared this kind of material for all the federal standards. The material includes material safety data sheets for workers that tell all the toxic effects that workers might expect from a particular agent and tell them what to do about effects, first aid measures to use, etc. If this program is implemented, there are requirements that the company inform the workers and provide these materials to them. The company is also given other information about how to handle this material safely, what kind of medical examinations should be done and how often, etc. When these are released, they should handle the 400 or so items on which we have standards.

Comment (Dr. Spirtas, NIOSH): I would also like to respond to the representatives of labor as well as management concerning confidentiality. Professional societies are coming up with standards and guidelines regarding confidentiality and privacy of information, e.g., the Office of Management and Budget has them. But these are not cast in concrete. We will provide whatever safeguard we can think of and whatever safeguards you can suggest to us. To the extent possible that we can guarantee this confidentiality, we will do so.

Question (Dr. Lamm, Tabershaw Occupational Association): With what frequency do you expect to recontact people to know what their health status is once they are in the case registry? Or is the intent to wait and eventually collect the death certificates?

Answer (Dr. Spirtas): We hope to do epidemiologic followup. There will be a national death registry--in 1979 or 1980--that will allow us to screen deaths annually.

There are problems, however. We have a finite amount of money, and we have to worry about just keeping track of these people, divorcing ourselves completely from the question of medical screening and what tests to do. If our only purpose was to keep track of them, we probably would screen the people in California more frequently (because they tend to move around more) than we would the people in a small town in Arkansas. As a general rule, we will use the types of followup mechanisms that we have. We don't

know if we will get IRS followup information back; we still have SSA followup. This field keeps changing--as we lose one source or gain another. So I can't give you a complete answer to the question. I believe we will follow these people at least once a year to make sure that we haven't lost them.

Comment (Mr. Kusnetz): I would like the record to show that the reports of both Dow and Shell were reported in the professional, technical, and open literature within a short time after those reports were developed by the researchers in the original proprietary manner.

I would be remiss if I left the impression that Shell does not or did not inform its employees of long-term effects. Our material safety data sheet program comprises some 3,000 sheets, which are updated on a continuing basis. Our sheets do indicate effects, such as cancer and other esoteric effects, as the literature reports them and as quickly as we can get them into the sheet program. This does not guarantee that any one sheet will be updated at the point when it is appropriate. Our continuing program of updating our operating manuals does include health and safety information, including the effects of the materials with which the employees work.

A continuing program of two-way communication is needed by Shell and everyone else. We know that information is transmitted, but we may take for granted that it is immediately absorbed. It must be reinforced, and there must be feedback.

Comment (Mr. Eller): I don't believe that because material about DBCP was published in a journal or because there is an ongoing material safety data sheet program the company is absolved of its responsibility to its workers. The record is fairly clear that the appropriate precautions were not taken in regard to DBCP exposure, nor were the workers informed as they should have been.

Comment (Dr. Whorton, University of California at Berkeley): When this symposium began, I asked a series of questions. I assumed that none of them would be answered, and true, the questions are still there. We are not going to answer them today. If blame is to be laid for the reasons we are in this situation with DBCP, the blame is with society. Society has a very low interest in this area, occupational health.

Comment (Dr. Meyer): To add one final comment. In a recent survey concerning physicians, people were asked to evaluate physicians' subspecialty occupations in terms of the most to the least respected. Preventive medicine people were last and occupational physicians were second last. That is where society is.

This is only the beginning; we will move on from here. All of you have helped me understand the directions in which we need to go.

APPENDIX A

EFFECTS OF DBCP ON FERTILITY: AN ANNOTATED BIBLIOGRAPHY

Joyce Salg*

Burek, J.D., F.J. Murray, K.S. Rao, A.A. Crawford, J.S. Beyer, R. R. Albee, and B. A. Schwetz. (1979).
A report from the Toxicology Research Laboratory. Dow Chemical USA., Midland, MI 48640.

The effects of DBCP on spermatogenesis were evaluated in rabbits and rats by inhalation exposure to 0.0, 0.1, 1.0 and 10.0 ppm of DBCP for up to 14 weeks. The onset, severity, and pathogenesis of testicular atrophy were studied by light and electron microscopy, by fertility breeding studies, and by correlating these findings with semen evaluation. Rabbits exposed to 10 ppm had nearly complete atrophy by 8 weeks: all stages of spermatogenesis were absent; seminiferous tubules were lined by relatively normal Sertoli cells; there were no germinal cells in the seminiferous tubules; and lipids within the Leydig cells were increased. Rabbits exposed to 1.0 ppm for 14 weeks had a 50% reduction in testicular size, decreased spermatogenesis, and increased abnormal spermatocytes within the seminiferous tubules. Rats exposed to 10 ppm showed approximately a 50% decrease in testicular weights and a patchy decrease in spermatogenesis. Rabbits exposed to 0.1 ppm and rats exposed to 0.1 and 1.0 ppm did not show any treatment-related testicular or reproductive alterations.

Cohen, D. 1978.
Guarding against cancer. EPA Journal, 4(3):12-13.

The U.S. Environmental Protection Agency has cancelled some or all uses of certain pesticides and has temporarily suspended uses of others, including DBCP. The rationale for such action has, in part, rested on the premise that the pesticide in question could expose a segment of the population to an increased cancer risk. The manner in which EPA arrived at their decisions is reviewed.

*Ph.D., National Institute for Occupational Safety and Health, Cincinnati, Ohio.

DBCP, chlorolecone, and the risk-benefit equation. 1978.
Lancet, 2(8080):79-80. 8 references.

The work of several investigators in the area of DBCP is briefly noted.

Dibromochloropropane--intent to suspend and conditionally suspend registrations of pesticide products. 1977.
Federal Register, 42(186):48915-48922.

DBCP has been indicted as a carcinogen in animals and has been shown to cause sterility in male workers exposed to relatively low levels. The risk of continued use of DBCP on food crops outweighs the known benefits of its continued use. Registration of DBCP use on specified crops is suspended. Restricted use is permitted for other specified applications.

Dow Chemical USA. 1977.
Report on study of DBCP-exposed employees in Midland, Michigan. Internal communication, Dow Chemical to EPA.

Sperm count tests were conducted with a potentially exposed group of 249 men and a nonexposed control group of 77 men. The mean age of the group of employees formerly associated with the production of DBCP in Midland was 40.4 years; for the control group, 41.1 years. The sperm counts of the control and exposed men were:

Control, 77 men, average age, 41.1
25 = less than 40 million/ml
11 = less than 10 million/ml
14 = between 20 and 39.9 million/ml

Exposed, 249 men, average age, 40.4 years
80 = less than 40 million/ml
39 = less than 10 million/ml
42 = between 20 and 39.9 million/ml

Dow Chemical USA. 1977.
Dow study suggests workers recovering from over exposure to DBCP. News release, December 13, 1977.

The recovery news involves Dow Chemical employees at their Magnolia, Arkansas, plant. August tests showed lowered or zero sperm counts in 47 of 86 workers examined. Using a sperm count

of 20 million/ml as the breakpoint of the 86 men originally tested in August, 61 were identified for further follow-up. Of the 61, a group of 35 men showed sperm counts increasing from below 20 million to above 20 million sperm per cubic centimeter (cc) of semen. In addition, five of the group showing no sperm count in the August count did show a significant number of sperm in the new tests made in November.

Sperm Count	August	November
0	13	8
1 to 2 mil/cc	14	12
above 20 mil/cc	8	15

Glass, R.I., R.N. Lyness, D.C. Mengle, K.E. Powell, E. Kahn. 1979. Sperm count depression in pesticide applicators exposed to dibromochloropropane. Am. J. Epidemiol. 109(3):346-351. 12 references.

A group of 112 professional applicators of pesticides were selected for study of the effects of exposure to DBCP. Of this group, 96 cooperated with the study. Nine of the 96 complained of clinical infertility. No relation was found between clinical infertility and exposure to DBCP. Extensive DBCP exposure in the current year (1977), but not in past years, was significantly correlated with sperm count depression (p less than 0.01) but accounted for only 7% (R^2) of the total variablility. Elevation of serum follicle stimulating hormone was associated with degree of DBCP exposure in the current year. No such effect was found for the luteinizing hormone. The frequency distribution of sperm counts in a group was the clinical test most sensitive to the toxic effects of DBCP. Applicators involved with certian pesticide practices, i.e., irrigators and equipment calibrators, had an increased risk of depressed sperm count and were responsible for many of the lower sperm counts in this sudy. Ten semen specimens were found to have morphologic abnormalities that were not related to DBCP exposure or to sperm count.

Griffith, J. 1979. Significance of epidemiology as viewed by a government scientist. Fed. Proc. 38(5):1888-90.

A generalized explanation of some of the methods employed by scientists to provide data on the risks associated with exposure to multiple environmental factors. An EPA epidemiologic study of field workers exposed to DBCP is used as an example of an analytical study.

Handke, J. 1979.
Neuropathy and pesticide workers. (From abstract.)
Toxicology Research Projects Directory, 4(1):1-45, #1.0405.

This study will monitor occupational exposure to pesticides (e.g., DBCP) and concurrently examine workers for adverse biological effects to determine if a dose-response relationship exists. Assessment of health effects will be made through the use of:

--a questionnaire specially designed to elicit relevant symptoms and medical information; a physical/medical examination including documentation of neurological findings;
--various quantitive neurological measures such as nerve conduction velocity (including sural nerve), sensory vibration assessment, tremor evaluation and visual field evaluation (e.g., eye saccade, perimetry); and
--relevant biochemical measures.

Multiple exposure of workers to more than one pesticide will be considered in the assessment of health effects and during analysis of the data.

Kapp, J.R., W. Robert, D.J. Picciano, and C.B. Jacobson. 1979.
Y-chromosomal nondisjunction in dibromochloropropane-exposed workmen. Mutation Res. 64:47-51. 15 references.

The authors report evidence of genetic toxicity (Y-chromosome nondisjunction) in the sperm of 18 workers exposed to DBCP. In the employed methodology, the identification of a fluorescent body within a human spermatozoon indicates the presence of a Y-chromosome (the entity made fluorescent by the quinacrine-staining technique is referred to as the YF body). When the spermatozoon containing two Y-chromosomes (YFF) is of normal size, one can assume Y-chromosomal nondisjunction. In this study, evaluation of 15 semen samples from individuals without any known exposure to DBCP showed an average YF frequency of 41.5% (range: 36.7% to 46.3%) and an average YFF frequency of 1.2% (range 0.8% to 1.6%). The evaluation of 18 semen samples from DBCP-exposed workers revealed an average YF frequency of 41.8% (range: 36.3% to 46.3 %), similar to that for nonexposed individuals. The DBCP-exposed workers, however, showed a higher average YFF frequency (3.8%; range: 2.0% to 5.3%) as compared with that for nonexposed individuals. In the Hazleton Laboratories, the background frequencies for YFF sperm is 1.3% as determined from the analysis of 262 semen specimens. All nonexposed individuals fell within the normal range whereas 16 of 18 DBCP-exposed workers fell outside the normal range. These differences between exposed and nonexposed individuals are statistically significant (P is less than .001) as determined by Chi-square analysis with one degree of freedom.

Marshall, S., D. Whorton, R.M. Krauss, W.S. Palmer. 1978.
Effect of pesticides on testicular function. Urology, 119(3):257-259.

Marked impairment of spermatogenesis in a group of men exposed to the pesticide DBCP was demonstrated by semen analyses, testicular biopsies, and hormone studies.

Olson, W.A., R.T. Habermann, E.K. Weisburger, J.M. Ward, and J.H. Weisburger. 1973.
Brief communication: Induction of stomach cancer in rats and mice by halogenated aliphatic fumigants. J. Nat. Cancer Inst. 51(6):1993-1995. 11 references.

Ethylene dibromide (EDB) and DBCP were administered to Osborne-Mendel rats and (C57BL X C3H)F mice via chronic oral intubation five times per week at experimentally predetermined maximally tolerated doses and at half those doses. As early as 10 weeks after initiation of treatment, both compounds induced a high incidence of squamous cell carcinomas of the stomach in both species. In addition, DBCP induced mammary adeno-carcinomas in the female rats. The authors recommend anyone exposed to DBCP or EDB should use protective clothing, masks, and other means to avoid absorption of either material. The extent to which these materials exist as residues of the original organic compounds should be determined, and long-term toxicity from inhalation exposure to these materials should be studied.

Posner, H.S., H.L. Falk, and T. Damstra. 1979.
Preventive surveillance of environmental chemicals for toxic potential. (From abstract.) Toxicology Research Projects Directory, 4(5):1-47, #5.0373.

The project uses a variety of techniques for early awareness and attempted reduction of chemical- and physical-agent-mediated health hazards. One of the projects involved transmittal of reports on the effects of DBCP on the number of sperm and fertility in workmen at pesticide preparation facilities. Information was collected on permitted agricultural and home garden uses and the general availability of the compound.

Prosser, P.R. 1979.
Silent glands. Arch. Intern. Med. 139:143-144. 11 references.

This letter to the editor notes two distinct clinically significant endocrine syndromes that are directly attributable to

exposure to commonly used pesticides. The second of the endocrine system changes results from exposure to DBCP, namely, infertility characterized by azoospermia or oligospermia, with elevated serum levels of follicle stimulating hormone and luteinizing hormone implying testicular failure. The degree of testicular response was related to the number of years the worker was exposed to DBCP.

Rao, K.S., F.J. Murray, A.A. Crawford, J.A. John, W.J. Potts, B.A. Schwetz, J.D. Burek, and C.M. Parker. (1979).
Effects of inhaled 1,2-dibromo-3-chloropropane (DBCP) on the semen of rats and the fertility of male and female rats. Toxicology Research Laboratory, Dow Chemical U.S.A., Midland, MI 48650.

Exposure of male workers to DBCP has been associated with low sperm counts. The effects of inhaled DBCP on spermatogenesis and fertility and the possible reversibility of these effects was studied by exposing rabbits and rats to 0, 0.1, 1, or 10 ppm of DBCP. Exposure to DBCP was for 14 consecutive weeks with the exception of the 10-ppm rabbits, which were exposed for only 8 weeks. Results indicated a potential for inhaled DBCP to interfere with spermatogenesis in rats and rabbits. Rabbits had decreased sperm counts at 1 and 10 ppm between the 8th and 14th weeks of the study. All of the 10-ppm rabbits appeared to be infertile when mated during the 14th week. A significant dominant lethal effect was seen in rats at 10 ppm as evidenced by an increased incidence of resorptions among unexposed females mated with exposed males. Exposure has been completed, and surviving animals are being monitored for the reversibility of the effects of DBCP on sperm counts in rabbits and fetal resorptions in rats.

Rebuttable presumption against registration and continued registration of pesticide products containing dibromochloropropane (DBCP). 1977.
Federal Register, 42(184):48026-48045. 41 references.

DBCP has been found to adversely affect the reproductive system of male laboratory animals. A summary presents regulatory history, chemistry, tolerances, food residues, metabolism, and toxicity of DBCP.

Rosenkranz, H.S. 1975.
Genetic activity of 1,2-dibromo-3-chloropropane, a widely used fumigant. Bull. Environ. Contam. Toxicol. 14(1):8-12. 12 references.

DBCP tested positive in microbial assays designed to detect mutagens and agents capable of altering the cellular DNA. Results

indicate that DBCP induces mutations of the base-substitution but not of the frame-shift type, suggesting that DBCP acts as an alkylating agent.

Scott, R. 1978.
Reproductive hazards. Job Safety and Health, 6(5):7-13.

A nontechnical presentation of reproductive hazards in the workplace including DBCP.

Temporary emergency standard of 10 ppb set for pesticide DBCP. 1978.
Occupational Health and Safety Letter, September 8.

OSHA established a temporary emergency standard of 10 ppb as an 8-hour time-weighted average for worker exposure to DBCP. In addition, a ceiling of 50 ppm for any 15-minute period during a workday was established by OSHA under the temporary emergency standard, which also issued detailed guidelines for the safe handling of the chemical soil fumigant. No Federal standard currently exists for DBCP. The standard exempts applicators, who may be the most exposed group.

Torkelson, T.R., S.E. Sadek, V.K. Rowe, J.K. Kodama, H.H. Anderson, G.S. Loquvam, and C.H. Hine. 1961.
Toxicological investigations of 1,2-dibromochloropropane. J. Toxicol. Appl. Phamacol. 3:549-559. 4 references.

This is an early report on two independent toxicologic animal studies of DBCP. DBCP was slightly irritating to the skin upon single exposure, and repeated applications caused necrosis of the dermis with the epidermis remaining fairly well preserved. The compound can be absorbed through the skin in toxic amounts.

The compound was found to have moderate to high toxicity from single respiratory exposure and high toxicity on repeated exposure, producing damage at 5 ppm, the lowest level studied. Excessive exposure to the vapors resulted in damage to the liver, kidneys and various tissues, dermis, bronchioles, renal collecting tubules, lens and cornea, and alimentary canal. Specific histologic alteration occurred in the testis of male rats receiving 50 repeated 7-hour exposures to 5 ppm. The effect upon testes resulting from exposure to higher concentrations was particularly severe, resulting in atrophy, degenerative changes, reduction of spermatogenesis, and the development of abnormal sperm.

U.S. Environmental Protection Agency, Office of Pesticide Programs. 1977.
Rebuttable presumption against registration and continued registration of pesticide products containing dibromochloropropane (DBCP). Federal Register, Thursday, September 22 1977, Part VI.

U.S. Environmental Protection Agency. 1978.
Spermatogenesis in agricultural workers potentially exposed to 1,2-dibromo-3-chloropropane (DBCP). A final report by the Epidemiologic Studies Program, Human Effects Monitoring Branch, Technical Services Division, Office of Pesticide Programs, Office of Toxic Substances, U.S. Environmental Protection Agency.

A total of 207 men in 10 states were identified and examined because their occupations in agriculture or agriculture-related industry potentially exposed them to DBCP. All individuals studied, except controls, had either formulated or used DBCP or had been physically associated with its usages (e.g., sales personnel). The study was done to determine if a problem of low sperm counts occurred among them as it apparently did among workers who formulated the compound. The collected and analyzed data showed significant differences among occupational groups in medium sperm counts (millions/ml of semen), and in medium serum levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH).

Comparison of sperm count data for several categories of estimated life-time use indicates lower median sperm densities (million/ml) and higher frequencies of counts below 20 million among the user groups compared to the MacLeod data. High FSH and LH levels were associated with low sperm counts. Levels of both hormones showed a significant negative correlation with sperm count (p is less than 0.0001) whereas testosterone levels did not correlate with sperm counts. Results are quite consistent with an occurrence of primary disruption of spermatogenesis at the testicular level.

U.S. Environmental Protection Agency. 1979.
Pesticide programs: intent to suspend registrations of pesticides products containing dibromochloropropane (DBCP). (FRL 1279-1; OPP-68005 A). Federal Register, 44(143):43335-43341. Tuesday, July 24, 1979.

Action under section 6(c) of the Federal Insecticide, Fungicide and Rodenticide Act, as amended (FIFRA), to control on an interim basis the hazards from use of pesticide products containing DBCP. (See Appendix C of this Proceedings).

Wheater, R.H. 1978.
Short-term exposures to pesticide DBCP and male sterility. J. Am. Med. Assoc. 239:2795.

In reply to a reader's question: data are still inconclusive regarding the reversibility of chemically-induced male sterility resulting from short-term exposure to DBCP. Retest data of 35 chemical production workers from one company indicated that in 21% the sperm count was returning to above the 20 million/cc mark, considered within the range of fertility; however, data from another cohort of workers, who were removed from DBCP exposure as much as 12 years ago, indicate azoospermia.

The most severely exposed DBCP workers showed the following five clinical signs and symptoms:
--normal levels of testosterone,
--normal levels of luteinizing hormone,
--increased levels of follicle-stimulating hormone,
--decrease in testicular size,
--but no notable loss in sexual potency or libido.

Whorton, D, R.M. Krauss, S. Marshall, T.H. Milby. 1977.
Infertility in male pesticide workers. Lancet, 2(8050): 1259-1261. 10 references.

A number of cases of infertility were found among workers in a pesticide factory. All 39 employees who worked in the Agricultural Chemical Division (ACD) that regularly formulated DBCP participated in the study. Of the 36 men in the group, 11 had had vasectomies. Only the length of the time they worked in the ACD could be used as a measure of exposure.

The major effects, seen in 14 of 25 non-vasectomised men, were azoospermia or oligospermia and raised serum levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). No other major abnormalities were detected, and testosterone levels were normal.

The relationship of length of chemical exposure (time of employment) to sperm count was striking. Workers with sperm counts less than 1 million/ml had been exposed at least 3 years. None with sperm counts above 40 million/ml had been exposed for more than 3 months. Preliminary evaluation of the testicular biopsy results of the severly affected men indicated loss of spermatogonia, with no evidence of inflammation or severe fibrosis. Three men who had sperm counts of 10 to 30 million/ml had exposures between 1 and 3 years--an observation that supports the notion of a direct relationship between length of exposure and degree of oligospermia.

Whorton, D., T.H. Milby, R.L. Davis. 1978. Testicular function among Shell Denver plant employees. A report to Shell Oil Company from Environmental Health Associates, Inc., September 1978.

This study involved 320 Shell Denver employees; 182 were classified as exposed to DBCP and 138 were classified as nonexposed. Ninety-one exposed workers and twenty-nine nonexposed workers (controls) participated in the medical evaluations. Only 64 of the exposed population and 20 of the control population provided technically satisfactory semen samples. Almost 22% of the exposed Denver population had sperm counts less than 20 million/ml, whereas only 10.0% of the nonexposed Denver population and 5.6% of Environmental Health Associate's composite groups had counts below this biologically important number. Four (6.3%) of the exposed Denver employees were azoospermic.

Whorton, D., T.H. Milby, R.L. Davis. 1978. Testicular function among Shell Mobile plant employees. A Report to Shell Oil Company from Environmental Health Associates, Inc., November 2, 1978..

Seventy-one individuals were categorized as exposed and thirty-four as controls. The cumulative percent distribution curves comparing Mobile-exposed, Mobile control, and Environmental Health Associate's composite control group clearly show that a substantially larger percentage (16.9%) of the Mobile DBCP-exposed group fall into lower sperm count categories (especially less than 20 million/ml) than either the internal (Mobile, 8.3%) or external (EHA, 5.1%) control groups. A cumulative percent distribution of sperm counts, significantly different at p less than 0.01, is interpreted as a result of the difference between the medians of the distributions. A highly significant association was found between the log transformation of both weighted exposure hours and sperm count.

Whorton, D., T.H. Milby, R.M. Krauss, and H.A. Stubbs. 1979. Testicular function in DBCP exposed pesticide workers. J. Occup. Med. 21(3):161-166. 10 references.

In this recent, large clinical-epidemiological study of DBCP under workplace conditions, 142 non-vasectomized men provided semen samples. Of these men, 107 had been exposed to DBCP and 35 had not been exposed. Clear-cut differences in both the distribution of sperm counts and the median counts between the exposed and nonexposed men were found. Of the exposed, 13.1% were azoospermic,

16.8% were severely oligospermic, and 15.8% were mildly oligospermic. Among the controls, 2.9% were azoospermic, none were severly oligospermic, and 5.7% were mildly oligospermic. A clear relationship was identified between exposure duration and sperm count. The histological pattern resulting from 10 bilateral, open testicular biopsies shows the seminiferous tubules to be the site of damage with the most severely affected individuals having a Sertoli cell only pattern. The information suggests that reversibility does occur in some cases, although at some point along the dose-response curve, damage appears to be irreversible.

Observations suggest that in a population of oligospermic men, the predictive ability of the hormone assay is greatly reduced. Thus, for DBCP exposure, a sperm count remains the best clinical laboratory test of testicular function.

