Intrauterine Growth Retardation in Iowa Communities with Herbicide-contaminated Drinking Water Supplies

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In a statewide survey of 856 Iowa municipal drinking water supplies in 1986–1987 the Rathbun rural water system was found to contain elevated levels of triazine herbicides. Rates of low birth weight, prematurity, and intrauterine growth retardation (IUGR) in live singleton births during the period 1984–1990 by women living in 13 communities served by the Rathbun water system were compared to other communities of similar size in the same Iowa counties. The Rathbun communities had a greater risk of IUGR than southern Iowa communities with other surface sources of drinking water (relative risk = 1.8; 95% CI = 1.3, 2.7). Multiple linear regression analyses revealed that levels of the herbicides atrazine, metolachlor, and cyanazine were each significant predictors of community IUGR rates in southern Iowa after controlling for several potentially confounding factors including maternal smoking and socioeconomic variables. The association with IUGR was strongest for atrazine, but all three herbicides were intercorrelated and the independent contributions of each to IUGR risk could not be determined. We conclude that communities in southern Iowa with drinking water supplies contaminated with herbicides have elevated rates of IUGR compared to neighboring communities with different water supplies. Because of the limitations of the ecologic design of this study, including aggregate rather than individual measures of exposure and limited ability to control for confounding factors related to source of drinking water and risk of IUGR, a strong causal relationship between any specific water contaminant and risk of IUGR cannot yet be inferred. The association between the water supplied to the Rathbun communities and the increased risk of IUGR should be considered a preliminary finding that needs to be verified by more detailed epidemiologic studies. *Key words*: atrazine, cyanazine, epidemiology, herbicide, intrauterine growth retardation, metolachlor, pesticide, reproduction. *Environ Health Perspect* 105:308–314 (1997)

Low birth weight, prematurity, and intrauterine growth retardation (IUGR) are known to be major determinants of health problems during the first year of life (*1–14*). Because birth weight is related to both rate of fetal growth and length of gestation, the construct of IUGR, usually defined as birth weight below the 10^{th} percentile of a reference standard for a given gestational age, has emerged as a useful tool in epidemiologic studies of reproductive health (*10*). IUGR has been associated with poor neonatal health including respiratory distress, apnea, hypocalcemia, bradycardia, transient neurologic signs, sepsis, cerebral palsy, and impaired development lasting into childhood (*1–14*). IUGR remains the second leading known cause of fetal death (*11*).

A large number of risk factors for problems of fetal growth and maturity have been identified (*4,7,13*). These include socioeconomic factors, access to medical care, medical conditions related to pregnancy, and environmental conditions. Smoking, poor nutrition, alcohol and other substance abuse, and certain occupational exposures have been established as important behavioral and environmental risks. The possibility that drinking water contaminants are a cause of spontaneous abortion and IUGR has been raised but remains controversial (*15–17*).

The state of Iowa offers an excellent setting for studies of the source and characteristics of municipal drinking water supplies in relation to low birth weight, prematurity, and IUGR. The population of Iowa includes a large number of small- to medium-sized communities that are supplied with drinking water from single sources. The characteristics of the water consumed by most Iowa residents can be reasonably inferred from the characteristics of the finished drinking water from the treatment plant in each community. This is in contrast to more heavily urbanized areas of the United States, where communities often receive drinking water from different sources, which has been mixed prior to or during distribution.

A study of municipal water supplies in Iowa during the period 1986–1987 found that the Rathbun Regional Water Association (RRWA), a water system that obtains its water from the Rathbun reservoir on the Chariton River and serves communities in 12 counties in southern Iowa, has had persistently elevated levels of herbicide contamination (*18*). The *s*-triazine herbicide atrazine was the most notable contaminant with a mean level of 2.2 µg/l in the Rathbun communities versus 0.6 µg/l in all other Iowa surface water supplies ($p<0.01$). These levels remained high through at least 1991.

We conducted an ecological study of rates of low birth weight, prematurity, and IUGR in communities that obtain their drinking water from the RRWA in comparison to other Iowa communities.

