GENETIC EFFECTS ASSOCIATED WITH INDUSTRIAL CHEMICALS

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Each generation makes its own accounting to its children.
-- Robert F. Kennedy

In the past several decades, there has been an explosive proliferation of man-made chemicals in the environment and in the workplace. It is a subject of increasing concern that with few exceptions these chemicals have not been evaluated for their potential danger to this or future generations, either as carcinogens, mutagens or teratogens. At this Conference on Women and the Workplace, it seems only appropriate to review this spectrum of biological activity for select man-made industrial chemicals which have undergone evaluation and what the response of society to these findings has been.

In 1971, the toxicity of vinyl chloride (VC) broadened to include carcinogenesis (1). Inhalation studies by Maltoni and Lefemine demonstrated that VC induced adenomas and adenocarcinomas of the lung, lymphoma, neuroblastoma of the brain and angiosarcoma of the liver (2). Subsequent epidemiologic investigations of workers exposed to VC demonstrated an excessive number of deaths due to cancer of those same four organ systems: brain, liver, lung and lymphatic system (3). This observation of the carcinogenicity of VC, first in animals and subsequently in humans, had a profound positive effect on public health: first, in terms of the recognition of the need for rapid regulatory control of VC in the industrial setting; and second, in terms of an increased confidence and awareness of the value of animal bioassay.

VC also was demonstrated to induce tumors in the offspring of exposed pregnant rats (2). In addition, children born in communities contiguous to VC polymerization facilities were demonstrated to have an increased risk of birth defects, which included defects of the central nervous system (4). These two observations led many to propose that women of reproductive age should be excluded from employment in VC monomer production facilities or VC polymerization facilities, a "public health" approach in lieu of total containment of VC in the occupational setting (5). This public health response to the toxicity of VC is cause for serious reflection. From a scientific viewpoint, the toxicity of VC on subsequent generations must be assessed not only through exposure of the female (transplacental carcinogenesis, maternal toxicity and teratogenesis) but also through occupational exposure of the male (mutagenesis).

What evidence exists for the mutagenicity of VC? Several reports have indicated that VC is mutagenic in microbial test systems (E. coli, S. typhimurium, and S. pombe) (6-12), in insects (Drosophila) (13,14), in plants (Tradescantia) (15). VC metabolites also have induced mutations in mammalian cells (16). Likewise reports from four countries have shown an excess of chromosomal aberrations in lymphocytes of male workers exposed to VC as compared with controls not so exposed (17-20). Further evidence for the mutagenicity of VC has been provided by recent NIOSH investigations of fetal mortality among wives of male workers occupationally exposed to VC (21). Among pregnancies occurring prior to exposure, fetal death rates were 6.9% for the controls versus 6.1% after age adjustment for the primary VC exposure group, a difference not statistically significant (Table 1). Among pregnancies occurring subsequent to the husband's exposure, however, the difference in the fetal death rates between the study and the control group was significant, $p<0.05$. Whereas, the difference in fetal death between the controls prior to and subsequent to employment, 6.9% versus 8.8%, was not statistically significant, the difference in age-adjusted fetal death rate among pregnancies for the primary VC group for prior to exposure and subsequent to the husband's exposure was statistically significant at $p<0.02$. Additional analyses restricted to the pregnancies of women who had less than two, less than three and less than four fetal deaths, respectively, did not alter the findings of an association between male exposure to VC and an increased risk of fetal death (Table 2) (22). Unequivocal evidence for the mutagenicity of VC would be the finding of increased congenital anomalies among children born of males occupationally exposed to VC. Studies of abortions, however, have shown that most chromosomally abnormal embryos miscarry (23), thus making such unequivocal evidence for the mutagenicity of VC highly unlikely using the epidemiologic method. The finding of increased fetal mortality associated with occupational exposure of the male worker to VC, when taken in conjunction with the mutagenic response via microbial test systems, insects and plants and the observations of a significant increased risk of chromosomal aberrations among male workers exposed to VC point to germ cell damage in the father through direct VC exposure as the leading mechanism for these human observations. This spectrum of evidence for the mutagenicity of VC demonstrates that the only prudent public health approach to VC is through control of exposure at the source and not through the exclusion of women in the workplace.

Because of the carcinogenicity and mutagenicity of VC, a close look at other structurally similar chlorinated hydrocarbons seems in order. Two structural analogues of VC are vinylidene chloride

(VDC) and trichloroethylene (TCE), (Figure 1).