Appendix B

(From the Federal Register, 43(53):11514-11533, March 17, 1978)

Title 29--Labor

CHAPTER XVII--OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION, DEPARTMENT OF LABOR

PART 1910--OCCUPATIONAL SAFETY AND HEALTH STANDARDS

Occupational Exposure to 1,2-Dibromo-3-Chloropropane (DBCP)

[4510-26]

Title 29—Labor

CHAPTER XVII—OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION, DEPARTMENT OF LABOR

PART 1910—OCCUPATIONAL SAFETY AND HEALTH STANDARDS

Occupational Exposure to 1,2-Dibromo-3-Chloropropane (DBCP)

AGENCY: Occupational Safety and Health Administration, Department of Labor.

ACTION: Final rule.

SUMMARY: This standard is based on a determination by the Occupational Safety and Health Administration that the available scientific evidence establishes that employee exposure to DBCP presents a hazard of sterility and cancer. This standard replaces the emergency temporary standard (ETS) for exposure to DBCP (42 FR 45536 September 9, 1977), and limits employee exposure to DBCP to 1 part DBCP per billion parts of air (1 ppb) as an 8-hour time-weighted average concentration. The standard also prohibits eye and skin contact with DBCP. The standard provides for employee exposure monitoring, engineering controls and work practices, respirators, personal protective equipment and clothing, employee training, medical surveillance, regulated areas, hygiene practices and facilities, and record-keeping. The basis for this standard is OSHA's determination that human and animal data demonstrate that DBCP causes sterility and that animal data indicates that exposure to DBCP presents a cancer hazard to workers.

EFFECTIVE DATE: This new permanent standard is effective April 17, 1978. The provisions contained in the ETS are continued in effect until superseded by the new permanent standard.

FOR FURTHER INFORMATION CONTACT:

Mr. David Welsh, Office of Special Standards Programs, OSHA, Third Street and Constitution Avenue NW., Room N3663, Washington, D.C. 20210, 202-523-7174.

SUPPLEMENTARY INFORMATION: This permanent occupational safety and health standard is issued pursuant to sections 6(b), 6(c) and 8(c) of the Occupational Safety and Health Act of 1970 (the Act) (84 Stat. 1593, 1596, 1599; 29 U.S.C. 655, 657), the Secretary of Labor's Order No. 8-76 (41 FR 25059) and Title 29, Code of Federal Regulations (CFR) Part 1911. It amends Part 1910 of 29 CFR by revising 29 CFR 1910.1044, to provide a permanent standard for the regulation of occupational exposure to DBCP. In order to assure that affected employers and employees will be informed of the existence of these provisions and that employers affected are given an opportunity to familiarize themselves and their employees with the existence of the new requirements, the effective date of the revision to § 1910.1044 will be April 17, 1978. To provide continued protection for employees until that date, the provisions currently contained in § 1910.1044 are promulgated pursuant to sections 6(b), 6(c) and 8(c) of the Occupational Safety and Health Act as an occupational safety and health standard effective March 17, 1978. The revisions to § 1910.1044 will supersede the current provisions as of April 17, 1978. This standard applies to all employments in all industries covered by the Act, including "general industry", construction and maritime, excluding only agriculture. As discussed more fully below, only the labeling, training and emergency provisions of the standard apply to the handling of sealed, intact containers of DBCP.

I. Background

DBCP has been used as an agricultural nematocide since 1955. It is a dense yellow or amber liquid with a pungent odor at high temperatures. It has a low vapor pressure (0.8 mm Hg at 20° C) and is slightly soluble in water (1,000 ppm).

DBCP, a halogenated hydrocarbon, is produced primarily by the bromination of allyl chloride at room temperature, usually a vigorous reaction which requires cooling. DBCP is produced in the United States by Dow Chemical Company and Shell Oil Company. Mexico, Japan and Israel also manufacture DBCP and export DBCP to this country. About 12 million pounds of DBCP were consumed in 1972.

Following manufacture, DBCP is shipped to formulators who reprocess the chemical into products for consumer use. DBCP has been formulated into emulsifiable concentrates, liquid concentrates, powder, granules, and solid material. Formulating granular DBCP involves spraying liquid DBCP onto inert granules. The formulation of liquid and emulsified DBCP products usually involves the blending of technical grade DBCP with an emulsifier or solvent. The formulators may also distribute the technical grade product. About 80 formulators have labels registered with EPA for the approximately 160 products containing DBCP (42 FR 48026). The complete distribution chain generally includes the manufacture of technical grade DBCP, transportation to the formulator, formulation of DBCP-containing pesticides, distribution of DBCP-containing pesticides, and the agricultural consumption of DBCP pesticides. It is estimated that about 1,600 to 2,900 production employees in facilities manufacturing and formulating DBCP have been recently exposed to this chemical (exhibit 6, pp. 3-8).

Additionally, through the International Labor Organization's health hazard alert system OSHA has learned that, in addition to Japan, Mexico and Israel, the Netherlands, Finland and Sweden have also used DBCP. None of these nations was previously aware of the possible sterility effects of DBCP. All have suspended use of the substance, and Israel, Japan and the Netherlands have initiated further studies into the health effects of DBCP (exhibit 49).

II. History of Regulation

(1) Chronology of Events

In 1961, a research paper by Torkelson et al. recommended that occupational exposure to DBCP be controlled to less than 1 ppm in air (exhibit 4-56). This recommendation was based on observed reproductive effects in animals exposed to atmospheric concentrations of DBCP as low as 5 ppm. However, no national concensus standard of Federal standard for exposure to DBCP was developed prior to OSHA's emergency temporary standard discussed below.

In late July, 1977, preliminary results of semen analyses of 27 DBCP exposed employees at the Agricultural Chemical Division (a formulator of DBCP) of the Occidental Chemical Co. in Lathrop, Calif., indicated severely depressed sperm counts in eleven of these employees (exhibit 4-63). Based on these results, the Oil, Chemical and Atomic Workers (OCAW) requested on August 5, 1977, that the National Institute for Occupational Safety and Health (NIOSH) conduct a health hazard evaluation at this Occidental Chemical Co. plant. NIOSH contracted with Environmental Health Associates of Berkeley, Calif. to perform this evaluation, which later confirmed a high incidence of sterility and infertility at this plant.

Preliminary test results of employees at Dow Chemical Co.'s DBCP production facility in Magnolia, Ark., showed low sperm counts for several of these employees (exhibit 9, p. 54). On the basis of the results of these studies, Dow suspended production and sale of DBCP on August 12, 1977 (exhibit 9, p. 54). Shell Oil Co., the other major producer of DBCP in the United States, was not manufacturing DBCP at that time. Both Shell and Dow immediately requested the return of outstanding stocks of the substance (exhibit 4-60, 4-61).

In a telegram dated August 12, 1977, OSHA alerted approximately 80 man-

ufacturers and formulators to the potential hazard of worker exposure to DBCP (exhibit 4-56). On August 25, a guideline document detailing suggested work practices was forwarded to those same affected companies (exhibit 4-56).

On August 23, 1977, the Oil, Chemical and Atomic Workers International Union President, A. F. Grospiron, formally requested the Secretary of Labor to take immediate steps to prevent worker exposure to DBCP. Specifically OCAW requested that worker exposure be limited to one part DBCP per billion parts of air, and that a broad testing program to locate incidences of cancer and sterility among workers be established (exhibit 4-38).

(2) EMERGENCY TEMPORARY STANDARD

Based on a determination that the available data conclusively established that employee exposure to DBCP presented a grave danger of sterility as well as cancer, OSHA published an Emergency Temporary Standard (ETS) on September 9, 1977 (42 FR 45536) regulating DBCP exposure in the workplace. A correction document was published on September 16, 1977 (42 FR 46540). The emergency standard issued under sections 6(c) and 8(c) of the Act as 29 CFR 1910.1044, established an 8-hour time-weighted average (TWA) permissible exposure level of 10 parts DBCP per billion parts of air, with a permissible ceiling exposure level of 50 ppb as averaged over any 15 minute period in the workday. The ETS also established other requirements, including, for example, monitoring, methods of compliance, respiratory protection, medical surveillance and training.

Interested persons were invited to submit written data, views and arguments with respect to the issues raised by the ETS.

(3) THE SAN FRANCISCO INQUIRY

The California Department of Industrial Relations convened an inquiry to investigate the causes of the Occidental Chemical Co. DBCP incident, and to propose mechanisms to prevent any such occurrences in the future. The inquiry extended from October 12 through October 19, 1977. Participating were representatives of Occidental Chemical Co., Dow Chemical Co., Shell Oil Co., and the State of California as well as expert witnesses from the University of California at Berkeley. The transcripts of the inquiry and related exhibits were entered as exhibit 10 into the OSHA record for DBCP rulemaking.

(4) THE CINCINNATI CONFERENCE

A conference concerning DBCP was sponsored by NIOSH in Cincinnati, Ohio., on October 20 and 21, 1977. The purpose of the conference was to share information acquired by various groups concerning DBCP exposure. At this conference the findings of sterility at the Occidental Chemical Company were discussed, as well as the findings of Shell Oil Company and Dow Chemical Company at their DBCP manufacturing plants. Also, nationally recognized experts made presentations concerning DBCP-related issues such as semen analysis, mutagenicity, environmental monitoring and respiratory protection. The verbatim transcript of this conference was entered into the OSHA record as exhibit 9.

(5) THE PROPOSAL

In the November 1, 1977, issue of the FEDERAL REGISTER, OSHA published a comprehensive proposal for a permanent standard for occupational exposure to DBCP (42 FR 57266). The proposal called for an 8-hour TWA permissible exposure level of 1 ppb, with a ceiling of 10 ppb averaged over any 15 minute period. In addition, the proposal included a prohibition on skin exposure to the substance.

Unlike the ETS, the proposal required that the employer reduce employee exposures to or below the permissible exposure limit solely through engineering and work practice controls. Where these controls were not able to reduce exposures to within the permissible exposure limit, the proposal required that such controls be used to the greatest extent feasible and then be supplemented by the use of respirators.

The proposal allowed 30 days for interested parties to submit written comments, views and arguments, and announced that an informal public hearing for the submission of oral testimony would begin on December 13, 1977. Fourteen comments were received by OSHA. Twelve notices of intent to appear at the hearing were also received.

(6) THE HEARING

The OSHA rulemaking hearing (hereafter referred to as the hearing) was conducted from December 13 through December 15, 1977, before an Administrative Law Judge. The parties which were represented and presented oral testimony at the hearing were the Pesticide and Pollution Action Committee of Clemson University; South Carolina Peach Council; South Carolina Department of Agriculture; Industrial Union Department, AFL-CIO; Shell Oil Company; Oil, Chemical and Atomic Workers Union; California Department of Food and Agriculture; and California Department of Industrial Relations. All of these participants were given the opportunity to present testimony and to question other witnesses. Parties participating in the hearing were given until December 30, 1977, for the submission of new evidence, and until January 16, 1978, for the submission of post-hearing briefs and comments. Twenty-four post-hearing submissions were received.

(7) FINAL ENVIRONMENTAL IMPACT STATEMENT

In conjunction with the development of the proposed standard, OSHA prepared a draft environmental impact statement. The draft environmental impact statement was published in the FEDERAL REGISTER (42 FR 57266). On November 11, 1977, the Council on Environmental Quality published a notice of availability of the DBCP draft environmental impact statement (exhibit 7). In addition to the 45 day comment period specified in 29 CFR 1999.4 (g), the environmental impact of the proposed standard was also an issue at the DBCP hearing as provided by 29 CFR 1999.4 (h) and the notice of proposed rulemaking (42 FR 57266). A notice of availability of the final environmental impact statement for DBCP was published on March 3, 1978 by EPA (43 FR 8846).

(8) THE RECORD.

This permanent DBCP standard is based on a careful consideration of the entire record in this proceeding, including materials relied on in the emergency temporary standard, materials referenced in the proposal, and the record of the informal rulemaking hearing including the transcript, exhibits, and pre-hearing and post-hearing written comments. Copies of the official list of hearing exhibits, comments, and notices of intent to appear at the hearing can be obtained from the Docket Office, Docket H-061, Room S6212, U.S. Department of Labor, 3rd Street and Constitution Avenue, NW., Washington, D.C. 20210.

III. PERTINENT LEGAL AUTHORITY

The primary purpose of the Act is to assure, so far as possible, safe and healthful working conditions for every working man and woman. One means prescribed by Congress to achieve this goal is the authority vested in the Secretary of Labor to set mandatory safety and health standards. Occupational safety and health standards provide notice of the requisite conduct or exposure level and provide a basis for ensuring the existence of safe and healthful workplaces. The Act provides that:

The Secretary, in promulgating standards dealing with toxic materials or harmful physical agents under this subsection, shall set the standard which most adequately assures, to the extent feasible, on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity even if such employ-

ee has regular exposure to the hazard dealt with by such standard for the period of his working life. Development of standards under this subsection shall be based upon research, demonstrations, experiments, and such other information as may be appropriate. In addition to the attainment of the highest degree of health and safety protection for the employee, other considerations shall be the latest available scientific data in the field, the feasibility of the standards, and experience gained under this and other health and safety laws. (Section 6(b)(5))

Sections 2(b)(5) and (6), 20, 21, 22, and 24 of the Act reflect Congress' recognition that conclusive medical or scientific evidence including causative factors, epidemiological studies or dose-response data may not exist for many toxic materials or harmful physical agents. Nevertheless, standards cannot be postponed because definitive medical or scientific evidence is not currently available. Indeed, while final standards are to be based on the best available evidence, the legislative history makes it clear that "it is not intended that the Secretary be paralysed by debate surrounding diverse medical opinion." House Committee on Education and Labor, Report No. 91-1291, 91st Cong., 2d Session, p. 18 (1970). This Congressional judgment is supported by the courts which have reviewed standards promulgated under the Act. In sustaining the standard for occupational exposure to vinyl chloride (29 CFR 1910.1017), the U.S. Court of Appeals for the Second Circuit stated that "It remains the duty of the Secretary to act to protect the working man, and to act even in circumstances where existing methodology or research is deficient. "Society of the Plastics Industry, Inc. v. Occupational Safety and Health Administration", 509 F. 2d 1301, 1308 (2nd Cir. 1975), cert. den., sub. nom., "Firestone Plastic Co. v. United States Department of Labor," 95 S. Ct. 1998, 4 L. Ed. 2d. 482 (1975).

A similar rationale was applied by the U.S. Court of Appeals for the District of Columbia in reviewing the standard for occupational exposure to asbestos (29 CFR 1910.1001). The Court stated that:

Some of the questions involved in the promulgation of these standards are on the frontiers of scientific knowledge, and consequently as to them insufficient data is presently available to make a fully informed factural determination. Decision-making must in that circumstance depend to a greater extent upon policy judgments and less upon purely factual judgments.

"Industrial Union Department, AFL-CIO v. Hodgson," 499 F. 2d 467, 474 (D.C. Cir. 1974).

In setting standards, the Secretary is expressly required to consider the feasibility of the proposed standards. Senate Committee on Labor and Public Welfare, S. Rep. No. 91-1282, 91st Cong., 2d Sess., p. 58 (1970). Nevertheless, considerations of technological feasibility are not limited to devices already developed and in use. Standards may require improvements in existing technologies or require the development of new technology. "Society of Plastic Industry, Inc. v. Occupational Safety and Health Administration", supra at 1309.

Where appropriate, the standards are required to include provisions for labels or other forms of warning to apprise employees of hazards, suitable protective equipment, control procedures, monitoring and measuring of employee exposure, employee access to the results of monitoring, and appropriate medical examinations. Standards may also prescribe recordkeeping requirements where necessary or appropriate for enforcement of the Act or for developing information regarding occupational accidents and illnesses (section 8(c)). The permanent standard for DBCP was developed on the basis of the above legal considerations.

IV. Major Issues

OSHA has concluded from the evidence in the record that DBCP presents a hazard of cancer and sterility to exposed workers. The results of well-designed animal studies indicate DBCP to be a potent carcinogen in two sexes of two mammalian species at two dose levels. Furthermore. DBCP has been found to cause positive results in microbial assays designed to detect chemicals capable of mutagenesis. This evidence, which has not been seriously challenged by any of the participants in the proceeding, leads to the conclusion that DBCP must be regulated as a human carcinogen.

Animal studies have also demonstrated that oral dosages of DBCP induce degeneration of testicular tissue, accompanied by a reduction of sperm count and abnormal sperm cell development.

These testicular effects were confirmed in humans with the recent discovery of sterility and infertility in a large number of male employees exposed to low levels of DBCP in the manufacture and formulation of pesticides. This evidence was also uncontroverted by hearing participants.

Accordingly, OSHA has concluded that the proven carcinogenic and sterilant potential of DBCP warrants limiting exposure to the lowest level feasible. OSHA has therefore established an eight-hour time-weighted average permissible exposure limit of 1 part per billion (ppb). OSHA has concluded, based on evidence presented in the record, that this limit represents the lowest exposure level achievable using present technology.

Additionally, based on evidence that DBCP can penetrate the skin, and that skin exposure is a significant rout of entry, OSHA has prohibited any skin contact with the substance.

The following discussion deals with the major issues involved in the proceeding.

(1) Whether DBCP has been experimentally proven to be a carcinogen

The carcinogenicity of DBCP in both sexes of two mammalian species (rats and mice) at two dose levels has been documented on the record with a study conducted by the National Cancer Institute (NCI) (exhibit 16). For this study, discussed more fully in the preambles to the ETS and the proposal, NCI used 50 animals of each sex of two species at each of two dose levels (400 total experimental animals) in addition to controls. The two dose levels, administered orally, were selected on the basis of a preliminary subchronic toxicity test (exhibit 16, p. 7). The duration of treatments ranged from 47 to 78 weeks (exhibit 16, p.v).

Dr. Elizabeth Weisburger, Chief of the Carcinogen Metabolism and Toxicology Branch of NCI, gave the following testimony at the hearing:

[The] final report indicated that among rats given DBCP, 100 percent in males and 77 percent in females in the high dose had gastric cancer. This is very highly significantly different from the rate in the controls.

At the low dose, 96 percent of the males and 78 percent of the females had stomach tumors. In addition, 62 percent of females on the high dose and 48 percent on the low dose had mammary carcinoma compared to zero among the controls. Also very highly significantly different.

Hemangiosarcomas were also increased in both males and females at the lower dose level. Furthermore, there were many metastases of these gastric tumors which invaded the stomach wall into the peritoneal cavity and throughout the body. (tr 80-81)

Dr. Weisburger went on to state that among mice, 96 percent of the males and 98 percent of the females on the higher dose developed gastric cancer. On the low dose the percentages were 93 and 100 respectively. As in rats, metastases of these tumors were also noted (tr 81). Dr. Weisburger concluded that "the data from this bioassay thus show that DBCP is a carcinogen in two species and both sexes of two species of animals at two dose levels, inducing tumors which were relatively rare in control or untreated animals." (tr 81)

Dow Chemical suggested that the high dose levels used in the NCI study may have influenced the observed incidences of both stomach and mammary tumors (exhibit 5-8). However, interim results of a recent DBCP dietary study conducted by Hazelton Laboratories and sponsored by Dow Chemical demonstrate that carcinogenic effects are apparent even at dose levels "unlikely to have caused irritation sufficient to increase the induction of cancer" (exhibit 5-8, p. 22).

In the Dow experiment, DBCP was administered to the rats in their food in quantities sufficient to provide dose levels of 0, 0.3, 1 and 3 mg/kg/day. The study period lasted for 104 weeks. The preliminary gross autopsy results revealed "tumor-like" lesions in 6 percent (3/54), 31 percent (17/55), and 64 percent (24/37) of the rats at dose levels of 0.3, 1, and 3 mg/kg/day respectively. Three percent (2/63) of the controls developed such lesions (exhibit 5-8, p. 22). These data further confirm the NCI conclusion that DBCP is carcinogenic.

OSHA concludes, therefore, that DBCP has been experimentally proven to be carcinogenic in animals.

(2) WHETHER DBCP HAS BEEN EXPERIMENTALLY DEMONSTRATED TO BE MUTAGENIC

There are indications from in vitro experiments that DBCP may cause mutagenic effects. Rosenkranz (1975) examined the effects of DBCP on two strains of *E. coli* and on two tester strains of *Salmonella typhimurium*, strains of bacteria normally used for mutagenic research. He concluded that DBCP causes positive results in microbial assays designed to detect chemicals capable of mutagenesis (exhibit 4-45, p. 10).

Dr. Arlene Blum, Research Associate in Biochemistry at the University of California, stated at the San Francisco inquiry (exhibit 10, p. 32) and Cincinnati conference (exhibit 9, p. 134) that DBCP also gave positive results using the Ames test, a bacterial screening test designed to detect chemicals capable of mutagenesis. She noted that DBCP produced results similar to those of the substance benzidine, a known human carcinogen (exhibit 9, p. 140).

Furthermore, a high correlation has been found between the results of in vitro mutagenicity tests and long-term animal carcinogenicity studies (exhibit 9, pp. 134, 135). OSHA finds that based on the evidence in the record, which was unchallenged, DBCP has been experimentally demonstrated to be mutagenic.

(3) WHETHER DBCP SHOULD BE REGULATED AS POSING A CARCINOGENIC RISK TO HUMANS

For all practical purposes, the detection of carcinogenic activity of chemicals is based on animal experimentation. Because of the difficulties of epidemiologic studies on humans exposed to potential carcinogens, there are usually no data which provide us definitive evidence as to whether cancer in man is due to a chemical that has been shown to be carcinogenic in animal studies. Moreover, ethical considerations cannot allow human experimentation where cancer is the expected response. However, nearly all chemical substances or mixtures that have been proven carcinogenic by direct observation in man have also been shown to be carcinogenic in experimental animals. OSHA maintains, therefore, that a substance which causes cancer in animals must be considered, as a policy matter, as posing a carcinogenic risk to workers. This view has been extensively discussed in other OSHA standards and forms the basis of this agency's and virtually every other agency's regulation of carcinogens. Furthermore, this view was not challenged during the course of the proceeding.

Based on the record, OSHA has concluded that animal experiments have conclusively demonstrated DBCP to be a chemical carcinogen, and therefore to pose a carcinogenic risk to workers. Accordingly in the absence of a demonstrated safe or no-effect level for human exposure to a carcinogen, OSHA believes that it must be assumed as a prudent policy matter, and in light of the scientific evidence available, that no safe level for exposure to DBCP exists (tr. 14-15). After a review of the complete record, OSHA has found no evidence which disputes this reasoning and accordingly concludes that DBCP should be regulated as posing a carcinogenic risk to humans.

(4) WHETHER DBCP HAS BEEN EXPERIMENTALLY SHOWN TO PRODUCE TESTICULAR EFFECTS

In 1961, Torkelson, et al. (exhibit 4-56) conducted experiments in which four animal species (rats, guinea pigs, rabbits and monkeys) were exposed to DBCP by inhalation. The test animals were subjected to 50-66 exposures of 12 ppm DBCP over 70 to 92 days (7 hours per day, 5 days per week). A 40 to 50 percent mortality was observed in the rat study groups which, in most cases, was attributed to lung infections. Examination at autopsy showed damage to the lungs, kidneys, digestive system, and "severe atrophy and degeneration of the testes of all species." In the rats this effect was accompanied by a reduced sperm count, abnormal cell development, and degeneration of the seminiferous tubules. As part of the study 15 male rats were exposed to 5 ppm 50 times in 70 days. At this exposure level the testicular weights of one half the rats were found to be reduced by 50 percent. This result was not statistically significant due to the large internal variation within the group. However, these findings did indicate a need for caution at low exposures to DBCP, and served as the basis for Torkelson's 1 ppm recommendation as a limit for occupational DBCP exposure.

