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Reproductive Toxicology of Disinfection By-Products

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The chronic exposure of large segments of the population to disinfected drinking water has necessitated an evaluation of the health effects of the by-products of the chlorination process. This paper reviews the available information concerning the reproductive consequences associated with exposure to disinfection by-products. Four groups of compounds are discussed: the trihalomethanes, in particular chloroform; the chlorinated phenols; chlorinated humic substances; and the haloacetonitriles. In the pregnant female, chloroform and the 2- and 2,4-chlorophenols produced low levels of embryo- and fetotoxicity. Chloroform induced terata when administered by inhalation. The chlorinated humic substances and 2,4,6-trichlorophenol were without significant reproductive effects. The haloacetonitriles showed *in utero* toxicity, becoming more severe with increasing halogen substitution.

Introduction

The chlorinated organic compounds formed during water disinfection are largely the result of the interaction of chlorine with humic substances. Humic substances form in natural waters from the slow decomposition of lignins and other phenolic plant constituents. Combined with the metabolites from bacterial degradation of carbohydrates and proteins, they comprise a complex substrate for the action of chlorine that does not readily yield to precise characterization. Some of the major classes of compounds generated from humics during the disinfection process, for example, the trihalomethanes (*1,2*) and chlorophenols (*3*), have, for some time, been an established focus of concern in drinking water health studies. More recently, attention has centered on the mutagenic activity associated with water chlorination (*4–6*). The chemicals responsible for this activity have been difficult to identify because they are present in a complex mixture and in minute quantities. However, their analysis has been facilitated by the demonstration that a commercially derived humic substance produces, when chlorinated, a range of halogenated and mutagenic compounds comparable to those derived from natural sources (*7,8*). Attempts have been made to associate mutagenic activity with specific compounds (*9,10*) so that the components of genotoxic, and thus potentially carcinogenic and reproductive, hazards present in drinking water can be quantified. This paper reviews the information available concerning the reproductive hazard from disinfection by-products. For most of the by-products identified, no such data have been found in the existing literature. Some studies have been made, however, of the chlorinated humics, the haloacetonitriles, the trihalomethanes (in particular chloroform), and the chlorinated phenols.

Humic Substances

Natural aquatic humic substances, a recognized integral component of surface waters, are not readily available in sufficient mass for use in animal toxicity studies. The need to investigate the potential reproductive hazard associated with chlorination of these substances arises from their known genotoxic properties (*4–6*), and form the enormous exposed population associated with potable water supplies. The validation of model humic compounds as a substitute for naturally concentrated material has made laboratory studies feasible.

Michael et al. (*11*) studied the developmental effects of chlorinated humics using an *in vivo* teratology screen (*12*) adapted for application to the rat. Solutions of commercially obtained humic substances (Fluka) were prepared, chlorinated in the laboratory (chlorine to carbon ratio 1:1), and subsequently provided to pregnant rats as their sole source of drinking water. The study was performed in two phases. In the prenatal phase, groups of 24 pregnant rats received either a blank control, unchlorinated humic-rich water, or chlorinated humic-rich

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water from day 1 of gestation until birth. The concentration of humic material was 0.8 g/L, and the pH was about 3.5. In the second phase of the study, the dams continued to drink humic-rich material after parturition, and their pups received the same substances by oral intubation at a dose of 0.01 mL/g body weight from postpartum day 6 to day 21. Thereafter, the pups drank humic-rich waters until sacrifice at day 41. For the second phase, the humic materials were prepared at 1.0 g/L and neutral pH.

Neither the prenatal nor the combined pre- and postnatal exposures resulted in statistically significant changes in any of the parameters measured, namely, pup number and weight. However, beginning at weaning, postnatal growth retardation was seen in the group receiving chlorinated humics. Although not statistically significant, this delay did not result from water deprivation caused by taste aversion, since fluid consumption was unchanged across all groups. Therefore, a low level of developmental toxicity may be associated with the chlorinated humic material. At the concentrations used, no other reproductive effects appeared evident; the consequences of using higher doses, however, are uncertain.

Haloacetonitriles

The haloacetonitriles have been identified as a class of compounds present in chlorinated natural waters and generated during the disinfection of model humic substances. They have been shown to be both genotoxic and carcinogenic (*13,14*), but few studies have been made to determine their potential for reproductive toxicity. George et al. (*15*) examined the haloacetonitriles for developmental toxicity in Long-Evans rats and compared the effects of these compounds to those of acetonitrile. They used the *in vivo* teratology screen (*12*), exposing pregnant rats to a single maximum tolerated dose between days 7 and 21 of gestation and monitoring reproductive success in the dam and growth and viability in the pups.