Methods

Data on finished water quality were obtained from the statewide municipal water survey of 1986–1987 mandated by the state of Iowa (*18*). This survey included testing of the finished water of all 856 municipal supplies in Iowa for 35 pesticides and 35 other volatile organic contaminants. Water systems were stratified by county and type including surface supplies and wells of various depths, and then randomly selected so that samples within each stratum were evenly distributed over the 12-month sampling period of 1 November 1986–31 October 1987. Drinking water was sampled from the main outflow tract in each community. Analyses were performed by gas chromatography and mass spectrometry at the Hygienic Laboratory of the University of Iowa, Iowa's primary laboratory for analyses of public drinking water. Analytical methods used were approved by the U.S. Environmental Protection Agency. Data on water source and treatment practices of each municipality were obtained by the Geological Survey Bureau of the Iowa Department of Natural Resources and the Center for Health Effects of Environmental Contamination (CHEEC) at The University of Iowa. These data were

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This work was supported by awards from the Centers for Disease Control and Prevention and the Agency for Toxic Substance and Disease Registry, Atlanta, GA; the Center for Health Effects of Environmental Contamination, the University of Iowa, Iowa City, IA; the Health Effects Research Laboratory, U.S. Environmental Protection Agency, Cincinnati, OH; and the Vice-President's Office for Research and the Agricultural Experiment Station, Utah State University, Logan, UT.

Received 8 August 1996; accepted 29 October 1996.

available from a computerized database maintained by CHEEC.

Exposures to drinking water contaminants were assigned to mothers by relating the drinking water data by municipality to maternal residence at the time of giving birth. Infants born to mothers residing in rural areas were excluded from these analyses because of the uncertain sources and characteristics of their drinking water from private wells. Major sources of water were defined as surface (rivers, lakes, impoundment reservoirs), groundwater from shallow alluvial or glacial drift, or groundwater from deeper bedrock aquifers. A major source was assigned to each municipality if at least 75% of the finished water supply was derived from one of the three major sources. Communities that regularly obtained 25% or more of their water from a second source or changed their supply to another source during the study period were excluded from the analyses.

Data from the 1980 U.S. census were used to estimate population characteristics of Iowa communities, including the percentage of women in the labor force and median income. For community populations of 2,500 or greater, data were available by individual community. For towns of fewer than 2,500, data were available only for the county average for towns of this size.

Birth certificate data on individual mothers and infants were obtained from state vital records. Birth weights of singleton white infants born during the years 1984–1990 were obtained from data tapes provided by the Iowa Department of Public Health. Births to nonwhite mothers were excluded because of their small numbers (less than 5% of all live births). Multiple births were excluded because these infants have a well-recognized reason for their small size. Maternal residence at the time of birth, including whether or not the residence was within city limits, was also available. Birth weights and maternal addresses were available on 98.2% of the certificates. Date of last menstrual period (LMP), education of the mother, number of prenatal visits, prior parity, age of mother, and maternal smoking during pregnancy (1989 and 1990 only) were also available from the birth data tapes.

Low birth weight was defined as birth weight less than 2,500 g. Births at less than 37 weeks of gestation were considered premature. IUGR was defined as weight less than the 10th percentile for gestational age as defined by California standards for non-Hispanic whites (*19*). The California standard was used because of the statistical robustness allowed by the large population sample. Infants with missing gestational ages were excluded from analyses of prematurity and IUGR. Case definitions were not mutually exclusive, and some infants were classified as having low birth weight, prematurity, and IUGR if all three case definitions were met.

Rates of maternal smoking during pregnancy were estimated for each community by using the percentage of mothers who reported on the birth certificate ever smoking during pregnancy. Adequacy of prenatal care was determined by the reported number of prenatal visits on the birth certificate, adjusted for gestational age according to the method described by Kessner (*20*). Education rates were calculated as the percentage of women over age 20 that had completed a high school education. As an index of the completeness of birth certificate data and perhaps social class, the proportion of missing data for the date of LMP was recorded for each community.