A 1970 study by Faydysh et al. (exhibit 4-22) showed that a 70 mg/kg/day dose of DBCP, administered orally for 45 days, produced a necrotic action on the testicles of white rats.

A report in 1971 by Rakmatullaev (exhibit 4-43) disclosed that chronic (8 month) dietary exposures to DBCP at 5 mg/kg/day produced a distinct decrease in sperm motility (the ability of the sperm to move) for male rats and a decrease in the fertility rate of female rats mated to DBCP-exposed males.

Also, Reznik and Sprinchan reported in 1975 (exhibit 4-78) that acute (single dose, 100 mg/kg) and chronic (10 mg/kg/day for 4-5 months) doses of DBCP severely affected spermatogenesis in male rates.

Based on the above data which was unchallenged on the record, OSHA concludes that DBCP has experimentally produced testicular effects in animals.

(5) WHETHER DBCP HAS CAUSED INFERTILITY IN MALE WORKERS

As mentioned above, fertility studies were initiated in July 1977 as a result of increasing concern among workers of the Agricultural Chemical Division of Occidental Chemical Co. in Lathrop, Calif., that their low birth rate might be related to pesticide poisoning. Preliminary studies performed by Dr. Donald Whorton, a specialist in internal medicine and occupational diseases, indicated a surprising prevalence of abnormal sperm counts (exhibit 4-63) (tr. 223-225). As a result of these findings, NIOSH contracted with Environmental Health Associates to perform a Health Hazard Evaluation (exhibit 26) in August 1977. The results of this evaluation were that of the 107 workers studied, 13.1 percent (14) had azoospermia (no sperm) and an additional 16.8 percent (18) were oligospermic (having an abnormally low number of sperm present in the ejaculate causing infertility) (tr. 233). In a control group of 35 workers, one individual (2.9 percent) was azoospermic and none were oligospermic. Exposure levels at this plant had been found to range from 0.29 to 0.43 ppm as an 8-hour TWA (exhibit 9, p. 150 Tables IV and V). DBCP had been formulated at Occidental Chemical since 1957 (exhibit 10, p. 116).

Also of importance were Dr. Whorton's findings that reduced sperm counts correlated well with the number of months an employee was exposed to DBCP (tr. 232). He found that the longer an employee had been exposed to DBCP, the more likely the worker was to have a reduced sperm count. This evidence indicates a possible dose-response relationship in DBCP's toxic effects. Equally important were Dr. Whorton's findings that the observed sperm counts were the result of massive damage to the cells of the spermatogenic tubule. When viewed microscopically these tubules normally appear full with developing sperm cells (tr. Appendix I, p. 6). In the case of DBCP-affected males, how-

ever, the tubules appear empty (tr. Appendix I, p. 8).

In September 1977, Dow Chemical Co. reported that of 86 employees exposed to DBCP at a production facility in Magnolia, Ark., 24.2 percent (21) were found to be azoospermic, and 30.2 percent (26) were oligospermic (exhibit 9, p. 67-j, 67-k). During DBCP production, 8-hour TWA exposures were measured to range between 0.04 and 0.4 ppm (exhibit 4-77B). No local non-exposed group was studied as a control, but these results do show striking sperm count reduction when compared to those of control groups at other plants. These results, like those of Dr. Whorton, also indicated a correlation between sperm count depression and the degree of DBCP exposure (exhibit 9, p. 57). The duration of DBCP production at Magnolia was from mid-January, 1976 through August 11, 1977 (exhibit 10, p. 188).

In November 1977, Shell Chemical Company announced the final results of fertility tests of employees exposed to DBCP at their Denver and Mobile plants (exhibit 11). At Mobile, of 80 workers tested only 2.5 percent (2) were azoospermic while 13.8 percent (11) were oligospermic. These rates reportedly do not differ from control values. The duration of DBCP production at Mobile, however, was only slightly in excess of one year (April 1976 through July 1977).

At the Shell Denver plant, where DBCP production had begun in 1955 and ended February 1976, the results indicated abnormally low sperm counts. Of the 49 workers tested, 10.2 percent (5) were azoospermic and 14.3 percent (7) were oligospermic (exhibit 11—average of second and third semen analysis). Shell maintained that these data were similar to certain literature values (exhibit 11). However, Dr. Marshall cautioned against such a comparison at the OSHA hearing (tr. 237), indicating that much of the data in the literature may itself reflect a bias toward low sperm counts. For instance, many of the studies did not consider a continence (sexual abstinence) period before semen collection. Dr. Marshall made the point that a standardized continence period for semen collection is necessary in order to make valid comparisons of sperm counts (tr. 239).

A control group of 31 non-exposed Denver employees contained no azoospermics, but a surprising incidence of oligospermia (22.6 percent) (exhibit 11). Attempts to correlate length of exposure with sperm count using these data have not been successful. As a whole, the Denver results seem to indicate a DBCP effect as reflected in the high incidence of azoospermics among exposed employees, but such an analysis cannot be regarded as conclusive.

From the time industrial hygiene measurements were initiated in 1972 through the cessation of DBCP production in 1976, 8-hour TWA exposures at Denver consistently were measured to be in the range of 0.2 to 0.4 ppm (exhibit 9, p. 81).

Dow Chemical also reported, however, that studies on a DBCP-exposed population at their Midland, Mich., plant indicated that the sperm counts of 249 "potentially exposed" workers were comparable to those of 77 controls (exhibit 12). DBCP had been produced at the Midland plant from 1957 to 1976. In 1975, employee 8-hour TWA exposures to DBCP were measured to be between "none detectable" and 0.17 ppm (ehxibit 4-77B) Although these results are encouraging, they do not establish a safe or no effect level. The danger of DBCP exposure at very low levels (see Lathrop and Magnolia) are such as to discourage reliance on a no effect level based on one study.

In December 1977, OSHA was notified by telegram that initial tests had indicated sterility in five workers at Bromine Compounds, Ltd., Beersheva, Israel (exhibit 46-d). No data on levels of exposure has been received. Bromine Compounds, Ltd., had manufactured 300 tons of DBCP annually until production was halted in August, 1977.

A point of controversy on the record was the determination of what sperm count value would constitute oligospermia (an abnormally low number of sperm present in the ejaculate causing infertility). It is, of course, necessary to have some agreed upon standard against which to compare the results of the various studies. Values, indicating an abnormally low sperm count, which were suggested by participants at the Cincinnati conference ranged from ten million to 40 million sperm per milliliter ejaculate (exhibit 9, p.39, 57, 61, 125, 133-c). OSHA has selected for the purposes of this discussion a level of 20 million sperm per milliliter ejaculate below which a man is to be considered oligospermic. This selection was based on the testimony of Dr. Summer Marshall (a urologist in private practice in Berkeley, Calif., and an Associate Clinical Professor of Urology, School of Medicine, University of California at San Francisco) (tr. 236) as well as careful analysis of other expert testimony and literature sources.

Based on the above evidence OSHA concludes that exposure to DBCP has been demonstrated to produce infertility (reduced sperm count) and sterility in male workers at very low levels of exposure.

(6) WHETHER DBCP ALONE WAS THE CAUSAL AGENT OF THE OBSERVED INFERITILITY IN WORKERS

A problem encountered in assessing DBCP-induced infertility was the possibility that the observed effects were due to exposure to other substances present in these workplaces. For example, Dr. Whorton stated at the Cincinnati conference that some 224 chemicals were used in Occidental Chemical's Agricultural Chemical Division (exhibit 9, p. 29). DBCP was, however, immediately suspect at the Occidental plant due to: (1) The large amounts of DBCP handled there, and (2) the Torkelson report which showed substantial effects on rat testicles when atmospheric concentrations of DBCP were as low as 5 ppm. These suspicions were confirmed when the results of semen analyses of employees at the Shell and Dow DBCP plants showed severely depressed sperm counts (exhibit 11) (exhibit 9, p. 67-i, 67k). Although ethylene dibromide (EDB), a chemical which has experimentally been shown to produce reproductive effects in animals, was also being manufactured at Magnolia, this chemical was removed from suspicion by the preliminary results of sperm counts of employees from other EDB-producing plants (exhibit 9, p. 219, 235). These results indicated that the sperm counts of the employees exposed to EDB alone were in the normal range.

Based on the above evidence OSHA concludes that DBCP was the causative agent of the observed sterility and infertility effects in exposed workers.

(7) WHETHER DBCP-INDUCED INFERTILITY IS REVERSIBLE ONCE EXPOSURE HAS CEASED

At the Cincinnati conference Dr. John MacLeod, a nationally recognized fertility expert from Cornell University, discussed infertility studies concerning reversibility that were carried out with bis-dichloro acetyl diamine and X-radiation using prison volunteers. Bis-dichloro acetyl diamine "has similar effects to that of DBCP" in that "you get profound depression in testicular function to the point of azoospermia". This effect was found to be totally reversible, though the time period of recovery was not given (exhibit 9, p. 114-115). Dr. MacLeod also referred to "the extraordinary capacity of the human testes to recover from devastation" following bombardment with high doses of X-radiation (exhibit 9, p. 256). Recovery times were noted as ranging from 18 months to 2 years. However, there is a paucity of data concerning the reversibility of the effects of DBCP. As Dr. Whorton stated at the OSHA hearing:

> We have scant data with which to address the question of reversibility of DBCP-suppressed testicular function. The information that we do have suggests that a reversibility can occur in some cases, but that at some point along the dose-response curve, the damage may be permanent (tr. 234).

The question of the reversibility of DBCP-induced testicular effects therefore remains unanswered at this time.

Even if currently affected workers fully recover at some point in the future, the issue of reversibility is not determinative for regulatory purposes. OSHA can not allow workplace conditions which result in severe physical impairment such as sterility, regardless of possible future reversibility.

(8) DOES SUITABLE TECHNOLOGY EXIST IN ORDER TO COMPLY WITH THE REGULATION?

The technological feasibility of the DBCP standard has been assessed by JRB Associates, Inc. in a report entitled, "Economic Impact Assessment of the Occupational Safety and Health Administration's Standard on Occupational Exposure to 1, 2-Dibromo-3-chloropropane (DBCP)" (exhibit 6).

This study has concluded that compliance with the permissible exposure limit of 1 ppb is technologically feasible (exhibit 6, pp. 4-1). Furthermore, OSHA maintains that it is feasible to achieve ambient levels of 1 ppb solely through the implementation of engineering and work practice controls. These controls consist of totally enclosing the DBCP manufacturing and formulating facilities, maintaining such enclosures under negative air pressure, and removing the DBCP in the exhaust air via charcoal adsorption.

Evidence on the record indicates that DBCP manufacturers now routinely control 8-hour TWA exposures to levels ranging from 40 to 430 ppb in response to an informal exposure limit of 1 ppm (part per million) established prior to a full understanding of the serious nature of the DBCP hazard (exhibit 4-77B; exhibit 9, p. 150 Tables IV and V). Furthermore, the record indicates that these levels were maintained without the use of local exhaust ventilation (exhibit 10, p. 128, 129) or other control techniques. This indicates that there exists a great capacity for exposure reduction.

Moreover, exposure to bischloromethylether, a chemical known to be a human carcinogen, is currently controlled to 1 ppb (exhibit 6, p. 42). Therefore it may be concluded that in certain operations the technology currently exists to control airborne contaminants to ppb levels.

In the finding of feasibility OSHA has considered the relative sophistication of the companies presently manufacturing DBCP. Dow Chemical Co. and Shell Oil Co. are both large organizations with vast experience in the area of exposure control to toxic substances. It is not unreasonable to conclude therefore, that these companies are able to implement state-of-the-art control technologies given sufficient financial incentive to do so. Due to the lack of substitutes for DBCP (exhibit 15, p. 2) and the estimated magnitude of crop losses should DBCP not be available (exhibit 39-2), OSHA finds that such incentives should exist. The economic considerations appear even more favorable in light of the fact that up to the promulgation of the ETS, only two plants were active in the production of DBCP. Control technologies and resources can thus be concentrated in the relatively few workplaces where exposures exist.

OSHA further recognizes that engineering and work practice controls are expensive to implement, and that many formulators may have to cease DBCP operations.

Due to the extremely serious nature of the hazard of exposure to DBCP, the concentration of DBCP formulating operations in those companies capable of providing the necessary protection for their employees is desirable and necessary.

Post-hearing comments received from one DBCP manufacturer suggested that achieving the permissible exposure limit of 1 ppb is not feasible (exhibit 53, p. 6). These comments raised some specific engineering questions regarding the suggested engineering controls including the issues of explosion potential, the amount of charcoal needed, and certain operational requirements for incinerators which may have to be used in the event that the charcoal method is unsatisfactory.

The commenter has asserted that the technological feasibility assessment has failed to consider explosion potential (Exhibit 53, pg. 7). OSHA believes that the potential for achieving concentrations in the explosive range has always existed in chemical production facilities and continues to exist. The addition of an enclosure surrounding the process equipment should not increase the explosion risk during normal production, assuming the process equipment is well maintained and properly operated, and that the engineering controls function properly. Under emergency conditions, such as rupture or leak, any increased explosion risk attributable to the enclosure would be counteracted with controls similar to those that would be needed to guard the process equipment if it were not totally enclosed. These controls would include fixed explosion suppression systems triggered by the detection of potentially explosive mixtures, or similar devices.

In addition, to reduce explosion risk, enclosures should be designed with explosion-proof lighting, exhaust fans, and motors. This type of equipment is routinely used in chemical production facilities and its use is commonly considered good engineering practice. Use of this type of equipment was assumed by JRB in deriving the cost estimates for installing engineering controls. (Exhibit 6, pp. 4-6, 4-7, 4-10, 4-11.)

As to the amount of charcoal required and the lack of available data demonstrating the effectiveness of the charcoal adsorption method (Exhibit 53, p. 7), OSHA does not believe that actual demonstration of the feasibility of charcoal adsorption is necessary. The charcoal adsorption method of air purification is widely used in such applications as air-purifying respirators, laboratory clean rooms, and industrial processes. Furthemore, that charcoal will absorb DBCP is demonstrated by the fact that personal exposure air monitoring methods for DBCP rely on charcoal adsorption. The additional costs for more frequent replacement of the charcoal would be approximately $9,000 per facility per month of operation, a sum which does not alter significantly the conclusions of the JRB report. This figure includes the cost of obtaining additional charcoal, additional labor costs for recharging the adsorber more frequently, and the cost of disposing of the additional used charcoal. The calculations for these additional costs are based on the unit costs presented in the Economic Impact Assessment (exhibit 6, p. 4-8).

The comment that operational requirements and effluent handling requirements for an incinerator to remove DBCP from exhaust air were not assessed in the technological feasibility assessment is not in point. Incineration was identified as an alternate control system in the technology feasibility assessment. Operating requirements for fuel, which is clearly the major operating cost, were estimated at $36,000 per month per incinerator. There is no evidence in the record to support the claim that special equipment would be required to handle effluent from the incinerator.

In light of these arguments, OSHA has determined that the compliance with the standard is technologically feasible by installing engineering controls and implementing work practices. It should be noted that no substantive evidence was put in on the record by affected parties which refutes this conclusion.

OSHA has also found that the sampling and analysis of DBCP airborne concentrations at and below the level of 1 ppb is feasible, and has provided one such method on the record (exhibit 28) and in Appendix B of the final standard. The feasibility of sampling was not controverted on the record, although one commenter indicated that the sampling tubes may have to be refrigerated during shipment to prevent the loss of DBCP from the charcoal adsorbant (exhibit 53, p. 4).

(9) WHAT ARE THE ESTIMATED COSTS OF COMPLIANCE WITH THE DBCP REGULATION?

An economic impact analysis of the DBCP regulation was conducted by JRB Associates, Inc. (exhibit 6). The study has estimated the capital cost of

compliance for each plant manufacturing DBCP to be approximately $1,100,000. Also, additional annual operating costs for each plant manufacturing DBCP have been estimated to be approximately $50,000. There are currently two plants in the United States which manufacture technical grade DBCP.

For formulating plants, the average capital cost of compliance would be on the order of $610,000, and the average increase in annual operating costs would be approximately $12,500.

For employers involved solely in the transportation and distribution of DBCP pesticides, there would be increased compliance costs attributable to labeling, employee training, and emergency planning. These are the only requirements for workplaces dealing only with sealed, intact containers of DBCP. These costs would be on the order of $1,400 per facility in one-time costs for such items as signs, training packages, and an emergency plan.

In addition, these workplaces would incur an additional $600 annually for operating costs including instructor's time, and employees lost time for training, and labels, assuming no more than ten employees per distribution facility needed to be trained (exhibit 6, p. 5-11, 5-17, 5-18). These costs for distribution facilities do not appear in the JRB report, but are calculated based on JRB's estimated costs for labeling, employee training, and emergency planning in manufacturing and formulating facilities. Although the number of workplaces involved in the distribution of DBCP is not known with great certainty, it is believed to be less than 2,000 (exhibit 39-1).

In total, the capital costs of compliance are estimated as $12,300,000 and the estimated annual operating costs are on the order of $1,650,000. When amortizing the capital costs and including the operating costs, the annual cost of compliance is estimated as $3,650,000. The continued production of DBCP, therefore, appears economically feasible in light of the United States Department of Agriculture estimate of $300 million in crop losses should DBCP not be available. Based on all the evidence in the record, OSHA concludes that compliance with the standard is economically feasible. Post-hearing comments have been received from one manufacturer of DBCP asserting that the cost of complying would exceed the threshold value used by the Department of Labor for defining a "major" economic impact and therefore, additional economic analysis should be performed (exhibit 53, pp. 6-8). This assertion is based on additional costs of compliance projected for employers involved in the transportation, distribution, and application of DBCP pesticides. In addition, these comments have asserted that the installation of required engineering controls would result in a delay of 2-3 years before DBCP could be made available to the American farmer, and the crop loss attributed to such delay would be on the order of $300 million per year (exhibit 39-2).

OSHA finds that these assertions are not valid. With respect to the transportation and distribution of DBCP, those establishments dealing only with sealed containers of DBCP are required to comply with only the emergency, labeling, and employee training provisions. This constitutes a modification from the proposed standard on which the above mentioned comments were based. Therefore, although there will be some additional cost of compliance with the final standard for distribution facilities, these costs would not likely include the construction of separate facilities or the installation of shower and change room facilities, as the commenter has asserted, except where DBCP exposures can be reasonably anticipated. OSHA estimates the capital cost of compliance for DBCP distribution facilities to be approximately $1,400 per facility. In addition, OSHA estimates annual operating costs to be approximately $600 per facility. If these costs were added to the estimates provided by JRB to estimate the total cost to industry of compliance with the standard, the resultant total cost estimates still do not approach the threshold value used by the Department of Labor for defining "major" economic impacts.

The commenter's assertion that there will be increased compliance costs for DBCP applicators is incorrect. Applicators are exempt from coverage by the DBCP standard.

One commenter has asserted that there will be crop losses caused by delay in instituting engineering and work practice controls (exhibit 53). This assertion is believed by the provisions of the standard, which permits employers to provide respirators where engineering and work practice controls are not yet sufficient to reduce employee exposure within the permissible exposure limit. OSHA recognizes that there will necessarily be some lost time in DBCP producing and formulating facilities while engineering controls are being installed. However, since DBCP production and formulation is generally performed on a seasonal basis, rather than continually, it seems reasonable to conclude that the necessary engineering modifications could be made while DBCP would not otherwise be formulated, and that DBCP pesticides could be made available for distribution during the period when controls were being installed. Also, the standard does not prohibit the use of DBCP presently stockpiled by manufacturers. Therefore, there is no reason to believe DBCP will be unavailable because of the OSHA standard.

(10) PERMISSIBLE EXPOSURE LIMIT

On the basis of the observed carcinogenic and sterility effects of DBCP, OSHA has selected an 8-hour time-weighted average (TWA) permissible exposure level (PEL) of 1 part DBCP per billion parts air (ppb). Also, based on uncontroverted evidence that DBCP may be absorbed through the skin (exhibit 4-66), (exhibit 2-3, p. 5), OSHA has concluded that all skin contact with DBCP be prohibited.

There is no dispute that DBCP has been shown to be a highly potent carcinogen in animal experiments. However, any dose-response extrapolations of these results to human exposures are not possible using current scientific precepts, and the question of whether a "no effect" level exists with respect to carcinogenicity has not been answered on the record. No data is presently available to indicate that any given level of exposure to DBCP would, in fact, be free of carcinogenic risk to exposed individuals. However, even if specific levels of exposure could be demonstrated to be associated with the incidence of cancer, this could not, in and of itself, establish a safe level for exposure to DBCP. While specific thresholds to various carcinogens may theoretically exist for some individuals, such thresholds may vary substantially within any given population at risk as well as with time. Furthermore, the long latency periods involved in carcinogenesis make it difficult to demonstrate that an exposure level which appears not to induce cancer in the short run is in fact safe; 5-40 years may be required before exposure to a carcinogen might produce detectable cancers. However, since nearly all chemicals that have been proven carcinogenic by direct observation in man have also been shown to be carcinogenic in experimental animals, OSHA maintains that a substance which causes cancer in animals must be considered as posing a carcinogenic risk to workers.

The record also contains definitive evidence that DBCP has induced sterility and infertility in exposed workers. These effects were found to occur even at very low exposures ranging from 40 to 430 ppb DBCP. OSHA has found, however, that adequate epidemiologic data does not exist which provides sufficient information to accurately predict a "safe" or "no effect" level, assuming one exists, with respect to the sterilant effects of DBCP.

Therefore, considering (1) the very low levels at which DBCP induced sterility has been found to occur; (2) the remarkable carcinogenic potency of DBCP as demonstrated in animal experiments; (3) the nature of the has-

ards of DBCP exposure, namely sterility and cancer; and (4) the inability to determine an exposure level that will eliminate the risk of cancer and sterility, OSHA deems it necessary to set the permissible exposure limit for DBCP at the lowest level technologically feasible.

Within the confines of feasibility OSHA has determined that a permissible exposure limit of 1 ppb as an 8-hour TWA best minimizes the cancer and sterility hazards of DBCP.

The record indicates that DBCP exposures are now controlled in manufacturing and formulating operations to levels ranging from 40 to 600 ppb. Furthermore, these levels have been achieved without prior knowledge of the severe hazards of DBCP exposure and, therefore, without the full utilization of highly sophisticated engineering controls.

Evidence on the record also indicates that an economic incentive exists for the continued production of DBCP. Compliance costs have been estimated to be on the order of $1,100,000 capital and $50,000 annual costs for manufacturing facilities, and $610,000 capital and $12,500 annual costs for formulating facilities. These costs are well below the estimate of $300,000,000 annual crop loss should DBCP not be available. Furthermore, for the post-plant control of nematodes, no suitable substitutes for DBCP have been found to exist. The unavailability of substitutes indicates that compliance costs for manufacturers and the formulators should be recoverable through increases in the price of DBCP to the consumer.

DBCP is also manufactured on a relatively limited production scale. Only two plants were engaged in DBCP production up to the time of the promulgation of the ETS. It has also been estimated that with a 1 ppb permissible exposure limit, only six formulators will continue to formulate DBCP. The concentration of DBCP production and formulation facilities further enhances the economic feasibility of compliance since such a market structure would better allow the pass through of compliance costs to consumers benefiting from DBCP use.

Shell Oil Co. and Dow Chemical Co., the two companies operating DBCP production facilities up until the promulgation of the ETS, are large organizations with considerable expertise in the control of exposures to toxic chemicals. OSHA concludes that these companies are in a position to provide the control equipment necessary to reduce DBCP exposure to permissible levels.