Table 1 describes the compounds and doses used in this study and the effects on weight gain and pregnancy in the female rats. The doses used were established as the maximum tolerated levels in separate studies using nonpregnant animals. A vehicle control group (Tricaprylin-Sigma) was treated concurrently for each compound. The agents examined were acetonitrile (AN), chloroacetonitrile (CAN), dichloroacetonitrile (DCAN), trichloroacetonitrile (TCAN), bromochloroacetonitrile (BCAN), and dibromoacetonitrile (DBAN).

The figures presented for the control groups are the average outcomes for 10 vehicle control groups, each containing at least 20 animals. For statistical analysis, controls could not be pooled, in part because the studies were performed in three different laboratories. Each group was compared to its own control; individual control figures are not presented.

With the exception of BCAN, all the haloacetonitriles when administered during gestation induced maternal toxicity as evidenced by a reduction in maternal weight gain. Acetonitrile resulted in maternal toxicity only at the higher doses used (300, 500 mg/kg).

The denominator used for calculating the percentage of females delivering viable litters included in its total both maternal deaths during treatment (intubation errors excepted) and those females in which the litters were discovered, when sacrificed, to be resorbed. Females suspected never to have conceived were omitted. AN, DCAN, and TCAN all produced reductions in the number of viable litters delivered. However, no highly predictable relationship was observed between such reductions and the accompanying level of maternal toxicity.

The effects of the haloacetonitriles on litter size, weight, and viability are shown in Table 2. Gestational administration of acetonitrile, even at doses causing substantial maternal lethality, did not result in reduced pup birth weight, weight gain, or viability compared to

Table 1. Effects of acetonitrile and haloacetonitriles on female reproduction.

Compound	Dose, mg/kg	Dose, mmole/kg	No. of dams treated	Maternal weight gain (day 7-21 of gestation), %	Dams delivering viable litters, %
Vehicle control[a]	—		>200	35.8	98
Acetonitrile (AN)	50	1.2	20	31.6	85.7
	150	3.6	22	37	100
	300	7.2	20	37	47.6[b]
	500	12.2	20	6.1*	12.5[c]
Chloroacetonitrile (CAN)	55	0.72	21	26.6*	100
Dichloroacetonitrile (DCAN)	55	0.5	20	18.9*	71.4
			20	6.6*	81.8
Trichloracetonitrile (TCAN)	55	0.38	20	1.6*	62.5
			20	14.1*	90.9
Bromochloroacetonitrile (BCAN)	55	0.36	20	31.1	100
Dibromoacetonitrile (DBAN)	50	0.25	26	25.7*	83.3

[a]Controls for individual experiments have been averaged. However, for statistical evaluation each experiment was analyzed with its own concurrent control.

[b]11 females were moribund and were sacrificed at day 15 of gestation.

[c]n = 3. 16 females died from treatment-related toxicity.

*$p \leq 0.05$ using Duncan's new multiple range analysis, or two-tailed Student's t-test.

Table 2. Perinatal effects of acetonitrile and haloacetonitriles.

Compound	Mean no. of live pups/litter, day 1	Postnatal survival, day 4 %	Mean birth weight, g		Weight gain, day 4, %	
			Male	Female	Male	Female
Vehicle[a] control	11.5	96.5	6.35	5.99	41.4	40.7
AN (50)	10.7	99.5	6.13	5.81	42.2	40.6
(150)	11.9	97.2	6.67	6.25	35.1	39.3
(300)	12.8	92.2	6.21	5.87	31.2	35.1
(500)	12.0	91.7	5.66	5.25	48.0	57.1*
CAN	11.9	98.7	5.86*	5.51	49.8	51.2
DCAN	11.7	69.4*	4.94*	4.74*	19.5*	26.5*
	9.4	93.0	5.22*	4.82*	50.4	52.1
TCAN	9.0	76.7*	4.84*	4.62*	47.0	48.6
	10.8	69.0*	4.89*	4.86	52.0	42.0
BCAN	11.4	94.2	5.7*	5.4*	31.9*	31.5*
DBAN	11.9	95.3	5.8*	5.59*	30.7*	32.7

[a] Controls for individual experiments have been averaged. However, for statistical evaluation each experiment was analyzed with its own concurrent control.

*$p \leq 0.05$ using Duncan's new multiple range analysis.

the concurrent controls. The haloacetonitriles by contrast caused reductions in birth weight and, in some instances, reduced weight gain over the first 4 days of postnatal life. DCAN and TCAN were each tested twice. Although the outcomes from the two experiments for each were not fully consistent, there was clear indication that both compounds caused an increase in neonatal mortality. The premise of this screen is that in cases of reduced viability, structural anomalies that are not visible by cursory inspection of the newborn may exist, and therefore closer investigation of the compound would be merited.