VDC, a chemical widely used in the manufacture of plastics, has recently been reported to be carcinogenic in the rat (24). In addition to this reported oncogenic response, VDC also has been shown to induce mutations in several microbial test systems (6,11, 25,26) and in a plant assay system (15) (Table 3). To date, evidence in humans is lacking to negate this mutagenic property of VDC.

TCE, a higher order structural analogue of VC, has been used for many years as an anesthetic (27,28). It also is widely used as a degreasing agent for metals and as an extractant in the foodstuff industry (29,30). Like VC, TCE has been demonstrated to induce hepatocellular carcinoma in mice (31). As was the case for VC and VDC, TCE also has been shown to be mutagenic in microbial assays (6,25,32) as well as plant assay (15) (Table 4). No studies of genetic risks among humans, however, have yet been undertaken for TCE.

Another chemically-related compound, 2-chlorobutadiene (chloroprene) is used extensively in the chemical industry, being the starting material for the synthetic rubber, polychloroprene. As early as 1936, Von Oettingen et al. (33) demonstrated damage in the reproductive organs of male mice and rats following skin application and inhalation of chloroprene. Even in low concentrations, 0.434 mg/1 (120ppm) in rats and 0.042 mg/1 (11.6ppm) in mice, chloroprene by inhalation affected the male reproductive organs, inducing degenerative changes and causing sterility in up to 60 to 70 percent of exposed animals (Table 5). Investigations by Davtyan et al. (34) in 1973 demonstrated that whereas inhalation of chloroprene by male rats at a concentration of 0.0038 mg/1 (1.0ppm) did not affect fertilization capacity, it did nevertheless significantly increase embryonic mortality. They reported this same low concentration of chloroprene to induce chromosomal aberrations in bone marrow cells of mice.

A similar pattern of genetic effects in humans has been demonstrated following occupational exposure to chloroprene. Sanotsky reported that Fomenko and colleagues found functional disruption of spermatogenesis among males occupationally exposed to chloroprene for less than or equal to ten years and morphological disruption of spermatogenesis among men having greater than ten years of exposure to chloroprene (35). Sanotsky (35) in a survey of 143 workers exposed to chloroprene and 118 employees of an electromachine construction plant (controls) also found a threefold excess of cases of miscarriage among wives of workers occupationally exposed to chloroprene.

An excess of chromosomal aberrations in lymphocytes of male workers exposed to chloroprene has been reported (36,37). The spectrum of evidence for the mutagenicity of chloroprene and for VC shows a marked similarity, from microbial assay through animal assay to human observations (Table 6).

We must ask ourselves, what will be the response of Society to mutagens in the workplace:

> Will Society require the enumeration of fetal deaths and/or congenital anomalies in humans before regulatory control is implemented?
>
> Will Society now exclude the male worker from the industrial setting of chloroprene and vinyl chloride as previously proposed for women following the findings of transplacental carcinogenesis in animals exposed to vinyl chloride?
>
> Or will the legacy of Society to future generations be the rapid reduction of human exposure to mutagens at their industrial source?

The questions are now before us. What will be the accounting of this generation to its children?

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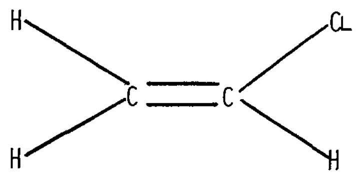
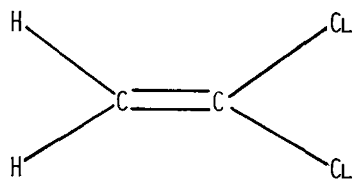
FIGURE 1

VINYL CHLORIDE
(VC)



VINYLIDENE CHLORIDE
(VDC)



TRICHLOROETHYLENE
(TCE)