An attempt was made to reduce the possibility of confounding bias related to geographic region in Iowa and size of community. The RRWA communities are all in southern Iowa and are not representative of the entire state. A review of demographic characteristics by region revealed that mothers in southern Iowa have a less favorable profile of characteristics related to reproductive outcome. A north-to-south gradient exists of increasing rates of IUGR, low birth weight, prematurity, maternal smoking, and poor prenatal care. Compared to other Iowa women, southern Iowa women have on average less education and a lower median income (data not shown). Since the Rathbun communities are all in southern Iowa and rates of IUGR and known demographic risk factors for adverse reproductive outcomes were more common in southern Iowa, the comparison communities used in the analysis of drinking water contaminants and reproductive health were restricted to those in southern Iowa of similar size (population<2,500). These comparison communities were further classified according to their major source of water supply including surface water, groundwater from shallow alluvial or glacial drift, and groundwater from deeper bedrock aquifers.

Data were reviewed on water contaminants that were previously reported to have been detected at least occasionally at elevated levels in the statewide Iowa survey (*18*) including the volatile organic compounds chloroform, bromodichloromethane, dibromochloromethane, bromoform, *p,m*-xylene, *o*-xylene, tetrachloroethane, and the herbicides alachlor (2-chloro-2′,6′-diethyl-*N*-(methoxymethyl) acetanilide), atrazine (2-chloro-4-ethylamino-6-isopropylamine-*s*-triazine), metolachlor (2-chloro-6′-ethyl-*N*-(2-methoxy-1-methylethyl)acet-*o*-toluidide, cyanazine (2-[[4-chloro-6-(ethylamino)-1,3,5-triazine-2-yl]amino]-2-methylpropanenitrile), and 2,4-D (2,4-dichlorophenoxyacetic acid). Means and standard deviations of contaminants were calculated for all Iowa communities grouped by type of water supply. Median values are also reported in Table 1 because of the skewed distribution of these variables. The percentage of positive detections, defined as the detection of a contaminant in a sample above the analytical detection limit, was tabulated for each group. The detection limit was 0.2 µg/l for herbicides and 1.0 µg/l for the other organic compounds.

Rates of low birth weight, prematurity, and IUGR were calculated for groups of communities as defined by source of water supply, using the total number of affected births in each group and the total number of live births in the same groups. All rates were adjusted for the mother's age by five-year groups, using as the standard the Iowa distribution of mothers' ages at delivery for all births in each year.

Multiple linear regression models were constructed with age-adjusted community rate of IUGR as the dependent variable. Independent variables used in the models were those with significant individual correlations with IUGR and included community levels of atrazine, cyanazine, metolachlor, and chloroform in drinking water, median income, previous mean parity, and the following proportions: women in the workforce, women with a high school education or greater, mothers who smoked during pregnancy, mothers with poor prenatal care, and births with missing date of LMP.

Results

The mean and median levels of contaminants of drinking water supplies and percentage of positive detections are listed in Table 1 by major source of supply for all southern Iowa communities sampled in the 1986–1987 survey. Most contaminants were detected more often in surface water sources than in groundwater sources and levels of the herbicides atrazine, cyanazine, metolachlor, and 2,4-D, as well as chloroform, bromodichloromethane, and dibromochloromethane were notably higher in the surface water sources.

The higher levels of chloroform and bromodichloromethane in the surface water compared to groundwater supplies reflected the greater use of chlorination in surface water systems, a pattern common in most of the United States (*21*). The Rathbun system did not have a higher mean level of chloroform or other trihalomethanes compared to other surface water supplies in Iowa, most likely due to the use of chloramination there rather than other standard methods of chlorination used commonly in other surface water communities.

Communities served by the RRWA, compared to the other groupings of Iowa communities by drinking water source, had greater rates of positive detections of the herbicides alachlor, atrazine, cyanazine, metolachlor, and 2,4-D. The elevated mean levels of the *s*-triazine herbicides atrazine (2.2 µg/l) and cyanazine (1.4 µg/l) were the most notable findings in the Rathbun communities. Further sampling of the RRWA communities revealed that atrazine and cyanazine levels have been elevated throughout each season and continued sampling during the period 1990–1991 showed levels comparable to the 1986–1987 survey (data not shown).

