

Can environmental or occupational hazards alter the sex ratio at birth? A systematic review

Metrecia L. Terrell¹, Kathleen P. Hartnett¹ and
Michele Marcus^{1,2*}

¹Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA;

²Departments of Epidemiology and Environment Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA

More than 100 studies have examined whether environmental or occupational exposures of parents affect the sex ratio of their offspring at birth. For this review, we searched Medline and Web of Science using the terms 'sex ratio at birth' and 'sex ratio and exposure' for all dates, and reviewed bibliographies of relevant studies to find additional articles. This review focuses on exposures that have been the subject of at least four studies including polychlorinated biphenyls (PCBs), dioxins, pesticides, lead and other metals, radiation, boron, and g-forces. For paternal exposures, only dioxins and PCBs were consistently associated with sex ratios higher or lower than the expected 1.06. Dioxins were associated with a decreased proportion of male births, whereas PCBs were associated with an increased proportion of male births. There was limited evidence for a decrease in the proportion of male births after paternal exposure to DBCP, lead, methylmercury, non-ionizing radiation, ionizing radiation treatment for childhood cancer, boron, or g-forces. Few studies have found higher or lower sex ratios associated with maternal exposures. Studies in humans and animals have found a reduction in the number of male births associated with lower male fertility, but the mechanism by which environmental hazards might change the sex ratio has not yet been established.

Keywords: *sex ratio; environmental; occupational; PCBs; dioxins; metals; pesticides; radiation; boron; g-forces*

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The ratio of male to female offspring at birth may be a simple and non-invasive way to monitor the reproductive health of a population. Except in societies where selective abortion skews the sex ratio (SR), approximately 104–107 boys are born for every 100 girls (1, 2). Certain chemicals that decrease fertility have also been associated with a higher or lower proportion of male births, leading some researchers to propose that departures from this fairly stable ratio could reflect damage to male or female reproduction.

Sex ratio at birth, commonly called the secondary sex ratio, is easy to measure, often recorded, and only rarely subject to recall bias. More than 100 studies have investigated whether environmental or occupational exposures can change the sex ratio. The first studies on environment and the sex ratio examined acute exposures such as the nuclear bombing of Hiroshima and Nagasaki or the Great London Smog. More recent research has

focused on the hormonal effects of endocrine disruptors including dioxins, pesticides, and PCBs.

The findings for many exposures have been inconsistent and the biological mechanisms remain elusive. But after nearly a century of active research, interest in the sex ratio persists. Newer research focusing on epigenetics, endocrine disruption, and gene-environment interaction may help to explain how toxicants interfere with human reproduction. This research may also settle the question of whether the number of boys and girls at birth can serve as an alert to environmental threats.

In this paper, we first highlight methodological issues and confounders important to this literature, then review exposure groups including dioxins, PCBs, pesticides, metals, non-ionizing radiation, ionizing radiation, g-forces, and boron. We examine possible biological mechanisms that might underlie a change in the sex ratio, present our conclusion, and provide recommendations for future research.

Methods

Article search strategy

To identify articles on sex ratio and environmental or occupational exposures, we searched Medline and Web of Science using the terms 'sex ratio at birth' and 'sex ratio and exposure' (Fig. 1). These searches, which were not limited by date, yielded a total of 3,007 articles. We then excluded those studies that examined the sex ratio in relation to chronic or infectious diseases, as well as those that analyzed sex ratio after exposure to pharmaceuticals. Studies have yielded conflicting findings on smoking and sex ratio, which we did not include in this review. We also eliminated studies with non-human subjects, papers written in languages other than English, and articles that only considered demographic or cultural factors.

After the electronic search, we had 68 studies that considered occupational or environmental exposure. We also searched literature reviews and the citation list of each study, which allowed us to identify 39 additional studies that met the same criteria for inclusion. Of the 107 articles included in the final review, we focused on 83 with exposures that were the subject of at least four studies. We organized these 83 articles into eight exposure categories and considered the remaining 24 articles separately.