In comparing effects among the haloacetonitriles, and to the parent compound acetonitrile, it appears that increasing halide substitution at the α-carbon is reflected in increased *in utero* toxicity. The metabolism of the haloacetonitriles has not been documented, and the moiety responsible for the *in utero* toxicity is currently unknown. Other aliphatic nitriles have, however, been examined for teratogenic potential. Acetonitrile, acrylonitrile, propionitrile, and succinonitrile have each been administered to pregnant hamsters (*16–18*). In all these studies, malformations (principally neural tube defects) were noted in the offspring. For each compound, concurrent administration of thiosulfate with the nitrile protected against malformation, suggesting that the teratogenic effect could be attributed to cyanide release. Doherty et al. (*19*) showed further that infusion of sodium cyanide in the pregnant hamster produced a range of fetal anomalies similar to those observed with nitriles, which could be prevented by cyanide antagonists. Few developmental studies of cyanogenic compounds in the rat have been made. Murray et al. (*20*) examined the teratogenic effects of acrylonitrile in the rat and showed that at 65 mg/kg/day, this compound induced terata predominantly comprising missing vertebrae; no antagonists were administered.

Pereira et al. (*21*) used urinary thiocyanate excretion as a measure of the metabolism of haloacetonitriles to cyanide in the rat. They found that increasing chlorine substitution in the administered haloacetonitrile corresponded to a concomitant reduction in thiocyanate in the rat urine. In the present study (*15*), TCAN and DCAN appeared to produce greater *in utero* toxicity than CAN or AN, in spite of the fact that they were administered at a much lower millimolar per kilogram dose. These observations together suggest that cyanide release was not responsible for the developmental toxicity observed. Rather, as suggested by Pereira et al. (*21*) the haloacetonitriles may be subject to different metabolic pathways, and thus the proximate metabolite with transplacental toxicity may be different for each.

Trihalomethanes

Of the trihalomethanes commonly identified in North American drinking waters, only chloroform (trichloromethane) has been extensively examined for its effects on development. Bromoform, bromodichloromethane, and chlorodibromomethane were investigated for developmental toxicity in the rat (*22*). None of these chemicals produced any teratogenic effects. Considering the fact that chloroform was the major agent in use for anesthesia until World War II, remarkably few comprehensive studies of its reproductive effects are available, and of those made, the results are equivocal. Since chloroform contaminates public drinking water at levels up to 300 μg/liter, chronic exposure may be unavoidable, and thus its reproductive effects are of substantial interest.

Table 3 summarizes the published information for teratogenicity studies of chloroform in rat, mouse, and rabit, both by oral and inhalation exposure. The treatment levels used were up to 300 ppm, 7 hr/day for inhalation and up to 400 mg/kg orally. At the highest doses, which produced adverse clinical effects in the females, both oral and inhalation studies showed some evidence of embryotoxic or fetotoxic effects, taking the form of reduced fetal size and weight, and retarded skeletal ossification.

Those studies, conducted using inhalation as the route of administration, suggest teratogenic effects from chloroform. Schwetz et al. (*23*) found that exposure of the pregnant rat to 100 ppm chloroform on days 6–15 of

Table 3. Chloroform: developmental studies.

Species	Dose	Gestational days administered	Route of administration	Result	Reference
Rat	30, 100, 300 ppm	6-15 7 hr/day	Inhalation	Embryotoxic Fetotoxic Teratogenic	(23)
Rat	20, 50, 126 mg/kg/day	6-15	Oral	Fetotoxic	(25)
Rat	100, 200, 400 mg/kg	6-15	Oral	Fetotoxic	(22)
Mouse	100 ppm	1–7 6–15 8–15 7 hr/day	Inhalation	Embryotoxic Fetotoxic Teratogenic	(24)
Rabbit	20, 35, 50 mg/kg/day	6-18	Oral	Fetotoxic	(25)

gestation resulted in a significant number of litters containing pups (number unspecified) with missing or shortened tail and imperforate anus. At 300 ppm, the number of litters available for analysis was severely reduced because of a decrease in the rate of conception and a high incidence of fetal resorption. Terata were not, however, observed in this group, a finding consistent with the low level of embryonic survival, since early embryonic death may mask malformation.

Murray et al. (*24*), using the mouse, also found teratogenic effects from chloroform at an inhaled dose of 100 ppm. Exposure from day 8 to day 15 of gestation resulted in a significant elevation in the incidence of cleft palate. Exposure from day 1 to day 7 or day 6 to day 15 caused reduced litter size but no malformations, suggesting, again, the possibility that lethality to the early embryo obscured other effects. In this study, however, the cleft palates were seen predominantly in fetuses with retarded growth, raising the question that chloroform might have induced an indirect, rather than a direct, teratogenic event.