Table 1. Contaminants of drinking water supplied in towns in the southern tier of Iowa counties with a population of 2,500 or fewer by source of water supply, 1984–1990

Variable	RRWA (n =13)	All water supplies in Rathbun counties excluding RRWA (n = 38)	Surface water supplies other than Rathbun (n = 21)	Groundwater from alluvial and glacial drift (n = 75)	Groundwater from bedrock aquifers (n = 42)
Alachlor (Lasso)					
Mean (mg/l) (SD)	<0.01 (0.1)	0.0 (0)	0.00 (0.00)	<0.1 (0.2)	0.0 (0)
Median (mg/l)	0	0	0	0	0
Positive detection (%)	7.7	0	0	4.0	0
Atrazine					
Mean (mg/l) (SD)	2.2 (0.4)	0.7 (1.2)	0.8 (1.1)	<0.1 (0.1)	<0.1 (<0.1)
Median (mg/l)	2.1	0	0.44	0	0
Positive detection (%)	100.0	42.1	76.2	5.3	4.7
Cyanazine (Bladex)					
Mean (mg/l) (SD)	1.4 (0.5)	0.3 (0.5)	0.7 (0.9)	0.0 (0)	0.00 (0.00)
Median (mg/l)	1.4	0	0.3	0	0
Positive detection (%)	100.0	26.3	57.1	0	0
Metolachlor (Dual)					
Mean (mg/l)) (SD)	0.2 (0.3)	0.2 (0.4)	0.1 (0.2)	<0.1 (<0.1)	0.0(0)
Median (mg/l)	0	0	0	0	0
Positive detection (%)	38.5	26.3	21	1.3	0
2,4-D					
Mean (mg/l) (SD)	<0.1 (<0.1)	<0.1 (<0.1)	<0.1 (<0.1)	<0.1 (<0.1)	0.00 (0.00)
Median (mg/l)	0	0	0	0	0
Positive detection (%)	7.7	5.3	4.8	2.7	0
Chloroform					
Mean (mg/l) (SD)	53.2 (9.3)	57.8 (94.9)	110.2 (81.8)	7.92 (20.9)	1.10 (6.0)
Median (mg/l)	55.0	1.0	89	2.0	0
Positive detection (%)	100.0	52.6	95.2	70.7	16.7
Bromodichloromethane					
Mean (mg/l) (SD)	10.0 (3.7)	9.6 (13.8)	18.00 (10.3)	5.19 (17.3)	0.45 (1.9)
Median (mg/l)	9.0	1	18	1.0	0
Positive detection (%)	100.0	52.6	90.5	61.3	14.3
Dibromochloromethane					
Mean (mg/l) (SD)	0.6 (0.5)	1.32 (1.7)	1.67 (1.2)	3.79 (12.4)	0.60 (1.3)
Median (mg/l)	1.0	0	2	1.0	0
Positive detection (%)	61.5	47.4	81.0	52.0	26.2
Bromoform					
Mean (mg/l) (SD)	0.00 (0.00)	0.9 (2.1)	0.05 (0.2)	1.1 (2.9)	1.6 (5.0)
Median (mg/l)	0	0	0	0	0
Positive detection (%)	0	25.0	4.8	28.0	26.2
p,m-Xylene					
Mean (mg/l) (SD)	<0.1 (<0.1)	0.2 (0.7)	0.4 (1.1)	0.0 (0)	0.62 (2.90)
Median (mg/l)	0	0	0	0	0
Positive detection (%)	7.7	10.5	14.3	0	9.5
o-Xylene					
Mean (mg/l) (SD)	0	0.05 (0.2)	0.10 (0.3)	0.0 (0)	0.14 (0.8)
Median (mg/l)	0	0	0	0	0
Positive detection (%)	0	5.3	9.5	0	4.8
Tetrachloroethane					
Mean (mg/l)) (SD)	0.0 (0)	0.0 (0)	0.0 0)	0.0 (0)	0.0 (0)
Median (mg/l)	0	0	0	0	0
Positive detection (%)	0	0	0	0	0

Abbreviations: RRWA, Rathbun Rural Water Association; *n*, number of communities; SD, standard deviation; 2,4-D, 2,4-dichlorophenoxyacetic acid.
Communities grouped by source of drinking water supply.