Review of methodological issues

There are a number of methodological issues common to the studies reviewed. One of the most important issues is how the exposure was defined. Some of the studies do not include actual exposure assessments, but inferred

exposure based on occupation, geography, or other indirect measures. This results in misclassification and can create substantial bias in the determination of whether the exposure is associated with an altered sex ratio. The misclassification is rarely related to the sex of the offspring and, therefore, most likely to cause bias toward the null.

Although individual-level exposure assessments are ideal, studies that classify workers by job titles are able to identify workers with similar exposures. Workers often have multiple exposures, however, which may interact to cause the effect.

Ecological studies, which have no individual exposure assessment, are limited in determining who in the population is exposed. Because of the variability in exposure assessments, we have given less weight to the ecologic studies. Other methodological concerns include timing of the births in relation to parental exposure. The cross-sectional studies are weakest in this area. Temporality issues are a concern when it is difficult to determine if the parents are exposed before the conception of the offspring.

Because our review of the demographic factors reported to be associated with sex ratio found very small effects, we did not consider it a limitation if a study did not adjust for demographic factors as potential confounders. In addition, we have not considered other factors such as trends in sex ratio over time, multiple births, the sex ratio during pre- or post-war times, or season of conception. While these factors may cause variations in the sex ratio, they are beyond the scope of this review.

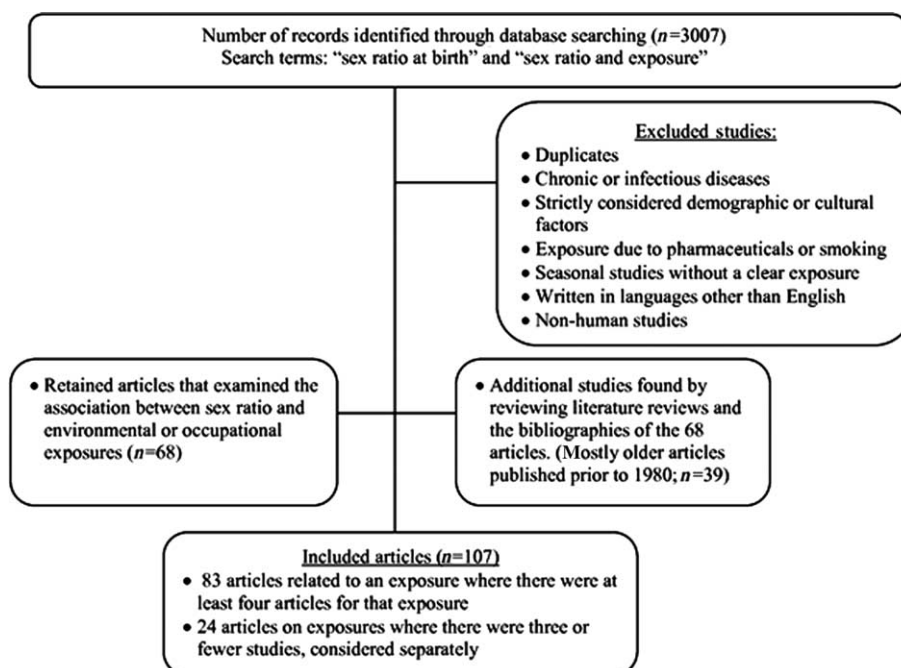


Fig. 1. Article search criteria for sex ratio literature review.

Many of the studies compare sex ratio in the exposed population to the expected sex ratio in the general population. Except for studies in countries where sex selection is common, we have assumed the expected sex ratio (male/female) in the general population is 1.06 (proportion male = 0.514) (2) throughout this review. We have computed 95% confidence intervals for the sex ratios using the score method (3, 4). A third of the studies report odds ratios and 95% confidence intervals. Because the referent populations varied across studies, we have only reported the odds ratio or risk ratio when there was not enough information given in the study to calculate the sex ratio in the exposed. In the text, we use the term 'significant' to indicate a *p*-value of less than 0.05.