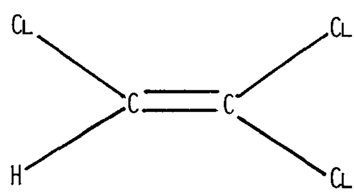


Figure Legend: Chemical Structure of three chlorinated ethylenes

TABLE 1

MEAN PATERNAL AGE, NUMBER OF PREGNANCIES AND FETAL DEATH RATES ACCORDING TO HUSBAND'S VC EXPOSURE

	CONTROLS	PRIMARY VC EXPOSURE
PRIOR TO HUSBAND'S EXPOSURE		
Number of Families	95	70
Mean Paternal Age at Conception (Years)	23.0	26.4
Number of Fetal Deaths Among Wives	11	15
Number of Pregnancies	159	148
Age-Adjusted Fetal Deaths/100 Preg.	6.9	6.1
SUBSEQUENT TO HUSBAND'S EXPOSURE		
Number of Families	113	62
Mean Paternal Age at Conception (Years)	30.4	30.2
Number of Fetal Deaths Among Wives	24	23
Number of Pregnancies	273	139
Age-Adjusted Fetal Deaths/100 Preg.	8.8	15.8*

SOURCE: Reference 21.

TABLE 2

NUMBER OF PREGNANCIES AND AGE-ADJUSTED FETAL DEATH RATES ACCORDING TO HUSBAND'S VC EXPOSURE EXCLUDING PREGNANCIES IN WOMEN WITH ≥2, 3 OR 4 FETAL DEATHS

	Controls		Primary VC Exposure	
	Number of Pregnancies	Fetal Death Rate	Number of Pregnancies	Fetal Death Rate
	≥2 Fetal Deaths Excluded			
Before Husband's Exposure	155	5.8%	126	1.7%
After Husband's Exposure	255	4.7%	111	6.2%
	≥3 Fetal Deaths Excluded			
Before Husband's Exposure	159	6.9%	141	3.1%
After Husband's Exposure	265	6.8%	120	10.8%
	≥4 Fetal Deaths Excluded			
Before Husband's Exposure	159	6.9%	142	5.8%
After Husband's Exposure	265	6.8%	127	11.8%

Rates for the primary VC exposure group are age-adjusted to the Control group.

Source: Reference 22.

TABLE 3

MUTAGENICITY TESTING FOR VINYLIDENE CHLORIDE (VDC)

TEST SYSTEM	RESULTS	REFERENCE-AUTHOR(YEAR)
I. Microbial System		
A. Salmonella Typhimurium	+ + +	McCann, et al. (1975) (11), Bartsch, et al. (1975) (25), Baden, et al. (1976)(26)
B. E. Coli	+	Greim, et al. (1975) (6)
II. Plant System		
A. Tradescantia	+	Sparrow (1976)(15)

TABLE 4

MUTAGENICITY TESTING FOR TRICHLOROETHYLENE (TCE)

TEST SYSTEM	RESULTS	REFERENCE-AUTHOR(YEAR)
I. Microbial System		
A. Salmonella Typhimurium	+ (?) +	Baden, et al. (1976) (26), Ramel (1975)(32)
B. E. Coli	+	Greim, et al. (1975) (6)
II. Plant System		
A. Tradescantia	+	Sparrow (1976)(15)

TABLE 5

EFFECT OF INHALATION OF CHLOROPRENE ON THE REPRODUCTION OF MALE MICE AND RATS

SPECIES	NUMBER OF ANIMALS	PREGNANCIES	FERTILITY RATE (%)
Mice 0.042 - 0.548 mg/l (11.6 - 151.4 ppm)	14	6	43
Controls	5	5	100
Rats 0.434 - 22/419 mg/l (120 - 6190 ppm)	19	6	32
Controls	5	5	100

From: Reference 33

TABLE 6

EVIDENCE FOR MUTAGENIC OR REPRODUCTIVE EFFECTS OF VINYL CHLORIDE AND CHLOROPRENE

TEST SYSTEM	AGENT: VINYL CHLORIDE	AGENT: CHLOROPRENE
<u>LABORATORY</u>		
Microbial (E. Coli, S. Typhimurium, S. Pombe)	+ (6-12)	+ (25)
Insect (Drosophila)	+ (13,14)	+ (38)
Plants (Tradescantia)	+ (15)	?
Mammals		
Metabolites in hamster cells	+ (16)	?
Chromosomal aberrations in male rats	?	+ (34)
Reproduction interference following exposure to male mice or rats	– (19)	+ (33,34)
<u>HUMANS</u>		
Chromosomal aberrations in male workers	+ (17-20)	+ (36,37)
Excess miscarriage in wives of male workers	+ (21,22)	+ (35)
Decrease in motility and number of sperm in workers	?	+ (35)

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