In the analysis of feasibility OSHA has considered (1) the levels of DBCP exposure attainable using existing controls; (2) the sophistication of existing control methodologies; (3) the economic incentives for continued DBCP production, including the costs of compliance, the inelasticity of demand, the limited scale of production, and the possible changes in market structure with respect to DBCP; and (4) the relative sophistication of the companies producing DBCP with respect to control technology. In light of these considerations OSHA finds that, for employee exposures to DBCP, a permissible exposure limit of 1 ppb is both technologically and economically feasible.

V. Summary and Explanation of the Standard

The final standard for occupational exposure to DBCP substantially reflects the provisions of the proposal (42 FR 57266) with two major exceptions.

The final standard, unlike the proposal, contains a limited exemption for workplaces where DBCP is present only in sealed, intact, containers. OSHA has determined that the likelihood of exposure and potential health risks to employees handling DBCP in sealed, intact containers does not justify the implementation of the more stringent provisions of the standard such as routine monitoring and medical surveillance. Moreover, such requirements are not necessary for the protection of employees handling sealed, intact, containers of DBCP. Accordingly, only the labeling, training and emergency provisions of the final standard apply to the storage, transportation, distribution and sale of sealed, intact containers of DBCP.

Also, OSHA has decided to delete the ceiling exposure requirement from the final standard. OSHA believes that compliance with the exposure limit of 1 ppb over an 8-hour day effectively limits the magnitude of short term exposures. For instance, a 30-minute exposure to 16 ppb DBCP, with no further DBCP exposure that day, represents a daily dose equal to an 8-hour exposure to 1 ppb.

All other language changes in the final as compared to the proposed standard are essentially non-substantive and are intended only to enhance the clarity of the particular requirement with respect to employer and employee understanding as well as enforceability of the provision.

Few comments or objections to the specific provisions of the standard were received. Where issues were raised in the course of the proceeding, they are discussed in the explanation of the major provisions of the standard which follows.

1. Paragraph (a)—*Scope and application.* The standard applies to all employments where DBCP is present with the two exceptions discussed below. The principal activities covered include the manufacture of DBCP, the formulation of pesticides containing DBCP, and related activities of packaging, repackaging, storage, transportation, and disposal of DBCP.

OSHA has determined that the storage, transportation, distribution and sale of sealed, intact containers of DBCP should be subject only to the labeling, training, and emergency provisions of the final standard. This is a change from the proposed standard and the ETS which did not contain the limitation. Participants in the rulemaking pointed out that the proposal would require employers to monitor exposure and require medical surveillance of employees who have only casual or limited contact and no discernible exposure to DBCP. Examples of such employees are maritime employees occasionally handling sealed drums of DBCP (exhibit 5-5) or distributors, jobbers and employees of retail outlets (exhibit 5-7). This limited exemption serves to maximize employee protection while minimizing unnecessary burdens.

The final rule distinguishes between "closed," and "sealed," containers. OSHA is concerned that containers, after being opened, may be closed in such a fashion as to expose employees to DBCP. For this reason, the exemption applies only to "sealed" containers, intending by the use of that term to exempt only containers of DBCP which are closed in such a manner as to contain the DBCP vapors. Additionally, since sealed containers may, during handling, develop leaks, the exemption is further limited to intact containers.

Therefore, where breakage of the container occurs, employers will be required to monitor, provide protective equipment and medical surveillance, and to comply with any other applicable provisions of the standard. To assure that all employees are aware of the hazardous nature of the contents of the containers, and are familiar with appropriate procedures for handling in case of emergency exposure, and because at some point in downstream occupational activities the containers will be opened, the training, labeling and emergency provisions apply to the handling of sealed, intact containers.

Finally, it should be noted that the regulation of sealed containers in this standard is consistent with that in other carcinogen standards (§§ 1910.1003-1910.1016) and the recently promulgated benzene standard (43 FR 5918).

The standard does not apply to exposures which result solely from the application and use of DBCP as a pesticide. On September 8, 1977, concurrent with OSHA's issuance of the ETS, the Administrator of the Environmental Protection Agency announced his intention to take two sus-

pension actions with respect to pesticide products containing DBCP (42 FR 48915), pursuant to his authority under section 6(c) of the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, (FIFRA). This Act allows the Administrator to suspend the registrations of a pesticide product whenever he determines that such action is necessary to prevent an "imminent hazard" during the time required for cancellation or change in classification proceedings.

On October 27, 1977, EPA issued a suspension order (42 FR 57543) which effected two suspension actions: A suspension of all pesticide products registered for food crop uses with respect to which residues of DBCP have been found or are anticipated on the edible portions of the food crops; and a conditional suspension with respect to all uses, based upon the Administrator's finding that an imminent hazard exists for pesticide applicators if DBCP products are used in accordance with current label restrictions.

The regulatory actions announced by EPA will have two important effects leading to increased protection of workers engaged in the application and use of DBCP as a pesticide. First, the suspension of use of DBCP pesticides for certain food crops will substantially reduce the number of applicator personnel and field workers who would otherwise have been exposed to DBCP.

Second, under the conditional suspension announced for all other uses, persons using DBCP for other uses will have to be certified applicators (and in some instances certified commercial applicators), or be working under the direct supervision of a certified applicator. Additionally, persons using DBCP for conditionally suspended uses will be required to wear protective clothing and respirators.

OSHA believes that this strategy of combined and cooperative regulatory actions by both EPA and OSHA is an effective approach to protecting all workers against the hazards of exposure to DBCP. Accordingly, this standard does not apply to exposures to DBCP which result solely from its application and use as a pesticide.

2. Paragraph (c)—*Permissible exposure limit.* The standard establishes a permissible exposure limit of 1 part DBCP per billion parts of air (1 ppb) as an 8-hour time-weighted average.

As discussed more fully above, the reported exposure of employees at concentrations significantly less than one part per million at several manufacturing and formulating plants and the resulting sterility in a substantial proportion of the exposed employees even at that level clearly indicates that a substantial reduction in exposure must be accomplished to mitigate the risk. There is, unfortunately, not complete information on the exact level necessary to eliminate the risk. Here, we cannot determine whether there is a safe level or threshold level below which reproductive effects would not occur.

Evidence from several animal tests in mammalian species conclusively demonstrates the carcinogenicity of DBCP.

OSHA policy, which is based on the best available scientific evidence, and which is consistent with the policies and recommendations of nearly all public bodies which have addressed the problem of exposure to cancer-causing substances, has been and is that a substance which causes cancer in animals must be regulated as posing a carcinogenic risk to workers. In the absence of a demonstrated "safe" or "no effect" level for human exposure to a carcinogen, it must be assumed, as a prudent policy matter, that no safe level exists.

Accordingly, the setting of an exposure level for DBCP cannot be based on a determination of a "safe" level which will eliminate the cancer and sterility hazard, but rather on a determination of a level which will minimize these hazards to the greatest extent possible, within the confines of feasibility.

Based on evidence that DBCP is absorbed through the skin, OSHA prohibits all skin contact with DBCP.

For the final standard, OSHA has not included the provision for a 15 minute ceiling exposure limit of 10 ppb which appeared in the proposal. OSHA believes that compliance with the exposure limit of 1 ppb over an eight-hour day effectively limits the magnitude of short term exposures.

Our assessment of technological feasibility, discussed above, indicates that an exposure limit of 1 ppb is technically feasible for both DBCP manufacturing and formulation operations (see exhibit 6, p. 4-1).

OSHA believes that isolation of workers from the process equipment may be necessary to minimize exposure to DBCP, and that this can be accomplished by totally enclosing the equipment in a building or in a separate room within a building. Automatic or remote control of the different loading, process, and packaging operations would be necessary, to eliminate any requirement for workers to enter the enclosure during the operation (exhibit 6, p. 4-4).

3. Paragraph (d)—*Notification of use.* The ETS required employers to notify the OSHA Area Director of the location of workplaces where DBCP is present, and to describe the conditions of use and exposure and the protective measures in effect. The standard does not require employers to report the same information again. Rather, any employer who has not yet notified the OSHA Area Office or who subsequently introduces DBCP into a workplace is required to report to the Area Director in the same manner as required by the ETS.

4. Paragraph (e)—*Regulated areas.* The standard requires the establishment of regulated areas where airborne concentrations of DBCP are in excess of 1 ppb. The purpose of establishing regulated areas is to limit DBCP exposures to as few employees as possible by barring access to these areas to all but those specifically authorized to be in the area. OSHA believes that control of employee exposures, appropriate exposure monitoring, medical surveillance, and limitation of potential exposure to the smallest number of workers all require regulated areas. The employer must designate as "authorized" any person whose duties require his or her presence in the area.

5. Paragraph (f)—*Exposure monitoring.* Section 6(b)(7) of the Act (29 U.S.C. s655) mandates that any standard promulgated under 6(b) of the Act shall, where appropriate, "provide for monitoring or measuring of employee exposure at such locations and intervals, and in such manner as may be necessary for the protection of employees." The purposes of monitoring are to determine the extent of exposure, to identify the source of exposure, to enable the employer to select proper control methods and to evaluate the effectiveness of the selected methods. Thus, monitoring enables employers to meet the legal obligations of the standard to assure that their employees are not exposed to DBCP in excess of the prescribed levels. Additionally, monitoring enables employers to notify employees of their exposure level, as required by section 8(c)(3) of the Act, and to provide information necessary to the examining physician.

The exposure monitoring provisions intend that the employer determine the exposure for each employee exposed to DBCP. This does not require separate measurements for each employee. If a number of employees perform essentially the same job under the same conditions, it may be sufficient to monitor a significant fraction of such employees and obtain results that are representative of the exposures of the remaining employees.

Where exposures are determined to be above the permissible exposure limit, the employer is required to monitor monthly. Otherwise the employer must monitor quarterly. "Exposure" in this connection means the airborne concentrations in the workers' breathing zone, without regard to the use of respirators.

The employer is also required to redetermine the exposure of affected employees by monitoring if any

changes in production, processes, control measures or personnel occur which might cause new or additional exposures to DBCP.

One commenter stated that the required frequency of monitoring does not take into account the stability of airborne concentrations, and that in closed-system operations such frequent and repeated personal monitoring may be unnecessary (exhibit 4–8, p. 9). OSHA finds, however, that frequent monitoring is crucial considering the very low magnitude of the permissible exposure limit. Small leaks in control equipment, which may not be detectable during routine visual inspection, could lead to exposures well in excess of 1 ppb. The fact that DBCP has no detectable odor until 180 ppb, 180 times the permissible exposure limit, further supports the need for frequent monitoring.

An assessment of available methodology for sampling and analysis of airborne concentrations of DBCP indicates that it is possible to monitor employee exposures of 1 part per billion and below (tr. 317). Furthermore, at these concentrations sampling and analytical methodologies are available which have an accuracy, to a confidence level of 95 percent, of not less than plus or minus 25 percent. Using one method, for example, the samples may be collected by adsorption of DBCP on charcoal contained in a suitable holder such as glass tubing through which a volume of air is drawn. Analysis is then performed by gas chromatography, using electron-capture detection. These techniques, although they require care, are readily available and should pose no special difficulties for employers covered by this standard (tr. 319).

6. Paragraph (g)—*Methods of Compliance.* The standard requires the employer to institute engineering and work practice controls to reduce employee exposures to or below the permissible limit. This requirement is in accord with OSHA's policy that feasible engineering and work practice controls must be used as the primary methods of reducing employee exposures to toxic substances. This policy is based on the view that the most effective means of controlling employee exposures is to contain emissions at their source through use of mechanical means, combined with work practices, rather than reliance on the variability of human behavior so critical to the successful use of respirators.

In situations where engineering and work practice controls do not reduce exposures to the permissible exposure limit, these controls must nonetheless be used to reduce exposures to the lowest feasible level and be supplemented by the use of respirators. OSHA realizes that, under some particular circumstances, engineering and work practice controls may not be technologically feasible in a particular work operation. Therefore, the standard explicitly recognizes that an employer may demonstrate the infeasibility of engineering and work practice controls as to one or more operations in a particular process, and in these circumstances use respirators to provide the required protection. The question of whether an employer has met his burden of establishing that engineering and work practice controls are infeasible in a particular work operation involves the consideration of many complex factors and a rational balancing process. Factors such as levels of exposure, useful remaining life of the equipment and the effort made by the employer to implement such controls are relevant.

Respirators are the least satisfactory means of control because of certain difficulties inherent in their use. Respirators are capable of providing good protection only if they are properly selected for the concentrations of airborne contaminants present, properly fitted to the employee, worn by the employee and replaced when they have ceased to provide protection. While it is theoretically possible for all of these conditions to be met, it is more often the case that they are not. As a consequence, the protection of employees by respirators is not always effective.

In addition, a compliance program to reduce exposures to within the permissible exposure limits solely by means of engineering and work practice controls must be developed and implemented when the engineering and work practice controls presently being used do not reduce employee exposures to within the permissible exposure limit. Written plans for this program must be developed and furnished upon request to representatives of the Secretary, representatives of the Director, and affected employees. These plans must be reviewed and updated periodically to reflect the current status of the program.

7. Paragraph (h)—*Respirators.* The final standard provides that, whenever the permissible exposure limit is exceeded, in spite of implementation of all feasible engineering and work practice controls, the employer must provide and assure that employees use respirators. The standard contains a respirator selection table (Table 1) so the employer will provide the type of respirator which affords the proper degree of protection based on airborne concentrations of DBCP to which the employee may be exposed. The respirator selections in the final standard are identical to those in the proposal.

The standard restricts the selection of respirators to atmosphere-supplying respirators. One participant commented that atmosphere-supplying respirators are cumbersome, restrict movement, and, in the case of self-contained breathing apparatus, require frequent changing of air cylinders (Exhibit 4–8, p. 10). OSHA does not deny the difficulties of use of atmosphere-supplying respirators. However, DBCP does not have any useful warning properties at concentrations where air-purifying respirators may be safely used, and consequently, there is no warning of respirator leakage or breakthrough. The odor threshold of DBCP is estimated to be 180 ppb (exhibit 4–8, p. 10), 180 times the permissible exposure limit. Because of the extremely serious consequences to employee health which have been found in human exposures at 40 to 430 ppb (exhibit 9, p. 150 Tables IV and V) (exhibit 4–77B), we believe it imperative to minimize the risk of undetected exposure, and accordingly permit only atmosphere-supplying respirators.

The standard requires that the employee be properly trained to wear the respirator, to know why the respirator is needed and to understand the limitations of the respirator. An understanding of the hazards involved is necessary to enable the employee to take steps for his or her own protection. The respiratory protection program implemented by the employer must conform with 29 CFR 1910.134 (b), (d), (e), and (f). This section contains the basic requirements for use, cleaning, and maintenance of respirators.

To prevent skin irritation and to minimize the discomfort of respirator use, the standard requires that employees must be allowed to periodically wash their faces and respirator facepieces in order to remove any accumulation of DBCP or to reduce the chance of irritation from the wearing of the facepiece itself, such as a heat rash.

The standard requires that respirators and other clothing and equipment required for protection from exposure to DBCP shall be provided at no cost to the employee. OSHA has allocated the costs of respirators and clothing and equipment required for protection from DBCP exposure to the employer in order to effectuate the purposes of the Act. This language clarifies OSHA's position which has long been implicit in health standards proceedings under section 6(b) of the Act.

8. Paragraph (i)—*Emergencies.* This provision requires employee evacuation and cleanup where spills or leaks occur. Only employees with appropriate respirators and impermeable protective clothing are allowed in the area until the situation is restored to normal. It is important to note that all employees covered by the standard, including those who handle only sealed, intact containers of DBCP, are covered by the emergency provisions.

The employer must also provide the medical surveillance testing as specified by paragraph (m) (6) to any employee exposed to an emergency release of DBCP.

9. Paragraph (j)—*Protective clothing and equipment.* The standard requires that the employer provide and assure that employees who are subject to any possibility of skin or eye contact use impermeable protective clothing or equipment in order to minimize these hazards. OSHA is aware that since many formulating and producing facilities are located in warm climates, as a practical matter the impermeable protective clothing requirement may necessitate use of full body air-conditioned suits.

Evidence onthe record indicates that DBCP may be absorbed through the skin (exhibit 4–56), and that even very small amounts of DBCP on the skin are potentially hazardous (exhibit 4–8, p. 5). Therefore the standard requires the prompt removal of protective clothing and equipment which becomes contaminated with DBCP-containing liquids or solids. The standard also provides that this clothing and equipment must not be reworn until the DBCP has been removed from the clothing and equipment. Under no circumstances may clothing and equipment contaminated with DBCP-containing liquids and solids be worn into lunchrooms or lavatories.

The standard also requires that the employer clean, launder, or dispose of the required protective clothing to eliminate any potential exposure that might result were the clothing to be laundered by the employee at home.

The standard requires that protective clothing be provided in a clean and dry condition daily. Since skin contact with DBCP creates a potential for skin absorption, OSHA believes that the regular cleaning of contaminated work clothing plays an important role in the protection against the hazard. The standard also requires that protective clothing and equipment be maintained and replaced as needed in order to ensure effectiveness.

The standard provides that the employer assure that all protective clothing is removed at the end of each work shift, and that the clothing that is to be laundered, cleaned, or disposed of be placed in a closable container. The container must be constructed so as to prevent the release of DBCP vapors into the atmosphere. The purpose of this requirement is to prevent the contaminants on the clothing from being released into the ambient air or from being contacted by an individual handling the container.

Finally, the standard requires employers to inform those who handle the contaminated protective clothing of the potentially harmful effects of exposure to DBCP. This provision is designed to make clear the need to use proper care in handling of the contaminated protective clothing.

10. Paragraph (k)—*Housekeeping.* Removal and prevention of visible accumulations of liquid deposits of DBCP, or dusts containing DBCP, on all surfaces are important aspects in minimizing employee exposure. To assure that DBCP is not reintroduced into the workplace air, the standard prohibits dry sweeping or the use of compressed air for cleaning floors and other surfaces where DBCP is found. The standard also requires that when DBCP is present in liquid form, or as a resultant vapor, that all containers or vessels be enclosed to the maximum extent feasible and tightly covered when not in use to prevent the release of DBCP vapor into the work atmosphere.

For disposal of waste scrap, equipment or debris containing DBCP, the standard requires that this material be collected and disposed of in sealed or closed containers which prevent the dispersion of DBCP outside the containers. State environmental protection agencies designate appropriate landfills for the disposal of such waste.

11. Paragraph (l)—*Hygiene facilities and practices.* The standard specifies hygiene facilities and practices required for employee protection.

Change rooms are required, with separate storage for street and work clothing. OSHA believes that these facilities are necessary to minimize possible contacts with contaminated clothing, since DBCP is skin absorbable, and an irritant as well.

The standard requires the employer to provide shower facilities for employees, and that employees be required to take showers at the end of the workshift to remove any DBCP from their bodies. Section 1910.141(d) (3), which would be triggered by the standard, lists requirements for adequate showers.

The standard also requires that lavatory facilities which comply with § 1910.141(d) (1) and (2) be provided in sufficient number to assure that sufficient facilities are available for employees to wash when leaving the regulated area to eat or use toilet facilities.

The standard prohibits eating, smoking, drinking, or the keeping of food or smoking materials in regulated areas. Additionally, the standard prohibits the keeping of cosmetics in regulated areas to avoid the possibility that DBCP contaminated cosmetics would be inadvertently applied to the body.

The standard requires employers to provide lunchrooms free of DBCP contamination which are readily accessible to employees working in a regulated area. The purpose of this requirement is to minimize the risk of employee exposure to DBCP by ingestion or inhalation during eating.

13. Paragraph (m)—*Medical Surveillance.* Pursuant to section 6(b)(7) of the Act, the standard requires that each employer institute a medical surveillance program for all employees who work in regulated areas. OSHA believes that a medical surveillance program is necessary in dealing with the problem of employee exposure to DBCP.

The standard requires an opportunity for a medical examination for each employee before the first assignment to work with DBCP and annually thereafter. Where employees have received medical examination under the provisions of the ETS, the examination need not be repeated until one year from the date of that examination.

All examinations and procedures are required to be performed by or under the supervision of a licensed physician and provided without cost to the employee. While the physician will usually be selected by the employer, the standard does not so mandate, leaving the employer free to institute alternative procedures such as joint selection with the employee or selection by the employee. Clearly, a licensed physician is the appropriate person to be conducting a medical examination, and such a requirement is contained in the standard. However, certain parts of the required examination (e.g. taking of a history) do not necessarily require a physician's expertise and may be conducted by another person under the supervision of the physician.

The standard provides that a work history, medical history and medical examination be performed. The content of the examination is consistent with identification of the adverse health effects that have been associated with exposure to DBCP.

A commenter suggested that a standardized procedure be mandated for the collection of sperm and subsequent sperm count procedures (exhibit 53, p. 1). Recognizing that differing procedures may produce equally valid results, OSHA chose not to require specific sperm count procedures in the standard. Rather, a suggested protocol has been included in Appendix C.

Both the ETS and the proposal required measurement of serum testosterone levels. This requirement has been eliminated in the final on the basis of evidence that serum testosterone levels do not correlate with DBCP-induced toxicity (tr. 232–233).

Though evidence indicates that sperm counts are the best indicators of DBCP toxicity, the record indicates that the determinations of serum levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and,

in the case of females, estrogen, are also important in fertility assessment (tr. 232, 233) (exhibit 9, p. 41-45). These tests are especially important for females, vasectomized males, and other males unable to produce a semen specimen.

The emergency medical surveillance provisions reflect OSHA's concern for those employees who, because of equipment breakdown, container rupture or other causes, may be exposed to massive doses of DBCP. These workers may be at a relatively high risk for developing adverse fertility effects.

If a worker is exposed to an unexpected release of DBCP, the employer must, as soon as practicable, provide the employee an opportunity for a sperm count, or, in instances where an employee is unable to produce a semen specimen, a determination of serum levels of FSH, LH and estrogen (females). The employer is also required to provide these procedures three months later. The purpose of the three month repeat is that evidence on the record indicates that, since sperm take three months to mature, testicular damage would not be reflected in sperm count results until that time. The initial results would then serve as a baseline against which the repeat result could be compared.

The standard requires that the employer provide the physician with certain information. This includes: (1) A copy of the regulation; (2) a description of the affected employee's duties as they relate to the employee's exposure; (3) the results of the employee's exposure monitoring; (4) if any personal protective equipment is used or is to be used; and (5) information from previous medical examinations of the affected employee to the extent that they are not readily available to the physician. The purpose of making this information available to the physician is to aid in evaluation of the employee's health in relation to his assigned duties, and fitness to wear personal protective equipment when required.

The employer would be required to obtain and provide the employee with a written opinion from the examining physician containing: (1) The results of the medical tests; (2) the physician's opinion as to whether the employee has any detected medical conditions which would place the employee at increased risk of material impairment of health from exposure to DBCP; and (3) any recommended limitations upon the employee's exposure to DBCP and upon the use of protective clothing and equipment such as respirators. This written opinion must not reveal specific findings or diagnoses unrelated to occupational exposure to DBCP. A copy of the opinion must be provided to the affected employee by the employer.

The requirement that the employee be provided with a copy of the physician's written opinion will assure that the employee is informed of the results of the medical examination and may take any appropriate action. The purpose in requiring that specific findings or diagnoses unrelated to occupational exposure be excluded from the written opinion is to encourage employees to submit to medical examinations by removing the fear that employers may find out adverse or embarrassing information about their physical condition that has no relation to occupational exposures.