We did not exclude studies that had small sample sizes. Although these studies have limited power to find an association, they may still be valuable when assessed collectively with other similar studies. Many studies of environmental hazards have a sample size that is fixed based on the number of individuals exposed. However, small studies with positive findings are often over-represented in the literature due to publication bias, and substantial sample sizes are needed to detect subtle shifts in the sex ratio. In a study of boron workers in China, Chang and colleagues (5) estimated that 3,400 births, evenly split between exposed and unexposed, would be needed to detect a significant difference between their referent sex ratio of 1.19 and the sex ratio of 1.10 in the offspring of boron-exposed men.

Review of potential confounding factors

A number of demographic factors have been reported to be associated with the sex ratio. The factor found most consistently in the literature is race. Blacks typically have a lower sex ratio than Whites; although it has been noted that the magnitude of this effect is small (sex ratio roughly 1.03 for Blacks and 1.06 for Whites; reviewed in James (6) and Khoury et al. (7)) and has been diminishing over time in the United States (1). Following race, maternal age, paternal age, and birth order have been considered in many studies. When these factors are considered individually, younger parental age or lower birth order are associated with a higher sex ratio. However, these factors are highly correlated and when adjusted for one another, the effect of paternal age and birth order remain, but the effect of maternal age is often attenuated or disappears (8–10). It is suggested that the birth order effect alone explains less than 10% of the variation in the sex ratio (11). Since the magnitude of the effects from parental ages and birth order is small, it is unlikely they are important as confounders.

Other factors in the literature are parental socioeconomic status (SES), coital frequency, and timing of intercourse relative to ovulation. Studies of SES have produced conflicting results and may be confounded by

birth order (reviewed in James (6) and Chahnazarian (8)). There are also conflicting results for studies of timing of fertilization and sex ratio (reviewed in Martin (12)). Although researchers infer that coital rates may have an underlying association with the sex ratio, this has not been directly examined in epidemiological studies. Some studies have considered pharmaceuticals, chronic diseases, or infectious diseases. The effect of fertility drugs on sex ratio appears strong (e.g. women prescribed gonadotrophin or clomiphene and low sex ratio; men prescribed methyltestosterone and high sex ratio; reviewed in James (6)), but studies are limited by small sample sizes. It is unlikely that pharmaceuticals would be important confounders because only a small portion of the population would be exposed; however, pharmaceuticals may be relevant in terms of elucidating the biological determinants of the sex ratio. Some studies have also found a change in sex ratio of fetal deaths after maternal exposure to acute stress. Bruckner and colleagues (13) found an increase in death of male fetuses after 20 weeks gestation across the United States in 2001, following the September 11 terrorist attack. The literature on chronic diseases or infectious diseases and effects on the sex ratio is limited and largely from single-report studies (reviewed in James (14)). However, consistency across three or more studies (e.g. prostate cancer and high sex ratio, testicular cancer and low sex ratio; females with multiple sclerosis and high sex ratio) might be relevant to biological mechanisms (reviewed in James (6, 14)).

Specific exposure groups

Table 1 summarizes the evidence for environmental or occupational exposures and the sex ratio for the 83 main studies reviewed. We summarize the findings of the main studies by exposure group below. Fig. 2 displays the sex ratios and 95% confidence intervals for the studies by exposure group with an indicator for the exposure route (paternal, maternal, or both).

Dioxins

Dioxins, PCBs, and furans, belong to a class of poly-halogenated aromatic hydrocarbons, which are persistent in the environment and have been recognized as having endocrine disrupting properties. The investigation of the effect of dioxin exposure on sex ratio originated from the landmark study of residents who were exposed to high levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) following a 1976 chemical plant explosion in Seveso, Italy. Mocarelli and colleagues (15) first reported a dramatically reduced sex ratio of 0.54 among 74 offspring born 9 months following the exposure in 1977–1984 to parents who lived in the most contaminated zone. This was later confirmed in a study of 674 births from 1977 to 1996 to families living in a wider area (16). There was a reduced sex ratio in offspring born to parents

Table 1. Summary of the evidence: environmental or occupational exposures and the sex ratio*