The number of births and rates of IUGR, low birth weight, and prematurity in the Rathbun communities in comparison to other southern Iowa communities of similar size are listed in Table 2 by source of water supply. These groupings included: the 13 communities that received all of their water from the RRWA; all communities within counties served by the system that did not receive RRWA water; other surface supplies; groundwater supplies from shallow alluvial and glacial drift; and groundwater from deeper bedrock. During the years 1984–1990, the percentage of live births with IUGR was 11.2 in the Rathbun communities compared to a range of 6.4–6.9 in the other groups of communities. The rate of live births with IUGR was 1.8 times greater (95% CI = 1.2, 2.6) in the Rathbun-served communities compared to the group of 38 communities in the same counties with sources of drinking water other than the RRWA. Low birth weight was marginally greater and prematurity was marginally less in the Rathbun communities compared to the other groups of communities.

The socioeconomic characteristics of women in southern Iowa communities are listed in Table 3. The Rathbun communities had higher rates of maternal smoking and poor prenatal care, less education, less participation in the workforce, and a lower median income than other communities in southern Iowa. The characteristics of the Rathbun communities, however, were similar to 38 communities in the same counties that obtained their drinking water from a source other than from the RRWA.

Spearman rank–order correlation coefficients between age-adjusted community rates of IUGR and water contaminants in all of the southern Iowa communities with a population of fewer than 2,500 were as follows: atrazine (r = 0.31, p = 0.001), metolachlor (r = 0.28, p = 0.004), cyanazine (r = 0.24, p = 0.02), and chloroform (r = 0.18, p = 0.07). The results were further explored in multiple linear regression models with age-adjusted IUGR rates as the dependent variable and the socioeconomic, lifestyle, and water variables entered as independent variables (Table 4). With communities as the unit of analysis, the best model fit with IUGR rates was found using atrazine levels (µg/l), rate of maternal smoking during pregnancy, and lack of recorded date of LMP on the birth certificate as independent variables (R^2 = 0.19). Because the herbicide levels were correlated (from r = 0.38 between cyanazine and metolachlor to r = 0.81 between atrazine and cyanazine), the independent contribution of each herbicide to IUGR risk cannot be determined in this analysis. The results of separate regression models for selected herbicides and chloroform, each with the same other covariates, are displayed in Table 4; after atrazine, the next best fits of the models included metolachlor (R^2 = 0.16), cyanazine (R^2 = 0.15), and chloroform (R^2 = 0.12).

Discussion

In the Iowa survey, drinking water derived from the Rathbun impoundment reservoir was found to have higher levels of triazine herbicide contaminants compared to other sources of drinking water in the same Iowa counties. Groundwater sources of drinking water were relatively free of herbicide contamination compared to surface water sources. Communities in southern Iowa with maternal exposure to drinking water from the Rathbun reservoir had a higher rate of IUGR than nearby communities of similar size with different sources of drinking water. The statewide survey of water characteristics in all Iowa municipal water systems is a strength of the present study. Water sampling was done systematically and laboratory analyses were performed in a central laboratory with strict quality control procedures.

IUGR is a concern because it is a predictor of increased infant morbidity and mortality (*1–14*). In contrast to the IUGR findings, only a marginal increase in rate of low birth weight was seen in the Rathbun communities compared to the others. Rates of prematurity were slightly lower in the Rathbun communities; thus, the specific effect of IUGR is obscured if only low birth weight is considered. Birth weight alone is a simple and accessible public health indicator, but may be inadequate and misleading in epidemiologic studies because it is determined by both growth status and maturity (gestational age). When birth weight is used to define birth cohorts for study of reproductive outcomes, the effect of IUGR is often distorted because most infants with retarded growth are also the most mature (*10,22*).