Among the issues in the DBCP rulemaking were whether OSHA should include a mandatory removal requirement—that is, a provision prohibiting the exposure of an employee to DBCP if the employee would be placed at increased risk of material impairment to health because of such exposure, and whether OSHA should include a rate retention provision—that is, a provision requiring the transfer of such employee to another job or providing that removal for medical reasons should not result in loss of earnings or seniority status to the affected employee. These issues, as OSHA has previously stated (41 FR 46780), are related and must be addressed together. Both employee and industry participants expressed their views as to several aspects of these issues in prehearing comments, in testimony during the hearing and in post hearing arguments. However, OSHA has conducted an informal public hearing on mandatory removal and rate retention for workers exposed to lead as part of the rulemaking proceeding on lead. Consideration of the critical issue of medical removal protection is being undertaken for several pending standards together. Once this consideration is completed, OSHA will determine the extent to which the conclusions on medical removal protection are appropriate for DBCP and whether to include those or similar provisions in the DBCP standard. The final standard published today, therefore, does not address the issues of mandatory removal and medical removal protection.

13. Paragraph (n)—*Employee information and training.* The standard requires the employer to provide a training program for employees potentially exposed to DBCP. OSHA believes that an information and training program is essential for the protection of employees, because an employee can do much to protect himself if informed of the nature of the hazards in the workplace. To be effective, an employee education system must, at the minimum, apprise the employee of the specific hazards associated with his work environment. For this reason, the employer would be required to inform each employee potentially exposed to DBCP of the nature of the related health problems, the necessity for exposure control, emergency procedures, and the medical and industrial hygiene monitoring programs.

The content of the training program is intended to apprise the employees of: (1) The hazards to which they are exposed; (2) the necessary steps to protect themselves, including avoiding exposures, using respiratory protection and availing themselves of the opportunity for medical examinations; (3) their role in reducing exposures; and (4) the contents of the standard. Section 6(b)(7) of the Act makes it clear that these are appropriate goals of an employee training program, and the standard, therefore, includes them.

The employer is also required to provide to the Secretary and the Director, upon request, all materials relating to the training program. This is intended to provide an objective check of compliance with the requirements of the standard.

14. Paragraph (o)—*Signs and labels.* OSHA believes that it is important, and section 6(b)(7) of the Act mandates, that appropriate forms of warning, including labels, be used to assure that employees are apprised of the hazards to which they are exposed in the course of their employment. OSHA believes, as a matter of policy, that employees should be given the opportunity to make informed decisions as to whether to work at a job under a particular set of working conditions. Furthermore, OSHA believes since control of safety and health problems involves the cooperation of employees, success of a safety and health program is highly dependent upon the employee's understanding of the hazards involved in the job.

In light of the serious nature of the hazard of exposure to DBCP, OSHA does not believe that periodic training alone will adequately apprise employees of the health hazards of DBCP. However, OSHA believes that the requirement to post warning signs and labels when coupled with the training requirements discussed above will adequately do so.

The standard requires that nothing which contradicts or detracts from the effect of any sign required by this paragraph shall appear on or near any such required sign.

Due to the hazardous nature of exposure to DBCP, OSHA believes that emphasis should be placed on warning employees and other persons about the danger of exposure. For this reason, the standard includes a requirement that warning labels be affixed to all containers containing DBCP or products containing DBCP. The labeling provisions of the standard also require the employer to assure that warning labels are affixed

to any product containing DBCP when such product leaves the employer's workplace. This requirement is designed to protect any other employees who will be handling, transporting, or using this product. When an employer manufactures, formulates or sells a product containing a toxic substance, that employer is exposing not only his own employees but also the employees of other employers involved in handling, transporting or using the product. The extent of the obligation to inform should be commensurate with the extent of the exposure. This is especially true where the manufacturer, formulator or seller will in many cases be the only employer capable, through his unique knowledge of the substance, of providing the information needed for protection of other employees. (See the discussion in the recently promulgated benzene standard, 43 FR 5918, 5960.) However, where DBCP or products containing DBCP are sold, distributed or otherwise leave the employer's workplace bearing labels required by EPA under the regulations in 40 CFR Part 162, the labels required by this paragraph for products leaving the workplace need not be affixed. OSHA feels that the EPA labels adequately alert downstream employers and employees to the hazards of DBCP.

15. Paragraph (p)—*Recordkeeping.* Section 8(c)(3) of the Act provides for the promulgation of regulations requiring employers to maintain accurate records of employee exposure to potentially toxic or harmful physical agents which are required to be monitored or measured. Accordingly, the final standard requires that employers keep records of both monitoring and medical surveillance.

The standard provides that records must be kept to identify the employee and to accurately reflect the employee's exposure. Specifically, it must include: (a) The names, social security numbers and job classifications of the employees monitored, (b) the dates, number, duration and results of each of the samples taken, including a description of the representative sampling procedure used to determine employee exposure where applicable, (c) the type of respiratory protective devices worn by the employee, if any, and (d) a description of the sampling and analytical methods used, and evidence of their accuracy.

The required retention time for medical surveillance records and exposure monitoring records would be extended to 40 years or the duration of exposure plus 20 years, whichever is longer. Carcinogenic induction, if it occurs in an exposed human population, has usually been found by medical surveillance 20 to 40 years after initial exposure. While present medical knowledge does not permit the establishment of exposure limits for carcinogens based on scientific information of the mechanism of carcinogenic induction, it is quite possible that such fundamental scientific knowledge will be developed within the next decade or two. At that point, knowledge of exposure levels of employees will be significant for both developing scientifically valid exposure limits, and for more precisely determining whether exposures may be safely continued for such employees, or perhaps safely raised.

The standard also requires that the employer keep an accurate medical record for each employee who is subject to medical surveillance. Section 8(c)(1) of the Act authorizes the promulgation of regulations requiring an employer to keep such records regarding the employer's activities relating to the Act as are necessary or appropriate for the enforcement of the Act or for developing information regarding the causes and prevention of occupational illnesses. OSHA believes that medical records (like exposure monitoring records) are both necessary and appropriate to both the enforcement of the standards and the development of information regarding the causes and prevention of illness.

As explained above, it is necessary to relate employees' medical conditions to their exposure in order to develop information regarding cause and prevention. Medical records are necessary and appropriate for this purpose. Medical records are also necessary for the proper evaluation of an individual employee's health as well as providing a baseline against which the results of subsequent examinations may be compared. For all of these reasons, medical records are required.

The standard requires that employees or their designated representatives be provided access to examine and copy records of required monitoring. The purpose of this provision is to assure current employees that their exposure is being properly monitored and recorded, and that they are working in a safe and healthful environment. This is consistent with section 8(c)(3) of the Act which directs the Secretary to promulgate regulations providing "employees or their representatives with an opportunity to observe monitoring or measuring and to have access to the records thereof".

Exposure monitoring records indicating their own exposure must be made available to former employees or their designated representatives. Section 8(c)(3) of the Act explicitly provides, "former employees to have access to such records as will indicate his own exposure to toxic materials or harmful physical agents". Records are available to designated representatives to assure access to the information by the current or former employee where he is incapacitated, unable to inspect or understand the records, or simply desires that his representative inspect them. The Act recognizes the legitimate role of employee representatives in assuring occupational safety and health.

The standard is also clarified to provide that medical records be made available upon request for examination and copying to a physician or other individual designated by the affected current employee or former employee. The purpose of the requirement is to protect the current or former employee's health by providing physicians and individuals designated by employees access to medical records useful in the diagnosis of illness. Records are available to designated representatives for the reasons noted above.

One commenter questioned the fact that the standard enables OSHA and NIOSH to have access to medical records without specifying confidentiality or otherwise limiting circulation of the information (exhibit 4–8, p. 14). OSHA recognizes that a physician's records may contain a wide range of personal and medical information deemed to be confidential or private. For this reason, the standard limits the contents of the medical record to such information as is related to DBCP exposure. Indeed, the standard requires in paragraph (m)(5)(ii) that the employer advise the physician that the physician's opinion, which becomes a part of the medical record, should not reveal findings unrelated to occupational exposure. The need of OSHA and NIOSH to have access to this information has already been thoroughly discussed. The privacy rights of the individuals would be appropriately protected by the Privacy Act and implementing regulations.

To assure that the records will be preserved for the required retention period, the standard requires an employer, who ceases to do business, to transfer his records to his successor and, in the event that there is no successor, to transfer the records to the Director of NIOSH.

16. Paragraph (q)—*Observation of monitoring.* Section 8(c)(3) of the Act authorizes the Secretary to require that employers provide employees or their representatives with the opportunity to observe monitoring of employee exposure to toxic substances or harmful physical agents. In accordance with this section, the standard contains provisions for such observation of DBCP monitoring. To assure that the right to observe is meaningful, observers are entitled to receive an explanation of the measurement procedure, to observe all steps related to the measurement procedure, and record the results obtained.

The observer, whether an employee or designated representative, must be

provided with, and is required to use, any personal protective devices required to be worn by employees working in the area that is being monitored, and must comply with all other applicable safety and health procedures.

17. Paragraph (r)—*Appendices.* The standard includes three appendices: Appendix A titled "Substance Safety Data Sheet", Appendix B titled "Substance Technical Guidelines", and Appendix C titled "Medical Surveillance Guidelines". It should be noted that appendices are for informational purposes only. None of the statements contained therein should be construed as imposing a mandatory requirement not otherwise in the standard or negating any requirement which is imposed by the standard.

The information in appendix A is specifically written for the employee. Appendix B contains additional scientific and technical information to aid the employer in complying with requirements of the standard. Appendix C gives the employer a means of providing the examining physician with an explanation of the potential health effects of exposure to DBCP and provides information needed by the physician to evaluate the results of the medical examination. Appendix C also lists other types of examinations, not required by the individual standard, which may help the physician in making an accurate determination of whether an employee should be exposed or should continue to be exposed to DBCP.

VI. Authority

This document was prepared under the direction of Eula Bingham, Assistant Secretary of Labor for Occupational Safety and Health, U.S. Department of Labor, 200 Constitution Avenue NW., Washington, D.C. 20210.

Accordingly, pursuant to sections 6(b), 6(c), and 8(c) of the Occupational Safety and Health Act of 1970 (84 Stat. 1593, 1596, 1599, 29 U.S.C. 653, 655, 657), the Secretary of Labor's Order No. 8-76 (41 FR 25059), and 29 CFR Part 1911, Part 1910 of Title 29, Code of Federal Regulations, is hereby amended by revising § 1910.1044 to provide a permanent occupational safety and health standard for exposure to DBCP.

In order to ensure that affected employers and employees will be informed of the existence of the new provisions and that employers affected are given an opportunity to familiarize themselves and their employees with the existence of the new requirements, the effective date of the revision to § 1910.1044 will be April 17, 1978. To provide continued protection for employees until that date, the provisions currently contained in § 1910.1044 are promulgated pursuant to sections 6(b), 6(c), and 8(c) of the Occupational Safety and Health Act as an occupational safety and health standard effective March 17, 1978. The revision to § 1910.1044 will supersede these provisions as of April 10, 1978.

Signed at Washington, D.C., this 10th day of March 1978.

Eula Bingham,
Assistant Secretary of Labor.

§ 1910.1044 1,2-dibromo-3-chloropropane.

(a) *Scope and application.* (1) This section applies to occupational exposure to 1,2-dibromo-3-chloropropane (DBCP).

(2) This section does not apply to:

(i) Exposure to DBCP which results solely from the application and use of DBCP as a pesticide; or

(ii) The storage, transportation, distribution or sale of DBCP in intact containers sealed in such a manner as to prevent exposure to DBCP vapors or liquid, except for the requirements of paragraphs (i), (n) and (o) of this section.

(b) *Definitions.* "Authorized person" means any person required by his duties to be present in regulated areas and authorized to do so by his employer, by this section, or by the Act. "Authorized person" also includes any person entering such areas as a designated representative of employees exercising an opportunity to observe employee exposure monitoring.

"DBCP" means 1,2-dibromo-3-chloropropane, Chemical Abstracts Service Registry Number 96-12-8, and includes all forms of DBCP.

"Director" means the Director, National Institute for Occupational Safety and Health, U.S. Department of Health, Education and Welfare, or designee.

"Emergency" means any occurrence such as, but not limited to equipment failure, rupture of containers, or failure of control equipment which may, or does, result in an unexpected release of DBCP.

"OSHA Area Office" means the Area Office of the Occupational Safety and Health Administration having jurisdiction over the geographic area where the affected workplace is located.

"Assistant Secretary" means the Assistant Secretary of Labor for Occupational Safety and Health, U.S. Department of Labor, or designee.

(c) *Permissible exposure limit.*—(1) *Inhalation.* The employer shall assure that no employee is exposed to an airborne concentration of DBCP in excess of 1 part DBCP per billion parts of air (ppb) as an 8-hour time-weighted average.

(2) *Dermal and eye exposure.* The employer shall assure that no employee is exposed to eye or skin contact with DBCP.

(d) *Notification of use.* Within ten (10) days following the introduction of DBCP into the workplace, every employer who has a workplace where DBCP is present, shall report the following information to the nearest OSHA Area Office for each such workplace;

(1) The address and location of the workplace:

(2) A brief description of each process or operation which may result in employee exposure to DBCP;

(3) The number of employees engaged in each process or operation who may be exposed to DBCP and an estimate of the frequency and degree of exposure that occurs; and

(4) A brief description of the employer's safety and health program as it relates to limitation of employee exposure to DBCP.

(e) *Regulated areas.* (1) The employer shall establish, within each place of employment, regulated areas wherever DBCP concentrations are in excess of the permissible exposure limit.

(2) The employer shall limit access to regulated areas to authorized persons.

(f) *Exposure monitoring.*—(1) *General.* (i) Determinations of airborne exposure levels shall be made from air samples that are representative of each employee's exposure to DBCP over an 8-hour period.

(ii) For the purposes of this paragraph, employee exposure is that exposure which would occur if the employee were not using a respirator.

(2) *Initial.* Each employer who has a place of employment in which DBCP is present, shall monitor each workplace and work operation to accurately determine the airborne concentrations of DBCP to which employees may be exposed.

(3) *Frequency.* (i) If the monitoring required by this section reveals employee exposures to be below the permissible exposure limit, the employer shall repeat these measurements at least quarterly.

(ii) If the monitoring required by this section reveals employee exposures to be in excess of the permissible exposure limit, the employer shall repeat these measurements for each such employee at least monthly. The employer shall continue monthly monitoring until at least two consecutive measurements, taken at least seven (7) days apart, are below the permissible exposure limit. Thereafter the employer shall monitor at least quarterly.

(4) *Additional.* Whenever there has been a production, process, control, or personnel change which may result in any new or additional exposure to DBCP, or whenever the employer has any reason to suspect new or additional exposures to DBCP, the employer shall monitor the employees potentially affected by such change for the

purpose of redetermining their exposure.

(5) *Employee notification.* (i) Within five (5) working days after the receipt of monitoring results, the employer shall notify each employee in writing of the measurements which represent the employee's exposure.

(ii) Whenever the results indicate that employee exposure exceeds the permissible exposure limit, the employer shall include in the written notice a statement that the permissible exposure limit was exceeded and a description of the corrective action being taken to reduce exposure to or below the permissible exposure limit.

(6) *Accuracy of measurement.* The employer shall use a method of measurement which has an accuracy, to a confidence level of 95 percent, of not less than plus or minus 25 percent for concentrations of DBCP at or above the permissible exposure limit.

(g) *Methods of compliance.*—(1) *Priority of compliance methods.* The employer shall institute engineering and work practice controls to reduce and maintain employee exposures to DBCP at or below the permissible exposure limit, except to the extent that the employer establishes that such controls are not feasible. Where feasible engineering and work practice controls are not sufficient to reduce employee exposures to within the permissible exposure limit, the employer shall nonetheless use them to reduce exposures to the lowest level achievable by these controls, and shall supplement them by use of respiratory protection.

(2) *Compliance program.* The employer shall establish and implement a written program to reduce employee exposures to DBCP to or below the permissible exposure limit solely by means of engineering and work practice controls as required by paragraph (g)(1) of this section.

(ii) The written program shall include a detailed schedule for development and implementation of the engineering and work practice controls. These plans shall be revised at least every six months to reflect the current status of the program.

(iii) Written plans for these compliance programs shall be submitted upon request to the Assistant Secretary and the Director, and shall be available at the worksite for examination and copying by the Assistant Secretary, the Director, and any affected employee or designated representative of employees.

(iv) The employer shall institute and maintain at least the controls described in his most recent written compliance program.

(h) *Respirators.*—(1) *General.* Where respiratory protection is required under this section, the employer shall select, provide and assure the proper use of respirators. Respirators shall be used in the following circumstances:

(i) During the period necessary to install or implement feasible engineering and work practice controls; or

(ii) During maintenance and repair activities in which engineering and work practice controls are not feasible; or

(iii) In work situations where feasible engineering and work practice controls are not yet sufficient to reduce exposure to or below the permissible exposure limit; or

(iv) In emergencies.

(2) *Respirator selection.* (i) Where respirators are required under this section, the employer shall select and provide, at no cost to the employee, the appropriate respirator from Table 1 below and shall assure that the employee uses the respirator provided.

(ii) The employer shall select respirators from among those approved by the National Institute for Occupational Safety and Health (NIOSH) under the provisions of 30 CFR Part 11.

TABLE 1.—*Respiratory protection for DBCP*

Airborne concentration of DBCP or condition of use	Respirator type
(a) Less than or equal to 10 ppb.	(1) Any supplied-air respirator; or (2) any self-contained breathing apparatus.
(b) Less than or equal to 50 ppb.	(1) Any supplied-air respirator with full facepiece, helmet, or hood; or (2) any self-contained breathing apparatus with full facepiece.
(c) Less than or equal to 1,000 ppb.	(1) A Type C supplied-air respirator operated in pressure-demand or other positive pressure or continuous flow mode.
(d) Less than or equal to 2,000 ppb.	(1) A Type C supplied-air respirator with full facepiece operated in pressure-demand or other positive pressure mode, or with full facepiece, helmet, or hood operated in continuous flow mode.
(e) Greater than 2,000 ppb or entry and escape from unknown concentrations.	(1) A combination respirator which includes a Type C supplied-air respirator with full facepiece operated in pressure-demand or other positive pressure or continuous flow mode and an auxiliary self-contained breathing apparatus operated in pressure-demand or positive pressure mode; or (2) a self-contained breathing apparatus with full facepiece operated in pressure-demand or other positive pressure mode.
(f) Firefighting	(1) A self-contained breathing apparatus with full facepiece operated in pressure-demand or other positive pressure mode.

(3) *Respirator program.* (i) The employer shall institute a respiratory protection program in accordance with 29 CFR 1910.134 (b), (d), (e), and (f).

(ii) Employees who wear respirators shall be allowed to wash their faces and respirator facepieces as needed to prevent potential skin irritation associated with respirator use.

(i) *Emergency situations.*—(1) *Written plans.* (i) A written plan for emergency situations shall be developed for each workplace in which DBCP is present.

(ii) Appropriate portions of the plan shall be implemented in the event of an emergency.

(2) Employees engaged in correcting emergency conditions shall be equipped as required in paragraphs (h) and (j) of this section until the emergency is abated.

(3) *Evacuation.* Employees not engaged in correcting the emergency shall be removed and restricted from the area and normal operations in the affected area shall not be resumed until the emergency is abated.

(4) *Alerting employees.* Where there is a possibility of employee exposure to DBCP due to the occurrence of an emergency, a general alarm shall be installed and maintained to promptly alert employees of such occurrences.

(5) *Medical surveillance.* For any employee exposed to DBCP in an emergency situation, the employer shall provide medical surveillance in accordance with paragraph (m) (6) of this section.

(6) *Exposure monitoring.* (i) Following an emergency, the employer shall conduct monitoring which complies with paragraph (f) of this section.

(ii) In workplaces not normally subject to periodic monitoring, the employer may terminate monitoring when two consecutive measurements indicate exposures below the permissible exposure limit.

(j) *Protective clothing and equipments.*—(1) *Provision and use.* Where there is any possibility of eye or dermal contact with liquid or solid DBCP, the employer shall provide, at no cost to the employee, and assure that the employee wears impermeable protective clothing and equipment to protect the area of the body which may come in contact with DBCP. Eye and face protection shall meet the requirements of § 1910.133 of this Part.

(2) *Removal and storage.* (i) The employer shall assure that employees remove DBCP contaminated work clothing only in change rooms provided in accordance with paragraph (l) (1) of this section.

(ii) The employer shall assure that employees promptly remove any protective clothing and equipment which becomes contaminated with DBCP-containing liquids and solids. This clothing shall not be reworn until the

DBCP has been removed from the clothing or equipment.

(iii) The employer shall assure that no employee takes DBCP contaminated protective devices and work clothing out of the change room, except those employees authorized to do so for the purpose of laundering, maintenance, of disposal.

(iv) DBCP-contaminated protective devices and work clothing shall be placed and stored in closed containers which prevent dispersion of the DBCP outside the container.

(v) Containers of DBCP contaminated protective devices or work clothing which are to be taken out of change rooms or the workplace for cleaning, maintenance or disposal, shall bear labels in accordance with paragraph (o)(3) of this section.

(3) *Cleaning and replacement.* (i) The employer shall clean, launder, repair, or replace protective clothing and equipment required by this paragraph to maintain their effectiveness. The employer shall provide clean protective clothing and equipment at least daily to each affected employee.

(ii) The employer shall inform any person who launders or clean DBCP-contaminated protective clothing or equipment of the potentially harmful effects of exposure to DBCP.

(iii) The employer shall prohibit the removal of DBCP from protective clothing and equipment by blowing or shaking.

(k) *Housekeeping.*—(1) *Surfaces.* (i) All workplace surfaces shall be maintained free of visible accumulations of DBCP.

(ii) Dry sweeping and the use of compressed air for the cleaning of floors and other surfaces is prohibited where DBCP dusts or liquids are present.

(iii) Where vacuuming methods are selected to clean floors and other surfaces, either portable units or a permanent system may be used.

(*a*) If a portable unit is selected, the exhaust shall be attached to the general workplace exhaust ventilation system or collected within the vacuum unit, equipped with high efficiency filters or other appropriate means of contaminant removal, so that DBCP is not reintroduced into the workplace air; and

(*b*) Portable vacuum units used to collect DBCP may not be used for other cleaning purposes and shall be labeled as prescribed by paragraph (o)(3) of this section.

(iv) Cleaning of floors and other surfaces contaminated with DBCP-containing dusts shall not be performed by washing down with a hose, unless a fine spray has first been laid down.

(2) *Liquids.* Where DBCP is present in a liquid form, or as a resultant vapor, all containers or vessels containing DBCP shall be enclosed to the maximum extent feasible and tightly covered when not in use.

(3) *Waste disposal.* DBCP waste scrap, debris, containers or equipment, shall be disposed of in sealed bags or other closed containers which prevent dispersion of DBCP outside the container.

(l) *Hygiene facilities and practices.*—(1) *Change rooms.* The employer shall provide clean change rooms equipped with storage facilities for street clothes and separate storage facilities for protective clothing and equipment whenever employees are required to wear protective clothing and equipment in accordance with paragraphs (h) and (j) of this section.

(2) *Showers.* (i) The employer shall assure that employees working in the regulated area shower at the end of the work shift.

(ii) The employer shall assure that employees whose skin becomes contaminated with DBCP-containing liquids or solids immediately wash or shower to remove any DBCP from the skin.

(iii) The employer shall provide shower facilities in accordance with 29 CFR 1910.141(d)(3).

(3) *Lunchrooms.* The employer shall provide lunchroom facilities which have a temperature controlled, positive pressure, filtered air supply, and which are readily accessible to employees working in regulated areas.

(4) *Lavatories.* (i) The employer shall assure that employees working in the regulated area remove protective clothing and wash their hands and face prior to eating.

(ii) The employer shall provide a sufficient number of lavatory facilities which comply with 29 CFR 1910.141(d)(1) and (2).

(5) *Prohibition of activities in regulated areas.* The employer shall assure that, in regulated areas, food or beverages are not present or consumed, smoking products and implements are not present or used, and cosmetics are not present or applied.