Exposure groups	Summary of evidence (by exposure route)			Studies
	Paternal	Maternal	Both	
Dioxins	↓↓	?	↓	Mocarelli et al. (16), Baccarelli et al. (17), Moshhammer and Neuberger (18), Ryan et al. (19), Schnorr et al. (20), Stellman et al. (21), Michalek et al. (22), Rogan et al. (23), Yoshimura et al. (24), del Rio Gomez et al. (25)
PCBs	↑↑	↑↓	↑	Karmaus et al. (26), Terrell et al. (27), Weisskopf et al. (28), Hertz-Picciotto et al. (29), Taylor et al. (30), Khanjani and Sim (31)
Pesticides				
DBCP	↓	n/a	n/a	Potashnik et al. (32), Potashnik and Porath (33)
Other	?	?	?	Karmaus et al. (26), Weisskopf et al. (28), Salazar-Garcia et al. (34), Cocco et al. (35, 36), Jarrell et al. (37), Khanjani and Sim (38), Zober et al. (39), Garry et al. (40), Garry et al. (41), Milham and Osslander (42), Savitz et al. (43), James et al. (44)
Metals				
Lead	↓	?	n/a	Simonsen et al. (45), Dickinson and Parker (46), Ansari-Lari et al. (47), Jarrell et al. (50)
Methylmercury	↓	?	?	Sakamoto et al. (51)
Other	?	?	?	Milham (52), Figa-Talamanca and Petrelli (53), Bonde et al. (54), Lyster (55), Lloyd et al. (56, 57), Fertmann et al. (58), Kozlov (59)
Non-ionizing radiation	↓	?	n/a	Knave et al. (62), Nordström et al. (63), Mubarak and Mubarak (64), Irgens et al. (65), Saadat (66), Mjoen et al. (67), Baste et al. (68), Larsen et al. (69), Guberan et al. (70)
Ionizing radiation				
Childhood cancer survivors	↓	?	n/a	Hawkins (71), Byrne et al. (72), Reulen et al. (73), Winther et al. (74), Green et al. (75)
Occupational	↑↓	?	n/a	Macht and Lawrence (76), Kitabatake (77), Tanaka and Ohkura (78), Hama et al. (79), Zadeh and Briggs (80), Dickinson et al. (81), Maconochie et al. (82), Magnusson et al. (83)
Nuclear	?	?	?	Schull and Neel (84), Schull et al. (85), Peterka et al. (86), Scherb and Voigt (87), Mudie et al. (88)
G-forces**	↓	n/a	n/a	Snyder (91), Little et al. (92), Irgens and Irgens (93), Goerres and Gerbert (94), Fujita et al. (95)
Boron	↓	n/a	?	Chang et al. (5), Sayli (97, 98), Whorton et al. (99), Yazbeck et al. (100)

Note: ↑ indicates limited evidence for increase in the sex ratio; ↑↑ indicates some evidence for increase in the sex ratio; ↓ indicates limited evidence for decrease in the sex ratio; ↓↓ indicates some evidence for decrease in the sex ratio; ? indicates insufficient evidence; ↑↓ indicates conflicting evidence, n/a indicates no studies;

*Eighty-one studies referenced above.

The remaining two studies are ionizing radiation studies (Kaplan 1958 (89) and Saadat 2003 (90)).

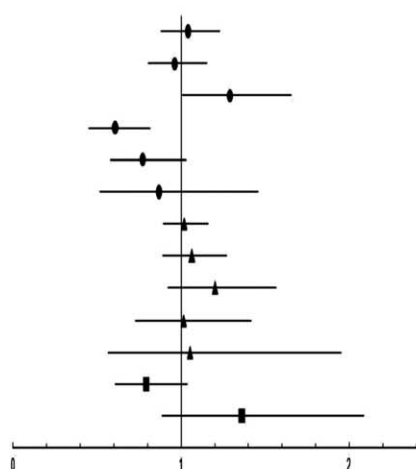
**G-forces experienced by military pilots and astronauts.

who both had TCDD levels >15 ppt (SR = 0.79). When the father only was exposed (TCDD levels >15 ppt) the sex ratio was 0.77. When the mother only was exposed (TCDD levels >15 ppt), the sex ratio (SR = 1.20) was not different from expected. When the father's age at the time of the explosion was considered, offspring to fathers <19 years had an even lower sex ratio of 0.62, compared to offspring born to fathers ≥19 years (SR = 0.88).