The association between the water supplied to the Rathbun communities and the increased risk of IUGR should be considered a preliminary finding that needs to be verified by more detailed epidemiologic studies with quantification of individual levels of exposure to water contaminants and potential confounding factors. Since the present study is based on the use of data at the community level rather than data collected from individuals, there are certain well-known limitations including uncertainties regarding the classification of exposure and the bias of confounding by regional factors related to both place of residence and IUGR. We attempted to control for potential confounding factors related to water characteristics and IUGR by restricting the comparison communities to those in southern Iowa of similar size and

Table 2. Number of births and percentage of infants with IUGR, low birth weight, and prematurity in towns with a population of 2,500 or fewer in the southern tier of Iowa counties by source of water supply, 1984–1990

Variable	RRWA (*n* =13)	All water supplies in Rathbun counties excluding RRWA (*n* = 38)	Surface water supplies other than Rathbun (*n* = 21)	Groundwater from alluvial and glacial drift (*n* = 75)	Groundwater from bedrock aquifers (*n* = 42)
Births[a]	492	1,267	1,488	3,800	2,504
Intrauterine growth retardation (%)	11.2[b]	6.6	6.4	6.9	6.8
Low birth weight (%)	5.5	4.9	4.0	5.8	4.5
Prematurity (%)	5.2	6.4	6.1	6.1	6.1

Abbreviations: IUGR, intrauterine growth retardation; RRWA, Rathbun Rural Water Association; *n*, number of communities.
Communities grouped by source of drinking water supply.
[a]Births with complete data on birth weight and gestational age for calculation of rates of IUGR.
[b]RRWA versus all other water supplies in Rathbun counties excluding RRWA communities, $p = 0.004$.

Table 3. Socioeconomic characteristics of towns in the southern tier of Iowa counties with a population of 2,500 or fewer by source of water supply, 1984–1990

Variable	RRWA (*n* =13)	All water supplies in Rathbun counties excluding RRWA (*n* = 38)	Surface water supplies other than Rathbun (*n* = 21)	Groundwater from alluvial and glacial drift (*n* = 75)	Groundwater from bedrock aquifers (*n* = 42)
Median population size[a]	501	219	606	433	712
Smokers (%)[b]	37.9	36.2	28.1	27.8	29.3
Poor prenatal care (%)[b]	4.5	3.9	2.4	3.3	2.1
LMP not recorded (%)[c]	14.6	16.2	12.5	15.8	14.7
High school or greater education (%)[a]	82.8	87.3	89.8	89.8	88.2
Women in workforce (%)[a]	40.3	40.3	42.7	44.4	45.4
Median income ($)[a]	12,526	11,569	12,686	14,620	15,291

Abbreviations: RRWA, Rathbun Rural Water Association; *n*, number of communities; LMP, last menstrual period.
Communities grouped by source of drinking water supply.
[a]Source: 1980 census.
[b]Source: birth certificate data.
[c]Date of last menstrual period, as recorded on birth certificate.

Table 4. Multiple linear regression analyses of age-adjusted rates of intrauterine growth retardation of communities with a population of fewer than 2,500 persons in southern Iowa in separate models with water contaminants and other independent variables,[a] 1984–1990.

Water contaminant in model and R^2	Independent variables	Regression coefficient	Standardized coefficient	*p*-value
Atrazine $R^2 = 0.19$	Atrazine	1.80	0.32	0.001
	No date of LMP recorded	0.05	0.17	0.067
	Maternal smoking	0.17	0.29	0.002
Metolachlor $R^2 = 0.16$	Metolachlor	8.20	0.26	0.006
	No date of LMP recorded	0.16	0.26	0.005
	Maternal smoking	0.05	0.18	0.052
Cyanazine $R^2 = 0.15$	Cyanazine	2.05	0.25	0.009
	No date of LMP recorded	0.17	0.29	0.002
	Maternal smoking	0.05	0.18	0.056
Chloroform $R^2 = 0.12$	Chloroform	0.01	0.18	0.063
	No date of LMP recorded	0.17	0.28	0.004
	Maternal smoking	0.05	0.19	0.049

LMP, last menstrual period.
[a]Variables included in all models and removed in stepwise backward elimination include percent of women in labor force, Kessner index of prenatal care, median income, and maternal education.

by including communitywide estimates of potential confounders in multiple linear regression analyses. Some of the estimates of communitywide characteristics were derived from the 1980 census and their present value depends on the assumption that the ranking of the communities relative to one another has remained relatively constant since 1980. Despite these measures, the possibility remains that the Rathbun communities differ from the comparison communities in characteristics other than water contaminants that are also associated with IUGR.