(m) *Medical surveillance.*—(1) *General.* (i) The employer shall make available a medical surveillance program for employees who work in regulated areas and employees who are subjected to DBCP exposures in an emergency situation.

(ii) All medical examinations and procedures shall be performed by or under the supervision of a licensed physician, and shall be provided without cost to the employee.

(2) *Frequency and content.* At the time of initial assignment, and annually thereafter, the employer shall provide a medical examination for employees who work in regulated areas, which includes at least the following:

(i) A medical and occupational history including reproductive history.

(ii) A physical examination, including examination of the genito-urinary tract, testicle size and body habitus, including a determination of sperm count.

(iii) A serum specimen shall be obtained and the following determinations made by radioimmunoassay techniques utilizing National Institutes of Health (NIH) specific antigen or one of equivalent sensitivity:

(*a*) Serum follicle stimulating hormone (FSH);

(*b*) Serum luteinizing hormone (LH); and

(*c*) Serum total estrogen (females).

(iv) Any other tests deemed appropriate by the examining physician.

(3) *Additional examinations.* If the employee for any reason develops signs or symptoms commonly associated with exposure to DBCP, the employer shall provide the employee with a medical examination which shall include those elements considered appropriate by the examining physician.

(4) *Information provided to the physician.* The employer shall provide the following information to the examining physician:

(i) A copy of this regulation and its appendices;

(ii) A description of the affected employee's duties as they relate to the employee's exposure;

(iii) The level of DBCP to which the employee is exposed; and

(iv) A description of any personal protective equipment used or to be used.

(5) *Physician's written opinion.* (i) For each examination under this section, the employer shall obtain and provide the employee with a written opinion from the examining physician which shall include:

(*a*) The results of the medical tests performed;

(*b*) The physician's opinion as to whether the employee has any detected medical condition which would place the employee at an increased risk of material impairment of health from exposure to DBCP; and

(*c*) Any recommended limitations upon the employee's exposure to DBCP or upon the use of protective clothing and equipment such as respirators.

(ii) The employer shall instruct the physician not to reveal in the written opinion specific findings or diagnoses unrelated to occupational exposure.

(6) *Emergency situations.* If the employee is exposed to DBCP in an emergency situation, the employer shall provide the employee with a sperm count test as soon as practicable, or, if the employee has been vasectomized or is unable to produce a semen specimen, the hormone tests contained in paragraph (m)(2)(iii) of this section. The employer shall provide these same tests three months later.

(n) *Employee information and training.*—(1) *Training program.* (i) The

employer shall institute a training program for all employees who may be exposed to DBCP and shall assure their participation in such training program.

(ii) The employer shall assure that each employee is informed of the following:

(*a*) The information contained in Appendix A;

(*b*) The quantity, location, manner of use, release or storage of DBCP and the specific nature of operations which could result in exposure to DBCP as well as any necessary protective steps;

(*c*) The purpose, proper use, and limitations of respirators;

(*d*) The purpose and description of the medical surveillance program required by paragraph (m) of this section; and

(*e*) A review of this standard, including appendices.

(2) *Access to training materials.* (i) The employer shall make a copy of this standard and its appendices readily available to all affected employees.

(ii) The employer shall provide, upon request, all materials relating to the employee information and training program to the Assistant Secretary and the Director.

(o) *Signs and labels.*—(1) *General.* (i) The employer may use labels or signs required by other statutes, regulations, or ordinances in addition to or in combination with, signs and labels required by this paragraph.

(ii) The employer shall assure that no statement appears on or near any sign or label required by this paragraph which contradicts or detracts from the required sign or label.

(2) *Signs.* (i) The employer shall post signs to clearly indicate all regulated areas. These signs shall bear the legend:

DANGER

1,2-Dibromo-3-chloropropane

(*Insert appropriate trade or common names*)

CANCER HAZARD

AUTHORIZED PERSONNEL ONLY

RESPIRATOR REQUIRED

(3) *Labels.* (i) The employer shall assure that precautionary labels are affixed to all containers of DBCP and of products containing DBCP in the workplace, and that the labels remain affixed when the DBCP or products containing DBCP are sold, distributed, or otherwise leave the employer's workplace. Where DBCP or products containing DBCP are sold, distributed or otherwise leave the employer's workplace bearing appropriate labels required by EPA under the regulations in 40 CFR Part 162, the labels required by this paragraph need not be affixed.

(ii) The employer shall assure that the precautionary labels required by this paragraph are readily visible and legible. The labels shall bear the following legend:

DANGER

1,2-Dibromo-3-chloropropane

CANCER HAZARD

(p) *Recordkeeping.*—(1) *Exposure monitoring.* (i) The employer shall establish and maintain an accurate record of all monitoring required by paragraph (f) of this section.

(ii) This record shall include:

(*a*) The dates, number, duration and results of each of the samples taken, including a description of the sampling procedure used to determine representative employee exposure;

(*b*) A description of the sampling and analytical methods used;

(*c*) Type of respiratory protective devices worn, if any; and

(*d*) Name, social security number, and job classification of the employee monitored and of all other employees whose exposure the measurement is intended to represent.

(iii) The employer shall maintain this record for at least 40 years or the duration of employment plus 20 years, whichever is longer.

(2) *Medical surveillance.* (i) The employer shall establish and maintain an accurate record for each employee subject to medical surveillance required by paragraph (m) of this section.

(ii) This record shall include:

(*a*) The name and social security number of the employee;

(*b*) A copy of the physician's written opinion;

(*c*) Any employee medical complaints related to exposure to DBCP;

(*d*) A copy of the information provided the physician as required by paragraphs (m)(4)(ii) through (m)(4)(iv) of this section; and

(*e*) A copy of the employee's medical and work history.

(iii) The employer shall maintain this record for at least 40 years or the duration of employment plus 20 years, whichever is longer.

(3) *Availability.* (i) The employer shall assure that all records required to be maintained by this section be made available upon request to the Assistant Secretary and the Director for examination and copying.

(ii) The employer shall assure that all employee exposure monitoring records required by this section be made available for examination and copying to affected employees or their designated representatives.

(iii) The employer shall assure that former employees and former employee's designated representatives have access to such records as will indicate the former employee's own exposure to DBCP.

(iv) The employer shall assure that employee medical records required to be maintained by this section be made available, upon request, for examination and copying to the employee or former employee and to a physician or other individual designated by the affected employee or former employee.

(4) *Transfer of records.* (i) If the employer ceases to do business, the successor employer shall receive and retain all records required to be maintained by paragraph (p) of this section for the prescribed period.

(ii) If the employer ceases to do business and there is no successor employer to receive and retain the records for the prescribed period, the employer shall transmit these records by mail to the Director.

(iii) At the expiration of the retention period for the records required to be maintained under paragraph (p) of this section, the employer shall transmit these records by mail to the Director.

(q) *Observation of monitoring*—(1) *Employee observation.* The employer shall provide affected employees, or their designated representatives, with an opportunity to observe any monitoring of employee exposure to DBCP required by this section.

(2) *Observation procedures.* (i) Whenever observation of the measuring or monitoring of employee exposure to DBCP requires entry into an area where the use of protective clothing or equipment is required, the employer shall provide the observer with personal protective clothing or equipment required to be worn by employees working in the area, assure the use of such clothing and equipment, and require the observer to comply with all other applicable safety and health procedures.

(ii) Without interfering with the monitoring or measurement, observers shall be entitled to:

(*a*) Receive an explanation of the measurement procedures;

(*b*) Observe all steps related to the measurement of airborne concentrations of DBCP performed at the place of exposure; and

(*c*) Record the results obtained.

(r) *Appendices.* The information contained in the appendices is not intended, by itself, to create any additional obligations not otherwise imposed or to detract from any existing obligation.

APPENDIX A—SUBSTANCE SAFETY DATA SHEET FOR DBCP

I. SUBSTANCE IDENTIFICATION

A. Synonyms and trades names: DBCP; Dibromochloropropane; Fumazone (Dow Chemical Company TM); Nemafume; Nemagon (Shell Chemical Co. TM); Nemaset; BBC 12; and OS 1879.

B. Permissible exposure:

1. *Airborne.* 1 part DBCP vapor per billion parts of air (1 ppb); time-weighted average (TWA) for an 8-hour workday.

2. *Dermal.* Eye contact and skin contact with DBCP are prohibited.

C. Appearance and odor: Technical grade DBCP is a dense yellow or amber liquid with a pungent odor. It may also appear in granular form, or blended in varying concentrations with other liquids.

D. Uses: DBCP is used to control nematodes, very small worm-like plant parasites, on crops including cotton, soybeans, fruits, nuts, vegetables and ornamentals.

II. HEALTH HAZARD DATA

A. Routes of entry: Employees may be exposed:

1. Through inhalation (breathing);
2. Through ingestion (swallowing);
3. Skin contact; and
4. Eye contact.

B. Effects of exposure:

1. *Acute exposure.* DBCP may cause drowsiness, irritation of the eyes, nose, throat and skin, nausea and vomiting. In addition, overexposure may cause damage to the lungs, liver or kidneys.

2. *Chronic exposure.* Prolonged or repeated exposure to DBCP has been shown to cause sterility in humans. It also has been shown to produce cancer and sterility in laboratory animals and has been determined to constitute an increased risk of cancer in man.

3. *Reporting Signs and Symptoms.* If you develop any of the above signs or symptoms that you think are caused by exposure to DBCP, you should inform your employer.

III. EMERGENCY FIRST AID PROCEDURES

A. *Eye exposure.* If DBCP liquid or dust containing DBCP gets into your eyes, wash your eyes immediately with large amounts of water, lifting the lower and upper lids occasionally. Get medical attention immediately. Contact lenses should not be worn when working with DBCP.

B. *Skin exposure.* If DBCP liquids or dusts containing DBCP get on your skin, immediately wash using soap or mild detergent and water. If DBCP liquids or dusts containing DBCP penetrate through your clothing, remove the clothing immediately and wash. If irritation is present after washing get medical attention.

C. *Breathing.* If you or any person breathe in large amounts of DBCP, move the exposed person to fresh air at once. If breathing has stopped, perform artificial respiration. Do not use mouth-to-mouth. Keep the affected person warm and at rest. Get medical attention as soon as possible.

D. *Swallowing.* When DBCP has been swallowed and the person is conscious, give the person large amounts of water immediately. After the water has been swallowed, try to get the person to vomit by having him touch the back of his throat with his finger. Do not make an unconscious person vomit. Get medical attention immediately.

E. *Rescue.* Notify someone. Put into effect the established emergency rescue procedures. Know the locations of the emergency rescue equipment before the need arises.

IV. RESPIRATORS AND PROTECTIVE CLOTHING

A. *Respirators.* You may be required to wear a respirator in emergencies and while your employer is in the process of reducing DBCP exposures through engineering controls. If respirators are worn, they must have a National Institute for Occupational Safety and Health (NIOSH) approval label (Older respirators may have a Bureau of Mines Approval label). For effective protection, a respirator must fit your face and head snugly. The respirator should not be loosened or removed in work situations where its use is required. DBCP does not have a detectable odor except at 1,000 times or more above the permissible exposure limit. If you can smell DBCP while wearing a respirator, the respirator is not working correctly; go immediately to fresh air. If you experience difficulty breathing while wearing a respirator, tell your employer.

B. *Protective clothing.* When working with DBCP you must wear for your protection impermeable work clothing provided by your employer. (Standard rubber and neoprene protective clothing do not offer adequate protection).

DBCP must never be allowed to remain on the skin. Clothing and shoes must not be allowed to become contaminated with DBCP, and if they do, they must be promptly removed and not worn again until completely free of DBCP. Turn in impermeable clothing that has developed leaks for repair or replacement.

C. *Eye protection.* You must wear splashproof safety goggles where there is any possibility of DBCP liquid or dust contacting your eyes.

V. PRECAUTIONS FOR SAFE USE, HANDLING, AND STORAGE

A. DBCP must be stored in tightly closed containers in a cool, well-ventilated area.

B. If your work clothing may have become contaminated with DBCP, or liquids or dusts containing DBCP, you must change into uncontaminated clothing before leaving the work premises.

C. You must promptly remove any protective clothing that becomes contaminated with DBCP. This clothing must not be reworn until the DBCP is removed from the clothing.

D. If your skin becomes contaminated with DBCP, you must immediately and thoroughly wash or shower with soap or mild detergent and water to remove any DBCP from your skin.

E. You must not keep food, beverages, cosmetics, or smoking materials, nor eat or smoke, in regulated areas.

F. If you work in a regulated area, you must wash your hands thoroughly with soap or mild detergent and water, before eating, smoking or using toilet facilities.

G. If you work in a regulated area, you must remove any protective equipment or clothing before leaving the regulated area.

H. Ask your supervisor where DBCP is used in your work area and for any additional safety and health rules.

VI. ACCESS TO INFORMATION

A. Each year, your employer is required to inform you of the information contained in this Substance Safety Data Sheet for DBCP. In addition, your employer must instruct you in the safe use of DBCP, emergency procedures, and the correct use of protective equipment.

B. Your employer is required to determine whether you are being exposed to DBCP. You or your representative have the right to observe employee exposure measurements and to record the result obtained. Your employer is required to inform you of your exposure. If your employer determines that you are being overexposed, he is required to inform you of the actions which are being taken to reduce your exposure.

C. Your employer is required to keep records of your exposure and medical examinations. Your employer is required to keep exposure and medical data for at least 40 years or the duration of your employment plus 20 years, whichever is longer.

D. Your employer is required to release exposure and medical records to you, your physician, or other individual designated by you upon your written request.

APPENDIX B—SUBSTANCE TECHNICAL GUIDELINES FOR DBCP

I. PHYSICAL AND CHEMICAL DATA

A. Substance Identification

1. Synonyms: 1,2-dibromo-3-chloropropane; DBCP, Fumazone; Nemafume; Nemagon; Nemaset; BBC 12; OS 1878. DBCP is also included in agricultural pesticides and fumigants which include the phrase "Nema———" in their name.
2. Formula: $C_3H_5Br_2Cl$.
3. Molecular Weight: 236.

B. Physical Data:

1. Boiling point (760 mm HG): 195C (383F)
2. Specific gravity (water=1): 2.093.
3. Vapor density (air=1 at boiling point of DBCP): Data not available.
4. Melting point: 6C (43F).
5. Vapor pressure at 20C (68F): 0.8 mm Hg
6. Solubility in water: 1000 ppm.
7. Evaporation rate (Butyl Acetate=1): very much less than 1.
8. Appearance and odor: Dense yellow or amber liquid with a pungent odor at high concentrations. Any detectable odor of DBCP indicates overexposure.

II. FIRE EXPLOSION AND REACTIVITY HAZARD DATA

A. Fire

1. Flash point: 170F (77C)
2. Autoignition temperature: Data not available.
3. Flammable limits in air, percent by volume: Data not available.
4. Extinguishing media: Carbon dioxide, dry chemical.
5. Special fire-fighting procedures: Do not use a solid stream of water since a stream will scatter and spread the fire. Use water spray to cool containers exposed to a fire.
6. Unusual fire and explosion hazards: None known.
7. For purposes of complying with the requirements of § 1910.106, liquid DBCP is classified as a Class III A combustible liquid.
8. For the purpose of complying with § 1910.309, the classification of hazardous locations as described in article 500 of the National Electrical Code for DBCP shall be Class I, Group D.
9. For the purpose of compliance with § 1910.157, DBCP is classified as a Class B fire hazard.
10. For the purpose of compliance with § 1910.178, locations classified as hazardous locations due to the presence of DBCP shall be Class I, Group D.
11. Sources of ignition are prohibited where DBCP presents a fire or explosion hazard.

B. Reactivity

1. Conditions contributing to instability: None known.
2. Incompatibilities: Reacts with chemically active metals, such as aluminum, magnesium and tin alloys.
3. Hazardous decomposition products: Toxic gases and vapors (such as HBr, HCl and carbon monoxide) may be released in a fire involving DBCP.
4. Special precautions: DBCP will attack some rubber materials and coatings.

III. SPILL, LEAK AND DISPOSAL PROCEDURES

A. If DBCP is spilled or leaked, the following steps should be taken:

1. The area should be evacuated at once and re-entered only after thorough ventilation.

2. Ventilate area of spill or leak.

3. If in liquid form, collect for reclamation or absorb in paper, vermiculite, dry sand, earth or similar material.

4. If in solid form, collect spilled material in the most convenient and safe manner for reclamation or for disposal.

B. Persons not wearing protective equipment must be restricted from areas of spills or leaks until cleanup has been completed.

C. Waste Disposal Methods:

1. For small quantities of liquid DBCP, absorb on paper towels, remove to a safe place (such as a fume hood) and burn the paper. Large quantities can be reclaimed or collected and atomized in a suitable combustion chamber equipped with an appropriate effluent gas cleaning device. If liquid DBCP is absorbed in vermiculite, dry sand, earth or similar material and placed in sealed containers it may be disposed of in a State-approved sanitary landfill.

2. If in solid form, for small quantities, place on paper towels, remove to a safe place (such as a fume hood) and burn. Large quantities may be reclaimed. However, if this is not practical, dissolve in a flammable solvent (such as alcohol) and atomize in a suitable combustion chamber equipped with an appropriate effluent gas cleaning device. DBCP in solid form may also be disposed in a state-approved sanitary landfill.

IV. MONITORING AND MEASUREMENT PROCEDURES

A. Exposure above the permissible exposure limit.

1. *Eight Hour Exposure Evaluation:* Measurements taken for the purpose of determining employee exposure under this section are best taken so that the average 8-hour exposure may be determined from a single 8-hour sample or two (2) 4-hour samples. Air samples should be taken in the employee's breathing zone (air that would most nearly represent that inhaled by the employee).

2. *Monitoring Techniques:* The sampling and analysis under this section may be performed by collecting the DBCP vapor on petroleum based charcoal absorption tubes with subsequent chemical analyses. The method of measurement chosen should determine the concentration of airborne DBCP at the permissible exposure limit to an accuracy of plus or minus 25 percent. If charcoal tubes are used, a total volume of 10 liters should be collected at a flow rate of 50 cc. per minute for each tube. Analyze the resultant samples as you would samples of halogenated solvent.

B. Since many of the duties relating to employee protection are dependent on the results of monitoring and measuring procedures, employers should assure that the evaluation of employee exposures is performed by a competent industrial hygienist or other technically qualified person.

V. PROTECTIVE CLOTHING

Employees should be required to wear appropriate protective clothing to prevent any possibility of skin contact with DBCP. Because DBCP is absorbed through the skin, it is important to prevent skin contact with both liquid and solid forms of DBCP. Protective clothing should include impermeable coveralls or similar fullbody work clothing, gloves, headcoverings, and workshoes or shoe coverings. Standard rubber and neoprene gloves do not offer adequate protection and should not be relied upon to keep DBCP off the skin. DBCP should never be allowed to remain on the skin. Clothing and shoes should not be allowed to become contaminated with the material, and if they do, they should be promptly removed and not worn again until completely free of the material. Any protective clothing which has developed leaks or is otherwise found to be defective should be repaired or replaced. Employees should also be required to wear splash-proof safety goggles where there is any possibility of DBCP contacting the eyes.

VI. HOUSEKEEPING AND HYGIENE FACILITIES

1. The workplace must be kept clean, orderly and in a sanitary condition;

2. Dry sweeping and the use of compressed air is unsafe for the cleaning of floors and other surfaces where DBCP dust or liquids are found. To minimize the contamination of air with dust, vacuuming with either portable or permanent systems must be used. If a portable unit is selected, the exhaust must be attached to the general workplace exhaust ventilation system, or collected within the vacuum unit equipped with high efficiency filters or other appropriate means of contamination removal and not used for other purposes. Units used to collect DBCP must be labeled.

3. Adequate washing facilities with hot and cold water must be provided, and maintained in a sanitary condition. Suitable cleansing agents should also be provided to assure the effective removal of DBCP from the skin.

4. Change or dressing rooms with individual clothes storage facilities must be provided to prevent the contamination of street clothes with DBCP. Because of the hazardous nature of DBCP, contaminated protective clothing must be stored in closed containers for cleaning or disposal.

VII. MISCELLANEOUS PRECAUTIONS

A. Store DBCP in tightly closed containers in a cool, well ventilated area.

B. Use of supplied-air suits or other impervious clothing (such as acid suits) may be necessary to prevent skin contact with DBCP. Supplied-air suits should be selected, used, and maintained under the supervision of persons knowlegeable in the limitations and potential life-endangering characteristics of supplied-air suits.

C. The use of air-conditioned suits may be necessary in warmer climates.

D. Advise employees of all areas and operations where exposure to DBCP could occur.

VIII. COMMON OPERATIONS

Common operations in which exposure to DBCP is likely to occur are: during its production; and during its formulation into pesticides and fumiganta.

APPENDIX C.—MEDICAL SURVEILLANCE GUIDELINES FOR DBCP

I. ROUTE OF ENTRY

Inhalation; skin absorption

II. TOXICOLOGY

Recent data collected on workers involved in the manufacture and formulation of DBCP has shown that DBCP can cause sterility at very low levels of exposure. This finding is supported by studies showing that DBCP causes sterility in animals. Chronic exposure to DBCP resulted in pronounced necrotic action on the parenchymatous organs (i.e., liver, kidney, spleen) and on the testicles of rats at concentrations as low as 5 ppm. Rats that were chronically exposed to DBCP also showed changes in the composition of the blood, showing low RBC, hemoglobin, and WBC, and high reticulocyte levels as well as functional hepatic disturbance, manifesting itself in a long prothrombin time. Reznik et al. noted a single dose of 100 mg produced profound depression of the nervous system of rats. Their condition gradually improved. Acute exposure also resulted in the destruction of the sex gland activity of male rats as well as causing changes in the estrous cycle in female rats. Animal studies have also associated DBCP with an increased incidence of carcinoma. Olson, et al. orally administered DBCP to rats and mice 5 times per week at experimentally predetermined maximally tolerated doses and at half those doses. As early as ten weeks after initiation of treatment, DBCP induced a high incidence of squamous cell carcinomas of the stomach with metastases in both species. DBCP also induced mammary adenocarcinomas in the female rats at both dose levels.

III. SIGNS AND SYMPTOMS

A. Inhalation: Nausea, eye irritation, conjunctivitis, respiratory irritation, pulmonary congestion or edema, CNS depression with apathy, sluggishness, and ataxia.

B. Dermal: Erythema or inflammation and dermatitis on repeated exposure.

IV. SPECIAL TESTS

A. *Semen analysis:* The following information excerpted from the document "Evaluation of Testicular Function", submitted by the Corporate Medical Department of the Shell Oil Company (exhibit 39-3), may be useful to physicians conducting the medical surveillance program;

In performing semen analyses certain minimal but specific criteria should be met:

1. It is recommended that a minimum of three valid semen analyses be obtained in order to make a determination of an individual's average sperm count.

2. A period of sexual abstinence is necessary prior to the collection of each masturbatory sample. It is recommended that intercourse or masturbation be performed 48 hours before the actual specimen collection. A period of 48 hours of abstinence would follow; then the masturbatory sample would be collected.

3. Each semen specimen should be collected in a clean, widemouthed, glass jar (not necessarily pre-sterilized) in a manner designated by the examining physician. Any part of the seminal fluid exam should be initialed *only after liquifaction* is complete, i.e., 30 to 45 minutes after collection.

4. Semen volume should be measured to the nearest $\frac{1}{10}$ of a cubic centimeter.

5. Sperm density should be determined using routine techniques involving the use of a white cell pipette and a hemocytometer chamber. The immobilizing fluid most effective and most easily obtained for this process is distilled water.

6. Thin, dry smears of the semen should be made for a morphologic classification of the sperm forms and should be stained with either hematoxalin or the more difficult, yet more precise, Papanicolaou technique.