Thompson et al. (*25*) and Ruddick et al. (*22*) noted no teratogenic effects of orally ingested chloroform in either the rat or the rabbit, although considerable maternal anorexia and reduced weight gain occurred at the high doses. The differences in outcome between the oral and inhalation studies may be attributed to disparity in the amount and persistence of blood chloroform levels resulting from the different routes of exposure. In the absence of a clear dose response for malformations in the inhalation studies, it may be premature to label inhaled chloroform teratogenic to the rodent. There is evidence, however, that the compound is embryo- and fetotoxic, interferes with early implantation, and may cause low levels of anomalies in the fetus.

No multiple generation studies on the effects of chloroform on other reproductive parameters have been reported. Land and co-workers (*26*) exposed mice to inhaled chloroform (400 and 800 ppm) for 4 hr/day over 5 days and found a dose-related increase in abnormal sperm forms 4 weeks later, suggesting the potential for reproductive hazard to the male.

Chlorinated Phenols

Halogenation of endogenous phenols resulting from disinfection occurs at the *ortho* and *para* positions in a stepwise manner, beginning at the 2, 4, and 6 positions, respectively. The most frequently detected chlorophenols formed in this manner are 2-chlorophenol (2-CP), 2,4-dichlorophenol (2,4-DCP), and 2,4,6-trichlorophenol (2,4,6-TCP). Each of these compounds has been the subject of a reproductive study.

Exon and Koller (*27*) examined 2-CP for reproductive toxicity to the female rat. They administered 5, 50, and 500 ppm of 2-CP to rats in their drinking water for 10 weeks before breeding and then throughout gestation. They reported that at 500 ppm, 2-CP caused a decrease in litter size and a small increase in the number of stillborn pups. Their data were unusual, however, in that they recorded an average pup birth weight of about 2.5 g in both control and treated groups. This surprisingly low figure (average rat pup birth weight is approximately 6–7 g) suggests additional complications in the study and raises some questions about the conclusions drawn.

Exon et al. (*28*) have also studied the prenatal toxicity of 2,4-DCP in the female rat at doses of 3, 30, and 300 ppm in the drinking water using a similar protocol. No significant reproductive effects were reported. However, litter size was decreased at the highest dose (controls = 9.8 ± 1.3; 300 ppm = 6.3 ± 1.6), a change that was recorded as not statistically significant. Such a decrease may well have been a biologically significant change since it occurred in the presence of normal birth weight and in the absence of maternal toxicity. The small size of the experimental sample (N = 8 per group) could have precluded satisfactory statistical evaluation.

Blackburn and co-workers (*29*) examined 2,4,6-trichlorophenol (2,4,6-TCP) for reproductive toxicity in the rat. 2,4,6-TCP was administered by intubation in corn oil at doses of 100, 500, and 1000 mg/kg. Males were treated for 11 weeks. Their baseline copulatory behavior and ejaculated semen profiles (sperm concentration, shape, motility) were evaluated before the beginning of treatment and again at week 10 of the treat-

ment period (*30*). After 11 weeks of treatment with 2,4,6-TCP, the males were mated to untreated females for fertility testing and to examine the potential for dominant lethal effects. They were then sacrificed and blood and cauda epididymal sperm collected. One-third of the males in the 1000 mg/kg group died as a result of treatment, suggesting that the high dose was at or above the maximum tolerated dose. No treatment-related differences were seen in any of the behavioral or semen parameters measured. No differences were apparent in organ weights, hormone levels, or caudal sperm counts, and fertility and fetal outcomes were similar across all treatment groups.

A companion study (*29*) of the effects of 2,4,6-TCP on the female reproductive system was also made. Using the same dose levels (0, 100, 500 and 1000 mg/kg) Blackburn and co-workers began treatment 2 weeks before breeding. Treatment continued through a 10-day breeding period and terminated at day 21 of gestation. The females were allowed to litter, and the pups were maintained until day 42 post partum. Litters were evaluated in terms of size and weight and then followed for growth and simple developmental landmarks.

The females also showed high mortality and other gross signs of toxicity in the 1000-mg/kg dose group (16/40 dead). A statistically significant reduction in weight gain was seen from the first treatment week until day 14 of gestation; however, "catch up" had occurred before parturition. In the 500- and 1000-mg/kg groups, litter weights at birth were significantly reduced. These differences had disappeared by post partum day 4. The postnatal development of the pups was similar in all groups. The authors concluded that at the maximally tolerated dose in this strain, 2,4,6-TCP does not selectively impair either the male or the female reproductive process.

The chlorinated phenols 2-CP and 2,4-DCP may exhibit a low level of fetotoxicity in the rat, although neither compound has been investigated for toxicity to the male reproductive system. Additionally, reproductive effects in the female following exposure to pentachlorophenol (e.g., 31, 32) have been reported by several authors. On the other hand, 2,4,6-TCP is not fetotoxic in the rat, nor does it affect male reproduction. Thus, no clear relationship can be drawn between the toxicity of the chlorinated phenols and the extent of their chlorination.

The research described in this article has been reviewed by the Health Effects Research Laboratory and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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