The definition of exposure of pregnant women to drinking water contaminants was based solely on their residence. Communities that received a mixture of water from the RRWA and other sources were excluded because of uncertainties regarding level of exposure. Women in the remaining communities were assigned the exposure levels of water contaminants that were measured at the outflow of the water plant in their community. These exposures may have varied somewhat because of changes in residence during pregnancy, use of bottled water, or individual treatment of water at home. Change in residence during pregnancy is not a trivial issue; a study of birth defects in Maryland revealed that 20% of the mothers studied changed address between time of conception and time of birth (*23*). The effect of residence misclassification is thought to weaken true associations between environmental characteristics and birth outcomes rather than to give rise to spurious associations. The dampening of true risk ratios due to misclassification of residence also was found in an Iowa study of water characteristics and cancer (*24*).

The use of bottled water by women in Iowa is not likely to be widespread. In 1989–1990 a survey of bottled water use was conducted by mail by one of us (P Isacson, unpublished data) among 675 randomly selected residents of 13 southern Iowa counties. Only 4% responded that they regularly used bottled water for drinking; the rate of use may increase, though, during pregnancy. In 1989 a survey of 100 consecutive visits by women to the prenatal clinic in the Department of Family Practice at the University of Iowa College of Medicine found that 8% used bottled water for drinking and cooking throughout their pregnancy (P Isacson, unpublished data). The women who attended this clinic were likely above the state average in education and income; thus, their rates of bottled water use may also be above the statewide average. Of the home systems used to treat water, only activated charcoal filters are likely to appreciably reduce levels of contamination by herbicides and other organic compounds.

The definition of IUGR used in the present study was based on birth certificate reports of birth weight, date of LMP, and date of birth. Head circumference, length, and weight gain during pregnancy may allow more precision in the definition of IUGR (*25*), but were not available in the present study. In 13% of births, date of LMP was not available. The rate of missing data on date of LMP on the birth certificate was not consistent throughout Iowa and may be a proxy for socioeconomic status; it was positively correlated with community rates of IUGR. Missing data on the date of LMP may have resulted in an underestimation of the rate of IUGR in the Rathbun communities.

A large number of medical complications of pregnancy are known to be associated with IUGR but data on them were not available for the present study. While we determined that the Rathbun mothers were not at an increased risk of delivering prematurely, further study of medical records are needed to determine if they had an increased risk of other pregnancy complications.

If the association between the Rathbun water and increased risk of IUGR is substantiated, the question of which contaminants are responsible will remain. The best fits with the available data are consistent with separate positive associations between atrazine, metolachlor, and cyanazine and community rates of IUGR in southern Iowa. Atrazine had the best fit in the regression models of IUGR, but independent effects of the other herbicides, which are intercorrelated, cannot be ruled out. Chloroform had a weak positive but statistically insignificant association with IUGR in the southern Iowa communities in the present study. An earlier study of all Iowa communities of 1,000–5,000 persons showed an association between low birth weight and chlorination of drinking water (*26*). A more recent study found that in all Iowa communities of 1,000–5,000 persons, levels of chloroform above 10 µg/l were associated with a 1.8-fold increase in the risk of IUGR (*17*). The present study may have had limited power to detect associations between IUGR and chloroform levels because the communities were smaller and fewer in number than in the previous studies cited.

Despite the large number of water contaminants examined in the Iowa survey, many others were not studied, including nonvolatile organic compounds, heavy metals, and trace elements. Differences in water treatment between communities also exist and are difficult to assess. The disinfection technique of chloramination, a combination of chlorine and ammonia treatment, was used in the RRWA system but rarely used elsewhere in Iowa, and there were too few other communities using chloramination to allow adequate analysis of its effect on IUGR. Chloramination has been used as an alternative to chlorination because it has fewer reaction by-products of chlorine that may be carcinogenic (*27*). The levels of chloroform, bromodichloromethane, dibromochloromethane, and tetrachloroethane were not significantly higher in the Rathbun communities compared to other surface water supplies.