Also of importance to record is obvious sperm agglutination, pyospermia, delayed liquifaction (greater than 30 minutes), and hyperviscosity. In addition, pH, using nitrazine paper, should be determined.

7. A total morphology evaluation should include percentages of the following:

a. Normal (oval) forms,

b. Tapered forms,

c. Amorphous forms (include large and small sperm shapes),

d. Duplicated (either heads or tails) forms, and

e. Immature forms.

8. Each sample should be evaluated for sperm *viability* (percent viable sperm moving at the time of examination) as well as sperm *motility* (subjective characterization of "purposeful forward sperm progression" of the majority of those viable sperm analyzed) within two hours after collection, ideally by the same or equally qualified examiner.

B. *Serum determinations:* The following serum determinations should be performed by radioimmuno-assay techniques using National Institutes of Health (NIH) specific antigen or antigen preparations of equivalent sensitivity:

1. Serum follicle stimulating hormone (FSH);

2. Serum luteinizing hormone (LH); and

3. Serum total estrogen (females only).

V. TREATMENT

Remove from exposure immediately, give oxygen or artificial resuscitation if indicated. Contaminated clothing and shoes should be removed immediately. Flush eyes and wash contaminated skin. If swallowed and the person is conscious, induce vomiting. Recovery from mild exposures is usually rapid and complete.

VI. SURVEILLANCE AND PREVENTIVE CONSIDERATIONS

A. *Other considerations.* DBCP can cause both acute and chronic effects. It is important that the physician become familiar with the operating conditions in which exposure to DBCP occurs. Those with respiratory disorders may not tolerate the wearing of negative pressure respirators.

B. *Surveillance and screening.* Medical histories and laboratory examinations are required for each employee subject to exposure to DBCP. The employer should screen employees for history of certain medical conditions (listed below) which might place the employee at increased risk from exposure.

1. *Liver disease.* The primary site of biotransformation and detoxification of DBCP is the liver. Liver dysfunctions likely to inhibit the conjugation reactions will tend to promote the toxic actions of DBCP. These precautions should be considered before exposing persons with impaired liver function to DBCP.

2. *Renal disease.* Because DBCP has been associated with injury to the kidney it is important that special consideration be given to those with possible impairment of renal function.

3. *Skin desease.* DBCP can penetrate the skin and can cause erythema on prolonged exposure. Persons with pre-existing skin disorders may be more susceptible to the effects of DBCP.

4. *Blood dyscrasias.* DBCP has been shown to decrease the content of erythrocytes, hemoglobin, and leukocytes in the blood, as well as increase the prothrombin time. Persons with existing blood disorders may be more susceptible to the effects of DBCP.

5. *Reproductive disorders.* Animal studies have associated DBCP with various effects on the reproductive organs. Among these effects are atrophy of the testicles and changes in the estrous cycle. Persons with pre-existing reproductive disorders may be at increased risk to these effects of DBCP.

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(Secs. 6, 8, 84 Stat. 1593, 1596, 1599, (29 U.S.C. 655, 657); Secretary of Labor's Order 8-76 (41 FR 25059); (29 CFR 1911)

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Appendix C

(Federal Register, 44(143):43335-43341, July 24, 1979)

Pesticide Programs; Intent to Suspend Registrations of Pesticide Products Containing Dibromochloropropane (DBCP)

[FRL 1279-1; OPP-68005 A]

Pesticide Programs; Intent To Suspend Registrations of Pesticide Products Containing Dibromochloropropane (DBCP)

I. Introduction

This notice announces my intention to take expedited action under section 6(c) of the Federal Insecticide, Fungicide and Rodenticide Act, as amended (FIFRA), to control on an interim basis the hazards from use of pesticide products containing dibromochloropropane (DBCP), since I have found that continued use of such products poses an "imminent hazard". As developed more fully below, this provision of FIFRA authorizes me to prohibit, on an interim basis, the distribution, sale and use of a pesticide in situations where the use of that pesticide appears likely to pose an unreasonable risk to man or the environment during the period necessary to conduct and complete more lengthy administrative proceedings in which the ultimate fate of the pesticide can be determined.

This document is organized into five parts. Part I is this introduction. Part II is a brief description of the provision of the statute under which this action is taken. Part III is a summary of the already lengthy and complex regulatory history of actions which the Agency has initiated within the last two years concerning DBCP. Part IV is a discussion of the interim remedy I have decided to impose together with my findings and conclusions that continued use of DBCP poses an imminent hazard. Part V is devoted to procedural matters concerning requests for an expedited hearing and the hearing itself if one is requested.

II. Legal Authority

In order to obtain a registration for a pesticide under FIFRA, a manufacturer must prove that the pesticide satisfies the statutory standard for registration. That standard requires (among other things) that the pesticide "perform its intended function without unreasonable adverse effects on the environment" section 3(c)(5)). "Unreasonable adverse effects on the environment" is defined to mean "any unreasonable risk to man or the environment, taking into account the

economic , social and environmental costs and benefits of the use of any pesticide" section 2(bb)). In effect, this standard requires a finding that the benefits of each use of the pesticide exceed the risks of the use.

The burden of proving that a pesticide satisfies the registration standard continues for as long as the registration remains in effect and is on the proponent of registration at all times. Under section 6 of FIFRA, the Administrator is required to cancel the registration of a pesticide whenever he determines that the pesticide no longer satisfies the statutory standard for registration. The administrative procedures for making and implementing pesticide cancellation decisions may be very time-consuming, and the Agency's experience has been that as much as two years may be necessary in order to reach a final decision in a contested case.

The suspension provisions in section 6(c) of the statute are designed to give the Administrator authority to take interim action pending the completion of the time-consuming procedures required for reaching final registration decisions. Pursuant to that section, the Adminstrator may suspend the registration of a product, and thereby preclude its distribution, sale or use, upon a finding that the pesticide poses an "imminent hazard" to man or the environemnt. "Imminent hazard" is defined in the statute to mean:

> "a situation which exists when the continued use of a pesticide during the time required for cancellation proceeding would be likely to result in unreasonable adverse effects on the environment or will involve unreasonable hazard to the survival of a species declared endangered by the Secretary of the Interior under Public Law 94-135."

As discussed above, "unreasonable adverse effects on the environment" is defined to mean a situation where the risks of the use of a pesticide outweigh the benefits of use. Thus, in order to find that an imminent hazard exists it is necessary to find that the risks of use during the period likely to be required for cancellation proceedings appear to outweigh the benefits.

The courts have repeatedly "cautioned that the term 'imminent hazard' is not limited to a concept of crisis: 'it is enough if there is *substantial likelihood* that serious harm will be experienced during the year or two required in any realistic projection of the administrative [cancellation] process' " *Environmental Defense Fund, Inc.* ["EDF"] v. *Environmental Protection Agency* ["EPA"], 510 F.2d 1292, 1297 (D.C. Cir. 1975) (Emphasis in original), quoting from *EDF* v. *EPA*, 465 F.2d 528, 540 (D.C. Cir. 1972). *Accord, EDF* v. *EPA*, 548 F.2d 998, 1005 (D.C. Cir. 1976). Moreover, the registrant bears the burden of proof during a suspension proceeding, because, as indicated above, the burden of proof under FIFRA always resides with the proponent of registration throughout the life of a registration. See, e.g., *EDF* v. *EPA*, 510 F.2d at 1297; *EDF* v. *EPA*, 465 F.2d at 540. Finally, the courts have repeatedly held that "the function of a suspension decision is to make a preliminary assessment of evidence, and probabilities, not an ultimate resolution of difficult issues." *EDF* v. *EPA*, 510 F. 2d 1292, 1298 (1975). *Accord, EDF* v. *EPA*, 548 F. 2d 998, 1005 (D.C. Cir. 1976).

Suspensions are not ordinarily effective immediately; instead, in most cases the Administrator is required to give registrants notice of his intention to suspend, and 5 days in which to request a hearing. If no hearing is requested, a suspension order may be issued, thereby making the suspension effective. However, if a hearing is requested, the Administrator is required to convene expedited administrative proceedings, in which the sole issue is whether or not an imminent hazard exists.

III. Regulatory History of DBCP Suspension and Cancellation Proceedings

On September 8, 1977, I issued a Notice of Intent to Suspend and Conditionally Suspend Registrations of Pesticide Products Containing Dibromochloropropane (DBCP) (42 FR 48915, September 26, 1977), based on my finding that the continued use of DBCP products posed an imminent hazard to man. That finding was based on my conclusion that exposure to DBCP posed a serious health risk since "it appears that not only is DBCP a powerful carcinogen in animals which provides strong evidence that it is a human carcinogen, but that it may also damage human reproductive functions, and may cause sterility in males." (42 FR at 48917). That notice therefore proposed two separate but related suspension actions: the unconditional suspension of DBCP products for use in nineteen (19) specific food crops in which DBCP residues occurred, or appeared reasonably likely to occur, in the edible portions of treated crops; and the conditional suspension of DBCP products for all other uses.[1] With respect to the conditionally suspended uses, I found that the risks to applicators could be sufficiently reduced at least on an interim basis by the imposition of appropriate restrictions (including limitation to certified applicators utilizing respirators and protective clothing) and accordingly indicated that relief from conditional suspension could be accomplished by obtaining an interim registration amendment to reflect those restrictions. I also indicated that such applications for interim registration amendments would be without prejudice to the registrant's right to challenge the unconditional suspension of the food crop uses, and without prejudice to the Agency's right to review the adequacy of the restrictions at a later date.

Pursuant to Section 6(c) of FIFRA, each registrant of a DBCP product was given an opportunity to request an expedited hearing before the Agency on the question of whether an imminent hazard existed. The Agency received only three timely requests for an expedited hearing, each of which was subsequently withdrawn. Consequently, on October 27, 1977, I issued a Suspension Order effectuating the suspension and conditional suspension actions which I had announced my intention to implement on September 8, 1977. (42 FR 57543, November 3, 1977.[2]

At the same time that I issued the Suspension Order, I also issued a Notice of Intent to Cancel the Registrations or Change the Classifications of Pesticide Products Containing DBCP, and Statement of Reasons (the "Original Section 6(b)(1) Notice") (42 FR 57545, November 3, 1977), in which I found that the continued use of pesticide products containing DBCP in accordance with then-current labeling restrictions appeared to pose unreasonable risks to man and the environment amounting to "unreasonable adverse effects on the environment", and I therefore announce my intention to cancel or change the classifications of all registered uses of DBCP pursuant to Section 6(b) of FIFRA.

In the Original Section 6(b)(1) Notice, I also acknowledged that the Agency's Office of Pesticide Programs (OPP) had issued a Notice of Rebuttable Presumption Against Registration and Continued Registration of Pesticide

[1] The conditionally suspended uses are: Cotton, soybeans, citrus, grapes, pineapples, peaches, nectarines, plums, almonds, commercial okra, commercial lima beans, commercial snap beans, commercial southern peas, berries (blackberries, blueberries, loganberries, dewberries, boysenberries, raspberries), strawberry nursery stock, apricots, cherries, figs, walnuts, bananas, turf (commercial and residential) and ornamentals (commercial and residential).

[2] I subsequently amended the Suspension Order to clarify that I did not intend to unconditionally suspend the use of DBCP on strawberry plants which are being grown as transplants or nursery stock and which are not allowed to fruit until after being transplanted (43 FR 23649, May 31, 1978).

Products Containing DBCP (the "RPAR Notice") (42 FR 48026, September 22, 1977), and noted that the RPAR process was designed to gather information about a problem pesticide and to make a decision concerning it in an open manner allowing maximum participation by all interested groups.[3] Accordingly, I found it to be in the public interest to continue the RPAR review of DBCP and I specifically stated that the decisions reached as the result of that RPAR review could form the basis of an amendment to the Original Section 6(b)(1) Notice. I therefore delegated to the Assistant Administrator for Toxic Substances the authority and responsibility: (1) For reviewing the evidence submitted in the RPAR process, Agency staff evaluations of that evidence, and Agency staff recommendations concerning possible amendments to the Original Section 6(b)(1) Notice, and (2) for issuing, filing and serving, if appropriate, an amended notice under Section 6(b)(1) of FIFRA.

On September 6, 1978, the Assistant Administrator for Toxic Substances issued at the conclusion of the RPAR review of DBCP an Amended Notice of Intent to Cancel Registrations of Pesticide Products Containing DBCP, and Statement of Reasons (the "Amended section 6(b)(1) Notice") (43 FR 40911, September 13, 1978). The Amended section 6(b)(1) Notice adopted as its statement of reasons and underlying support document the final Position Document issued at the conclusion of the RPAR. Based on the conclusions in the final Position Document that "DBCP presents a significant risk of cancer to human beings who are exposed to the chemical" (p. 16) and that "DBCP poses a risk of testicular toxicity, as evidenced by an increased incidence of reduced sperm counts, to males who are exposed to the chemical" (p. 31), the Amended section 6(b)(1) Notice proposed to: (1) Unconditionally cancel 23 uses of DBCP (the 19 unconditionally suspended uses plus 4 other non-commercial vegetable uses); and (2) conditionally cancel all remaining uses of DBCP (i.e., cancel them *unless* the terms and conditions of registration for those uses are modified to reflect the specific restrictions set forth in the Amended section 6(b)(1) Notice). With respect to the unconditionally cancelled uses, one registrant timely objected to and requested a hearing with respect to the tomato use and a section 6(b)(1) hearing concerning the tomato use is currently in progress.[4]

With respect to the conditionally cancelled uses, a coalition of farmworkers, migrant farmworker organizations and public interest groups objected that the restrictions proposed in the Amended section 6(b)(1) Notice were inadequate to protect farmworkers against various risks posed by those uses of DBCP, and contended that they should have been unconditionally cancelled. Because the Assistant Administrator for Toxic Substances determined after careful review that the farmworkers' objections were not frivolous and warranted serious consideration (especially since they relied in part on new data which were not available for review or analysis during the RPAR), he issued a Notice of Intent to Hold a Hearing to Determine Whether or Not the Registrations of Certain Uses of Pesticide Products should be cancelled, and Statement of Issues (the "section 6(b)(2) Notice") (44 FR 11822, March 2, 1979).[5] In the section 6(b)(2) Notice, he directed that a hearing be held under section 6(b)(2) of FIFRA to consider the matters raised by the farmworkers' objections and to determine whether or not to unconditionally cancel the uses which he previously proposed to conditionally cancel, or whether to conditionally cancel them subject to modifications to the terms and conditions of registration different (that is, more restrictive) than those which he proposed in the Amended section 6(b)(1) Notice. He also made it clear that at the conclusion of the section 6(b)(2) hearing, all uses covered by it (i.e, the uses proposed to be conditionally cancelled by the Amended section 6(b)(1) Notice) can be *unconditionally* cancelled, and a final order of unconditional cancellation can be issued for some or all of such uses.

The Assistant Administrator referred the section 6(b)(2) Notice to the Secretary of the Department of Agriculture (USDA) and to the Agency's Scientific Advisory Panel (SAP) for review and comment on the actions proposed in it, and later indicated that he would publish their comments, together with his responses to those comments, in the **Federal Register** and would make such changes in the section 6(b)(2) Notice as he determined to be appropriate in light of those comments and his responses. The Assistant Administrator has recently received the comments of both USDA and SAP, but has not yet responded to them.

IV. The Present Suspension Action

As discussed above, the Suspension Order currently in effect reflects decisions based on information available to me at the time that I issued it concerning the likelihood of DBCP residues occurring in the edible portions of treated crops, and on "my preliminary conclusion that applicator exposure can be controlled at least on an interim basis by imposition of appropriate restrictions" (42 FR at 48916). With respect to the food residue issue, however, I specifically indicated:

> "From available data the Agency is presently unable to reach a conclusion that there is a likelihood of DBCP residues in or on the remaining [i.e., conditionally suspended] food crops for which there are registered uses. However, further consideration will be given to those crops as additional residue information becomes available." (42 FR at 48917)

Moreover, with respect to the issue of applicator exposure from the use of DBCP on the conditionally suspended uses, I specifically stated that:

> "* * * I emphasize that my finding that these risk reduction methods [i.e., the restrictions imposed by the conditional suspension] adequately reduce pesticide applicator exposure is a tentative finding. If as a result of further review of this problem it appears that these measures are not providing adequate protection to applicators, other remedies including suspension and cancellation of all uses are available and can be implemented." (42 FR at 48916)

In other words, I made it clear at the time of suspension that if new or additional information were to become available and were to indicate that the use of DBCP even under the terms of the conditional suspension continued to pose risks to consumers or applicators, that I could and would take additional suspension actions in order to prevent any imminent hazard presented by such use.

Unfortunately, the Agency has received information since the date of the Suspension Order which indicates that the conditional suspension action is not adequate to satisfactorily reduce the risks associated with continued use of

[3] The RPAR process is set out in 40 CFR 162.11.

[4] On April 16, 1979, the Agency's Judicial Officer issued an Accelerated Decision in FIFRA Docket Nos. 401 *et al.* in which he affirmed in its entirety an order of the presiding Administrative Law Judge which denied the registrant's motion to amend its objections to include the other 22 unconditionally cancelled uses of DBCP. Those 22 uses are now unconditionally cancelled as a matter of law because no hearing was timely requested as to them within the statutory deadline.

[5] On April 9, 1979, the Agency's Judicial Officer rendered a Decision on Interlocutory Appeal in FIFRA Docket Nos. 401 *et al.* in which he ruled that the farmworkers' objections to the conditional cancellation actions were improper under section 6(b)(1) of FIFRA and could not be employed to expand the scope of relief which could be granted at the conclusion of the section 6(b)(1) hearing.

DBCP even on an interim basis. Briefly summarized, this new information shows that the Agency's previous assumptions concerning the manner in which treated crops may become contaminated with residues of DBCP are no longer valid, and that residues may occur even in crops which are not grown in contact with or in close proximity to treated soil; that treatment with DBCP may result in contamination of water supplies, including drinking water sources, with residues of DBCP; and that application of DBCP may result in ambient air levels of DBCP at sites outside the application area and may result in ambient air levels of DBCP at the site of application several days after application. Because of this information, I have undertaken a review of both the risks and benefits associated with the use of DBCP during the next year[6] in order to determine whether or not additonal regulatory actions are warranted.

A. *Risks.* With respect to risks, my determination concerning the adverse human health effects associated with exposure to DBCP—namely, carcinogenicity and testicular toxicity—has not changed since the time of the Suspension Order. However, my perception of the potential exposure to the population at large, and to farmworkers in particular, from continued use fo DBCP has changed dramatically.

First, the Agency's earlier assumptions concerning the reasons why DBCP residues apparently occurred in some crops but not in others now appear to be faulty. Specifically, Agency chemists had earlier hypothesized that DBCP itself is not absorbed and translocated within growing plants; rather, they hypothesized that residues of DBCP in crops grown in DBCP-treated soil probably result from the crops' contact with the treated soil, from volatilization of DBCP from the treated soil and condensation or absorption on crop surfaces in close proximity to treated soil, or from deposition of DBCP on the crop itself during application. They further concluded that root crops, which bear the highest residues, may be exceptions to this hypothesis, especially in light of the demonstrated ability of carrots to absorb organochlorine pesticides from the soil. Based on actual data from supervised trials, or extrapolation of that data to other related crops or crops with similar growing characteristics, the chemists identified crops in which residues could be expected to occur and crops as to which they were unable to reach such a conclusion.

Subsequently, the Agency received new residue data developed by the California Department of Food and Agriculture (CDFA), using a new and more sensitive analytical methodology than was previously available, indicating that residues of DBCP in fact occurred in several tree and vine crops—crops which the Agency had not predicted would have DBCP residues because the fruit was not grown in proximity to the treated soil, and because it was unlikely that DBCP would be deposited on the fruit during application. Based on an evaluation of that data, the Agency chemists determined that their previous conclusion that DBCP residues did not occur in certain crops was no longer appropriate, and that it had to be assumed that DBCP residues could occur in *all* treated crops. In other words, I can no longer assume that crops treated with DBCP under the terms of the conditional suspension action will *not* be contaminated with DBCP residues, and I must assume that there is potential ingestion exposure to DBCP for the population at large from the consumption of any crop grown in soil treated with DBCP.

Second, I have received disturbing information which indicates that there may be exposure to DBCP for the population at large from the previously unsuspected source—contaminated drinking water. Recent investigations by California state officials have found DBCP in active groundwater wells at levels as high as 39 parts per billion (ppb), and preliminary results indicate that community water supply wells in counties where DBCP was previously used may be contaminated with levels of DBCP as high as 15 ppb—findings which are particulary troubling since the State of California has itself prohibitied all uses of DBCP since 1977. DBCP has also been found in wells in Arizona, and in at least one sample taken from wells in Hawaii. Although preliminary investigations by the Agency in the Southeast have not as yet revealed a similar pattern of DBCP water contamination, the possibility that a more thorough and complete sampling program (intergrating use history and other data) *will* find DBCP in drinking water in the Southeast cannot be discounted. Accordingly, I believe that it is too early to hypothesize as to why DBCP has only been found to date in the Southwest. Rather, because of the uncertainty as to the size of the population at risk, and because of the grave consequences to the health of that segment of the population which is exposed to DBCP in drinking water, I believe that prudence dictates that I make regulatory decisions based on the assumption that continued use of DBCP in accordance with the conditional suspension action may result in contamination of drinking water supplies.

Third, other data submitted by CDFA since the time of the Suspension Order indicates that the terms of the conditional suspension action may not adequately protect applicators, farmworkers and bystanders from exposure to DBCP resulting from its continued use. In particular, the data show that there are ambient air levels of DBCP in or around treated fields for longer periods of time following application than previously estimated (in some cases, several days); but under the conditional suspension action, there is no requirement that re-entry into a treated area (without protective clothing and respirators) be prohibited for any amount of time. The data also show that DBCP was detected in the air at some distance from the application site using both irrigation and chisel injection application techniques; but under the conditional suspension action, there is no requirment of a "buffer zone" for unprotected bystanders (i.e., a prohibition on application within the specified distances of areas populated or frequented by unprotected bystanders). Finally, the data show that residues of DBCP may be expected to occur on the bark and leaves of trees and vines in treated areas, as well as on the fruit surface and in the soil; but under the conditional suspension action, no protective measures are required to minimize or eliminate any dermal exposure to farmworkers who work in or who harvest in treated areas.

In summary, I find that there continues to be potential exposure to DBCP as the result of its continued use under the conditional suspension action—potential ingestion exposure to the population at large through residues in treated crops and through contamination of drinking water, and potential dermal and inhalation exposure to applicators, farmworkers and others who live or work in the vicinity of treated areas. I also recognize that the extent of this potential exposure, although real, is at the present

[6] I have determined that one year (rather than two) is an appropriate estimate of the amount of time necessary for completion of the cancellation proceedings, since as a result of the in-depth RPAR evaluation of the risks and benefits of all uses of DBCP and the subsequent referral to the SAP, the issues involved in this case are fairly well-defined, and the Agency is prepared to go forward with its case. In addition, a pre-hearing conference has already been held and the parties have been directed to begin their pretrial preparations.

unknown; and that more data and information are both desirable and necessary in order to make *final* regulatory decisions concerning the ultimate fate of the registrations of DBCP. In the absence of definitive information, however, and in light of the demonstrated potential for exposure, I must conclude that the continued use of DBCP under the terms of the conditional suspension poses a serious risk of adverse human health effects.

B. *Benefits.* I have examined the benefits associated with the continued use of DBCP for the approximate one year required for completion of the DBCP cancellation proceedings in order to decide whether they outweigh the risks of continued use during this period. Based upon the analysis prepared by Agency staff as part of the RPAR review of DBCP, I conclude that the unavailability of DBCP for the conditionally suspended uses for the duration of cancellation proceedings will potentially result in a loss of approximately $42 million in production losses and increased costs of alternative chemicals.

The uses of DBCP which were conditionally suspended fall into three major categories: uses where application is made before or at the time of planting; uses where application is made in established orchards or vineyards; and other miscellaneous or minor uses.

With respect to the first group of uses, where application is made before or at the time of planting—which includes cotton, soybeans, pineapples, and certain commercial vegetables (lima beans, snap beans, okra and southern peas)—the economic impact of the unavailability of DBCP for one year would be approximately $33.7 million. For cotton and soybeans, increased control costs of alternative chemicals would be about $2.6 million and $23.5 million respectively, but with only negligible impacts in terms of production losses. For pineapples, the increased control costs would be approximately $0.2 million and the production loss would be about $5.8 million (realized at the time of harvest in about two or three years). For the commercial vegetables, the increased control costs would be approximately $1.2 million and the production loss would be about $0.4 million.

With respect to the second group of uses, where application is made in established orchards or vineyards—which includes citrus, grapes, peaches and nectarines, almonds and plums—the economic impact of the unavailability of DBCP for one year would be approximately $8.5 million in production losses less saved chemical costs (which reflects the fact that there are no registered alternatives for these uses). Since application for use on these crops is made post-plant, and since the application cycle is generally on an every-third-or-fourth-year basis, the effect of unavailability of DBCP for one year would be to defer or stagger the application cycle. The approximate production losses (less saved chemical costs) attributable to that deferral are: peaches and nectarines—$6.9 million; citrus—$1.6 million; grapes—no impact; almonds—no impact; and plums—no impact.[7]

With respect to the remaining miscellaneous or minor uses, the economic impact of the unavailability of DBCP will not be significant, although based on available information it is not possible to quantify all of the impact. Very little if any DBCP is currently used domestically on apricots, cherries, figs, walnuts, bananas, vine berries, and strawberry nursey stock, although DBCP is registered for those uses. Data concerning the use of DBCP on ornamentals (including green house and nursery as well as residential uses) are not available, nor are they available for residential lawn use. The extent of usage of DBCP on commercial turf (such as golf courses) is similarly unknown, although it has been estimated that treatment costs with alternatives might be two to three times higher per acre than treat-costs with DBCP.

C. Conclusion

On balance, I find that the risks of continued use of DBCP during the pendency of cancellation hearings outweigh the benefits of continued use during that period, and I therefore announce my intention to suspend all uses of all registrations of pesticide products containing DBCP.

Finally, it is important to emphasis that I do not assume—nor do I intend to imply by my action today—that it will be impossible to develop terms and conditions of registration which will adequately reduce or eliminate the potential exposures which I have discussed above. Those issues will be resolved in the cancellation proceedings, and will undoubtedly rely upon and utilize data yet to be developed. However, because of the uncertainty surrounding the safety of continued use of DBCP under the conditional suspension action, and because of the serious health consequences of exposure to DBCP, I believe that use of DBCP should be prohibited pending the resolution of those issues.

V. Procedural Matters

Under section 6(C)(2) of FIFRA, this suspension action cannot take effect against any registration until the registrant has had an opportunity for an expedited hearing before the Agency on the question of whether an imminent hazard exists. This section explains how registrants may request an expedited hearing, the consequences of requesting or not requesting an expedited hearing, and the procedures which govern an expedited hearing in the event one is requested.

A. *Procedures for Requesting a Hearing*

(1) *Who May Request a Hearing and When the Request Should Be Made.* Any registrant of a DBCP product currently registered for any use which was conditionally suspended under paragraph 2 of the Suspension Order of October 27, 1977 may request a hearing on *specific registered uses* of its product within five (5) days after receipt of this notice. No person other than the registrant may request a hearing with respect to any use of any registration.

In order to be timely made, a request for a hearing from a registrant in writing or by telegram must be *received* by the Hearing Clerk within five (5) days after the registrant's receipt of this notice [40 CFR 164.121(a)(2)].

(2) *How to Request a Hearing.* Registrants who request a hearing must follow the Agency's Rules of Practice Governing Hearings (40 CFR, Part 164). These procedures specify, among other things: (1) that all requests for a hearing must be accompanied by objections that are specific for *each use* for which a

[7] These benefits figures do not include losses attributable to the unavailability of DBCP in California, where DBCP is already unavailable as the result of actions taken at the State level. Since I am not aware of any information which indicates that California intends to lift its ban in the forseeable future, analysis of the impacts of the short-term unavailability or DBCP may as a matter of fact properly and justifiably exclude consideration of the impacts in California. I do note, however, that if risks and benefits from use of DBCP in California were to be included for purposes of determining whether or not there is an imminent hazard, my conclusion would be the same. On the risk side, the population at risk from potential exposure to DBCP would increase substantically (in proportion to the amount of DBCP used in California), while the concomitant benefits from the use of DBCP in California would be approximately $101 million, attributable to the second group of uses (citrus—$8.6 million; grapes—$44.4 million; peaches and nectarines—$25.3 million; almonds—$15.1 million; plums—$7.8 million.) In that regard, the benefits figures for California are for losses estimated for the *third* year following the unavailability of DBCP, since the losses attributable to the first two years of unavailability have presumably already accrued as the result of State action. On balance, I would find that the risks of continued use of DBCP (including California) during the pendency of cancellation proceedings outweigh the benefits of continued use (including California) during that period.

hearing is requested [40 CFR 164.121(a) and 164.22] and (2) that all requests must be *filed* with the Office of the Hearing Clerk within the applicable five (5) days [40 CFR 164.121(a)]. *Failure to comply with these requirements will automatically result in denial of the request for a hearing.*

Requests for hearings must be submitted to: Hearing Clerk (A-110), U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, D.C. 20460.

B. *Consequences of Filing a Hearing Request*

The statute provides that if a hearing is timely requested by a registrant within the five-day period, the hearing stage is to begin within five days after receipt of the request for the hearing, unless the registrant and the Agency agree that it shall begin at a later time. Hearings are subject to the provisions of subchapter II of Title 5 of the United States Code, except that the presiding officer need not be a certified hearing examiner. The presiding officer has ten days from the conclusion of the presentation of evidence to submit recommended findings and conclusions to the Administrator, who in turn has seven days to issue a final order on the issue of suspension.

C. *Consequences of Not Filing a Hearing Request*

Under the statutory scheme, if a registrant does not request a hearing as to its registration within the five-day period, a suspension order may be issued with respect to that registration, and such suspension order will *not* be reviewable by a court.

It is important to emphasize that the suspension action initiated by this notice will be implemented on a registration-by-registration basis. In other words, unless the *registrant timely* requested a hearing with respect to *its* registration, *that* registration will be subject to the issuance of a suspension order—*notwithstanding* that *other* registrants may have timely requested hearings with respect to *their* registrations (and notwithstanding that those other registrations may have identical registered uses). This registration-specific approach to the actions initiated by this notice will be strictly observed and no exceptions will be granted.

D. *Supplementary Procedures*

The Agency's rules of Procedure for expedited hearings are set forth at 40 CFR Part 164, Subpart C. I do not know if a hearing will be requested on these suspensions. If a hearing is requested, however, I am establishing the following procedures to supplement the existing regulations in governing its conduct.

(1) A deadline is being established for the completion of all hearing procedures and the rendering of a recommended decision under 40 CFR 164.121(j). That deadline is 60 calendar days from the first prehearing conference, which shall be held in accordance with the time requirements described below.

Deadlines for completing proceedings under FIFRA have been twice endorsed by the National Academy of Sciences [National Academy of Sciences, Decision Making in the Environmental Protection Agency, Vol. II, p. 84 (1977); National Academy of Sciences, Decision Making for Regulating Chemicals in the Environment, p. 30 (1975)]. In addition, Congress has demonstrated a concern for speedy action where suspensions based on a potential threat to human health are concerned. It has required a hearing on such a suspension to begin five days after it is requested and has allowed ten and seven days respectively for preparation of the initial and final decisions once the hearing is over [FIFRA section 6(c)(2)]. FIFRA was amended in 1975 to require consultation by the Agency with the Department of Agriculture and a scientific advisory panel before taking action in many cases; suspensions based on human health grounds, however, were exempted from those requirements to allow speedy action where speedy action was desirable [121 Cong. Rec. H 9895-96 (daily ed. Oct. 9, 1975); 121 Cong. Rec. Section 19820-21 (daily ed. Nov. 12, 1975)].

Deadlines for completing the hearing have been imposed in prior suspensions, including the earlier suspension of DBCP. See, also, *In re: Velsicol Chemical Co., et al.*, 41 FR 7552, 7553 (Feb. 19, 1976) [Notice of Intent to Suspend Heptachlor and Chlordane]. The requirements set forth in this order simply carry forward that practice.

(2) I am naming certain EPA employees to provide technical advice and assistance to the Administrative Law Judge who will preside at any hearing arising out of this notice. The Administrative Law Judge may consult these employees during the course of the hearing and in preparing his recommended decision, and he may allow these employees to question any witness who testifies at the hearing on behalf of any party. None of these employees is subject in the normal course of their duties to the supervision or direction of any employee or agent of the Agency who is a member of the Agency trial staff named below. See 5 U.S.C. Section 554(d)(2). These employees are identified in Appendix A.

Since 5 U.S.C. Section 554(d)(1) provides that those presiding at adjudicatory hearings may not "consult a person or party on a fact in issue [in the course of preparing their decision] unless on notice and opportunity for all parties to participate," neither myself nor my appellate staff (See below) will consult with the Administrative Law Judge or these Agency employees on any matters involving this case from the date of this notice until a recommended decision is issued.

(3) I am also designating an appellate staff to assist me in conducting an independent review of the questions presented on appeal of any recommended decision, and in preparing a final decision. Members of my appellate staff are also listed in Appendix A.

(4) The following Agency bureaus or divisions, and their staffs, are designated to perform all investigative and prosecutorial functions in this case: Office of the Deputy Administrator,[8] Office of Toxic Substances, the Office of General Counsel, and the Office of Enforcement.

From the date of this notice until any final decision, neither the Administrative Law Judge, the employees appointed to assist him, my appellate staff, or myself, shall have any *ex parte* contact with any trial staff employees, or any other interested person not employed by EPA, on any of the issues involved in this proceeding. However, persons interested in this case should feel free to contact any other EPA employee, including both trial staff and persons not explicitly named as assistants or appellate staff, with any questions they may have.

(5) The statute itself is silent on the question of intervention in expedited suspension hearings.

However, the Agency's Rules of Practice currently provide that "any person adversely affected" by the notice of intent to suspend may move to intervene in any hearing requested by a registrant, and they set out criteria governing the granting of such motions (40 CFR 164.121-(e)). Although the

[8] The Deputy Administrator may properly be included in the trial staff since the prohibitions of 5 U.S.C. Section 554(d) do not apply to "the agency". Her inclusion is necessary if guidance on general policy matters is to be available to the trial staff and to free a high agency official to talk to outside interested persons about the questions involved without the constraints otherwise imposed by the *ex parte* provisions of the APA and the Government in the Sunshine Act. The Deputy Administrator will take no part in the detailed work of preparing and presenting the Agency's case.

limiting "adversely affected" language as used in that section of the Rules of Practice does not have a statutory origin or basis, the Rules as written could be interpreted as precluding the intervention of persons who are not *technically* "adversely affected" by this notice but who have evidenced a high degree of interest and who have actively participated in the ongoing administrative proceedings on DBCP. Accordingly, I am directing that the opportunity to move to intervene in any hearing requested by a registrant be extended to "any interested person" as well as any person "adversely affected" by this notice. Such motions shall be subject to the existing provisions of 40 CFR 164.121–(e) concerning the time for their submission and the criteria for being granted.

(6) The scheduling of any hearing, particularly in its earlier stages, involves a balancing between the need to conduct an expeditious hearing and a concern that the hearing not proceed too far before the identity of those registrants requesting a hearing is established. I am therefore taking two steps in order to accommodate these concerns. First, I am hereby providing that service of this notice upon registrants may properly be made by means of federal "express mail," which guarantees delivery within 24 hours and which involves acknowledgement of receipt by the addressee. In this regard, the statute itself is silent on the question of how service of the notice upon registrants must be effected, although the Rules of Practice provide that it "shall either be personally served on the registrant or be sent to the registrant by registered or certified mail, return receipt requested" (40 CFR 164.120(b)). However, the underlying purpose of that section is to provide *the Agency* with either first-hand knowledge (after personal service) or documented evidence (by return receipt) of the *date* of receipt by the registrant—so that the Agency can accurately determine when the time for requesting a hearing has expired and when a suspension order may be issued and take effect. Relying exclusively upon these methods of service in the past, however, has proved to be both inefficient and unnecessarily time-consuming. Moreover, no registrant will be prejudiced if it is served by "express mail," since the statute measures a registrant's time for requesting a hearing from its *receipt* of the notice by *whatever* means.

Second, I am directing the Administrative Law Judge presiding at the hearing to convene the first prehearing conference within five days after (1) receipt by the Hearing Clerk of the last timely request for a hearing by a registrant or (2) 15 days after the issuance of this notice, whichever comes earlier. The 15-day maximum should ensure that all registrants wishing to participate in the hearing have been given ample time to file a hearing request after receiving notification of my suspension actions.

Dated: July 18, 1979.

Douglas M. Costle,

Administrator.

Appendix A

Technical Support Staff

Willert Smith,
Dr. Dennis L. Foerst,
Dr. Robert Kavolock.

Administrative Appellate Staff

Ronald L. McCallum,
Charles R. Ford,
Dr. Edwin H. Clark,
Ms. Mary Ann Massey,
Dr. Richard M. Dowd,
Dr. Stephen J. Gage.

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APPENDIX D

GLOSSARY

Adrenocortical hormone--	One of the steroids produced by the adrenal cortex belonging, on the basis of biological activity and structure, to four main types: estrogen, androgens, progesterone, and corticoids.
Aflatoxin--	A toxic factor--molds contaminating ground nut seedlings. Responsible for deaths of fowl and other farm animals fed with infected ground nut meal. Experimentally, it is regularly able to produce hepatomas in ducklings and rats.
Albuginea--	A tough, whitish layer of fibrous tissue investing a part; especially a dense, white membrane forming the immediate covering of the testicle.
Androgen--	A male sex hormone.
Angiosarcoma--	A malignant tumor formed by proliferation of endothelial and fibroblastic tissue.
Antimetabolite--	A substance that replaces or inhibits the utilization of a metabolite.
Autistic tumor--	A tumor sufficient unto itself.
Aspermia--	Failure of formation or emission of semen.
Azoospermia--	Lack of spermatozoa in the semen.
Benzene--	A colorless, liquid, flammable aromatic hydrocarbon used to manufacture styrene and phenol.
Bioassay--	Determining the active power of a drug sample by comparing its effect on a live animal or on an isolated organ preparation with the effect of a standard preparation.
Bromine (Br)--	A reddish-brown liquid element giving off suffocating vapors.

Butadiene-- A flammable gaseous hydrocarbon used in making synthetic rubber.

Calipers-- Compasses with bent or curved legs used for measuring the thickness or diameter of a solid.

Carbowax-- Trademark for a series of polyethelene glycols; used in compounding water-soluble ointment vehicles.

Carcinogen-- A substance or agent producing or inciting cancer.

Carcinoma-- A malignant tumor of epithelial origin.

Chromatography-- A process of separating a solution of closely related compounds by allowing the solution to seep through an absorbent so that each compound becomes absorbed in a separate, often-colored layer.

Colchicine-- An alkaloid; used as a suppressant for gout.

Creatinine-- A basic substance procurable from creatinine and from urine.

Cytology-- The study of cells--their origin, structure, function, and pathology.

Decapeptide-- A peptide containing 10 amino acids.

Dysfunction-- Impaired or abnormal functioning.

Endocrine-- Secreting internally; applied to organs and structures whose function is to secrete into the blood or lymph a substance (hormone) that has a specific effect on another organ or part.

Epidemiology-- The study of the relationships of the various factors determining the frequency and distribution of diseases in a human community.

Epididymis-- The elongated cordlike structure along the posterior border of the testis, in the ducts of which the spermatozoa are stored.

Epididymitis-- Imflammation of the epididymis.

Epithelium-- The covering of internal and external surfaces of the body, including the lining vessels and other small cavities.

Estradiol-- The most potent, naturally occurring estrogen in humans; also made synthetically.

Estrogen-- Sex hormones stimulating the development of secondary sex characteristics of the female.

Ethylene bromide-- Used in medicine as a solvent for oils, waxes, and other products.

Exogenous-- Growing by additions to the outside; developed or originating outside the organism.

FSH-- Follicle-stimulating hormone; it activates sperm-forming cells.

Germinal epithelium-- A layer of epithelial cells between the primitive mesentery and each mesonephros. It becomes epithelial covering of the gonad and perhaps gives rise to the germ cells.

Gonad-- A gamete-producing gland; an ovary or testis.

Gonadotrophic-- Stimulating the gonads; applied to hormones of the anterior pituitary that influences the gonads.

Gonadotropin-- A substance having affinity for or a stiumalting effect on the gonads.

Gynecomastia-- Excessive development of the male mammary glands, even to the functional state.

Halogen-- An element of a closely related chemical family, all of which form similar (saltlike) compounds in combination with sodium and most other metals. The halogens are bromine, chlorine, florine, and iodine.

Hematopoiesis-- The formation of blood or of blood cells in the living body.

Hepatitis-- Inflammation of the liver.

Hepatomas-- A tumor of the liver; Sabourin's term for a transition stage between adenoma and carcinoma of the liver.

Hexane-- Any of several isomeric volatile liquid paraffin hydrocarbons found in petroleum.

Histidine-- An alpha-amino acid, beta 4-imidazolyl alanine, essential for optimal growth in infants.

Histology-- A branch of anatomy that deals with the minute structures of animal and plant tissues as discernible with the microscope.

Hormone-- A product of living cells that circulates in body fluids or sap; produces a specific effect on the activity of cells remote from its point of origin.

Hypertrophy-- Excessive development of an organ or part; increase in bulk without multiplication of parts.

Hypothalamus-- The portion of the diencephalon (the posterior division of the forebrain) lying beneath the thalamus and forming the floor of the third ventricle; it is usually considered to include vital autonomic regulatory centers.

Infertility-- Absence of the ability to conceive or to induce conception.

Inhibin-- A postulated water-soluble hormone secreted by the testicles that is supposed to restrain the stimulating effect of the pituitary on the tubules of the testes.

Interstitial-- Pertaining to or situated between parts or in the interspaces of a tissue.

In vitro-- Observable in a test tube; within a glass; in an artificial environment.

In vivo-- Within a living body.

Klinefelter's syndrome-- A condition characterized by the presence of small testes, with fibrosis and hyalinization of seminiferous tubules, impairment of function, and clumping of Leydig cells, and by increase in urinary gonadotropins; associated with an abnormality of the sex chromosomes.

Latency-- A state of seeming inactivity, as that occurring between the instant of stimulation and the beginning of response.

Lesion-- An abnormal change in structure of an organ or part due to injury or disease.

Leydig cells-- The interstitial cells of the testes that furnish the internal secretion of the testicle; mucous cells that do not pour their secretion out over the surface of the epithelium.

Lumen-- The cavity or channel within a tube or tubular organ.

LH-- Luteinizing hormone; in the female, it stimulates the development of corpora lutea and in the male, the development of interstitial tissue.

Malathion-- A thiophosphate insecticide less toxic than parathion.

Malignant-- Tending to become progressively worse and to result in death.

Meiosis-- A special method of cell division, occurring during maturation of the sex cells, by which each daughter nucleus receives half the number of chromosomes characteristic of the somatic cells of the species.

Metabolite-- A substance essential to the metabolism of a particular organism.

Metastasis-- The transfer of disease from one organ or part to another not directly connected with it. The capacity to metastasize is a characteristic of all malignant tumors.

Miotic-- An agent that causes the pupil to contract.

Mirex-- A chlorinated hydrocarbon insecticide used especially against ants.

Morphology-- The science of forms and structure of organized beings.

Motility-- The ability to move spontaneously.

Mutagen-- A chemical or physical agent that induces genetic mutations.

Nanogram-- One billionth of a gram.

Nematocide-- An agent that destructs nematode worms.

Nitrofurantoin-- Lemon-yellow, odorless crystals or powder with a bitter aftertaste; used as an antibacterial agent in infections of the urinary tract.

Oligospermia-- Deficiency in the number of spermatozoa in the semen.

Orchidometer-- An instrument for measuring the testis.

Palpate-- To examin by the hand; to feel.

Parathion-- An extremely toxic thiophosphate insecticide.

Peptide-- Any member of a class of compounds of low molecular weight that yields two or more amino acids on hydrolysis.

Picogram-- One trillionth of a gram.

Pituitary gland-- A small, oval endocrine organ that produces various internal secretions directly or indirectly impinging on most basic body functions.

Prolactin-- A protein hormone of the anterior lobe of the pituitary that induces lactation in mammals.

Prostatitis-- Inflammation of the prostate.

Prosthesis-- An artificial substitute for a missing body part.

Radio-immunoassy-- Determination of antigen or antibody concentration by means of a radioactive-labelled substance that reacts with the substance under test.

Seminal fluid-- The part of the semen that is produced by various accessory glands; semen, excepting the spermatozoa.

Seminal vesicle-- A pouch on either side of the male reproductive tract that serves for temporary storage of semen.

Seminiferous tubules-- Channels in the testis in which the spermatozoa develop and through which they leave the gland.

Sertoli cells-- Elongated cells in the tubules of the testes to which the spermatids become attached; they provide support, protection, and apparently, nutrition until the spermatids become transformed into mature spermatozoa.

Silastic-- Trademark for polymeric silicone substances having the properties of rubber; it is biologically inert and used in surgical prostheses.

Sonometer-- An apparatus for testing acuteness of hearing; an instrument for measuring ratios of sound vibrations in various bodies.

Spermatid-- A cell derived from a secondary spermatocyte by fission, and developing into a spermatazoon.

Spermatogenesis-- The process of formation of spermatozoa.

Spermatogonium-- A primitive male germ cell.

Spermatozoon-- A mature male germ cell, the specific output of the testes. It is the generative element of the semen that serves to impregnate the ovum.

Sterility-- The state of being free from microorganisms; the inability to produce offspring, i.e, the inability to conceive or to induce conception.

Styrene-- A fragrant liquid or oil hydrocarbon, vinyl benzene, from storax.

Testosterone-- The hormone produced by the interstitial cells of the testes, which functions in the induction and maintenance of male secondary sex characters. Its production depends on stimulation by LH of the anterior pituitary gland.

Titer-- The quantity of a substance required to produce a reaction with a given volume of another substance, or the amount of one substance required to correspond with a given amount of another substance.

Toluene-- A liquid, aromatic hydrocarbon resembling but less volatile, flammable, and toxic than benzene; used for a solvent, in organic synthesis, and as an antiknock agent for gasoline.

Torsion-- The act of twisting; the condition of being twisted.

Toxaphene-- A chlorinated camphene insecticide.

Toxicity-- The quality of being poisonous, especially the degree of virulence of a toxic microbe or of a poison.

Tubular fibrosis-- A formation of fibrous tissue in tube-like shapes.

Tunica-- A general term for a membrane or other structure covering or lining a body part or organ.

Turgor-- The condition of being turgid (swollen and congested); normal or other fullness.

Urethra-- The membranous canal conveying urine from the bladder to the exterior of the body.

Varicoceles-- A varicose condition of the veins of the pampiniform plexus; forms a swelling that feels like a "bag of worms" and appears bluish through the skin of the scrotum.

Vasectomy-- Surgical removal of the ductus vas deferens, or a portion of it; done to induce infertility.

Vesicocele-- Hernial protrusion of the bladder.

APPENDIX E

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