Two previous epidemiologic studies in California found clusters of spontaneous abortions and cardiac malformations in residential areas thought to contain well water contaminated by organic solvents (*15,16*). Subsequent studies found that hydrogeologic models did not support a causal association between the solvent exposure and adverse reproductive effects but that consumption of tap water, compared to bottled water, was associated with an increased risk of spontaneous abortion regardless of residence (*28*). In a later review of the California studies, the authors noted that no major source of water supply was involved and concluded that the association lacked biological plausibility and was likely the result of biased recall of water use by case (*29,30*). In contrast to the California studies, the Rathbun communities each received drinking water from a single major source with contaminant levels significantly higher than the nearby comparison communities. The classification of exposure was also not dependent on individual recall.

The hypothesis that water contaminants, including pesticides, can cause adverse effects on human growth and development has some biologic plausibility, but is controversial given the limitations of extrapolating from animal experiments and limited epidemiologic studies. Fetal growth in mice, as indicated by birth weight and crown–rump length, was reduced and fetal loss was increased in a dose-dependent manner when pregnant mice were exposed to Tordon 202c, an herbicide mixture composed of picloram and 2,4-D (*31*). Some pesticides, including the *s*-triazine herbicides, have hormone-like qualities and can bind to hormone receptors, interrupting hormone-directed control of cell functions (*32*). Atrazine at a dose of 120 mg/kg body weight (bw) resulted in a loss of body weight in male and female Sprague-Dawley rats. Females remained lower in body weight than controls for at least 2 weeks after the cessation of atrazine exposure (*33*) and atrazine also transiently prolonged the estrous cycle. Another study with Sprague-Dawley rats found that atrazine exposure in the range of 50–100 mg/kg bw/day disrupted reproductive cycling and hormonal activity. The authors concluded that the antiestrogenic action of atrazine disrupts critical hormone-mediated functions, resulting in the delay of ovulation and maintenance of estrogen secretion from ovarian follicles (*34*).

Atrazine has been used in a wide variety of genetic tests, with largely negative results (*35*). Atrazine has been found to be mutagenic after activation with plant cell material from maize as indicated by gene conversion at the *ade-2* and *trp-5* loci in *Saccharomyces cerevisiae* (*36*). Furthermore, the plant activation system has been shown to work under field conditions, i.e., field corn plants treated with atrazine exhibited increased mutagenic activity in their pollen grains while untreated plants did not (*37*). While the *s*-triazine compounds atrazine, cyanazine, and simazine showed the most pronounced mutagenic effect, alachlor and propachlor, neither of which had previously been shown to induce mutations with or without mammalian microsomal activation, gave positive results after plant cell activation (*38*). These findings have led to reconsideration of the appropriate means to assay for potential mutagenicity of agricultural chemicals.

Atrazine levels appear to be relatively stable in the Rathbun system seasonally and annually, perhaps because the RRWA obtains its water from a large impoundment reservoir rather than directly from a river with variable levels of runoff and rates of flow. The water intake for the RRWA is in the receiving stream below the dam where bottom sediments, possibly with high levels of contaminants, are discharged from the reservoir.

The current maximum concentration level for atrazine in drinking water, based on extrapolation from lower animal experimentation, is 3.0 μg/l, a level approached in the Rathbun communities. It has been assumed in the past that contaminants in water might be too low to cause detectable adverse health effects (*39*). The high levels of contamination reached in the Rathbun system and possibly in other areas with drinking water obtained from impoundment reservoirs in agricultural areas underscores the importance of more detailed studies of the effects of drinking water contamination on human reproduction.

The significance of herbicide-contaminated drinking water as a risk for reproductive health remains uncertain. The Iowa population served by the RRWA is unique because several communities have been exposed to elevated levels of herbicides in drinking water via the water system while neighboring communities have not been exposed. Because of the limitations of the ecologic design of this study, including aggregate rather than individual measures of exposure and limited ability to control for confounding factors related to source of drinking water and risk of IUGR, a causal relationship between any specific water contaminant and risk of IUGR cannot be inferred. More advanced study designs including case–control and cohort studies are needed to further investigate the possible reproductive hazards associated with herbicide-contaminated water supplies in Midwestern agricultural regions.

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