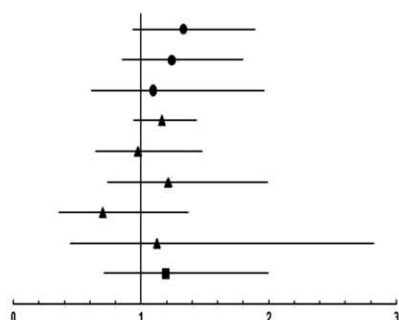
More than two decades after the Seveso accident, Baccarelli and colleagues (17) found a normal sex ratio

(SR = 1.06) in 481 offspring of women who lived in the most contaminated zones before 1980.

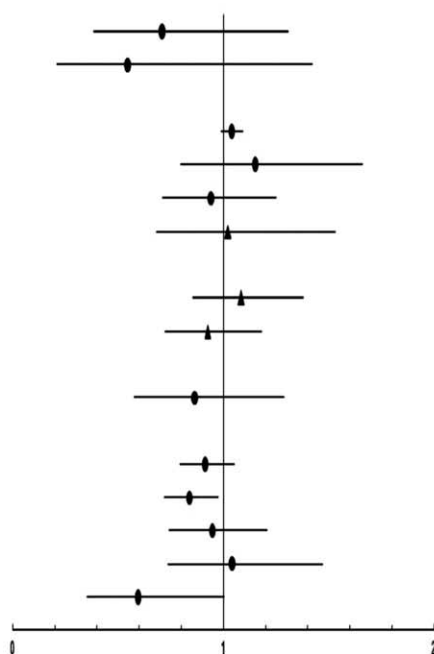
In two smaller studies, low sex ratios were reported among offspring of male workers that produced dioxin contaminated chemicals, 2,4,5-trichlorophenol (TrCP) or 2,4,5-trichlorophenoxy acetic acid (2,4,5-T). Austrian chemical plant workers had a sex ratio of 0.87 (18), and Russian workers a sex ratio of 0.61 (19). However, in a larger study of offspring to US plant workers that produced 2,4,5-T, there was a higher sex ratio in the

A. Dioxins**Study name****N births to exposed****Dioxin levels (ppt)**

Michalek (22)	557	≥ 10
Del Rio Gomez (25)	469	Not measured
Schnorr (20)	252	≥ 20
Ryan (19)	188	≥ 17 TEQ lipid
Mocarelli (16)	186	> 15
Moshammer (18)	56	≥ 19 blood fat
Del Rio Gomez (25)	902	Not measured
Baccarelli (17)	481	varied over time
Mocarelli (16)	220	> 15
Rogan (23)	137	Not measured
Ryan (19)	39	≥ 17 TEQ lipid
Mocarelli (16)	217	> 15
Yoshimura (24)	85	Not measured

B. PCBs**Study name****N births to exposed****PCB levels (ppb)**

Karmaus (26)	126	> 8.1
Terrell (27)	112	≥ 8
Weisskopf (28)	44	≥ 6.2
Terrell (27)	346	≥ 6
Karmaus (26)	89	> 8.1
Khanjani (31)	62	> 0.5 mg/kg milk fat
Weisskopf (28)	34	≥ 3
Taylor, 2007 (30)	17	> 5.9
Terrell, 2009 (27)	57	≥ 8 & ≥ 6

C. Pesticides**Study name****N births to exposed**

DBCP	
Potashnik (33)	41
Potashnik (32)	17
DDE/DDT	
Salazar-Garcia (34)	6180
Karmaus (26)	114
Cocco (35)	—
Karmaus (26)	93
HCB	
Khanjani (38)	269
Jarrell (37)	256
Vinclozolin	
Zober (39)	95
Multiple pesticides	
Garry (40)	781
Savitz (no prot. equip.) (43)	682
Garry (41)	261
James and De Cock (44)	127
Milham (42)	59

Fig. 2. (Continued)

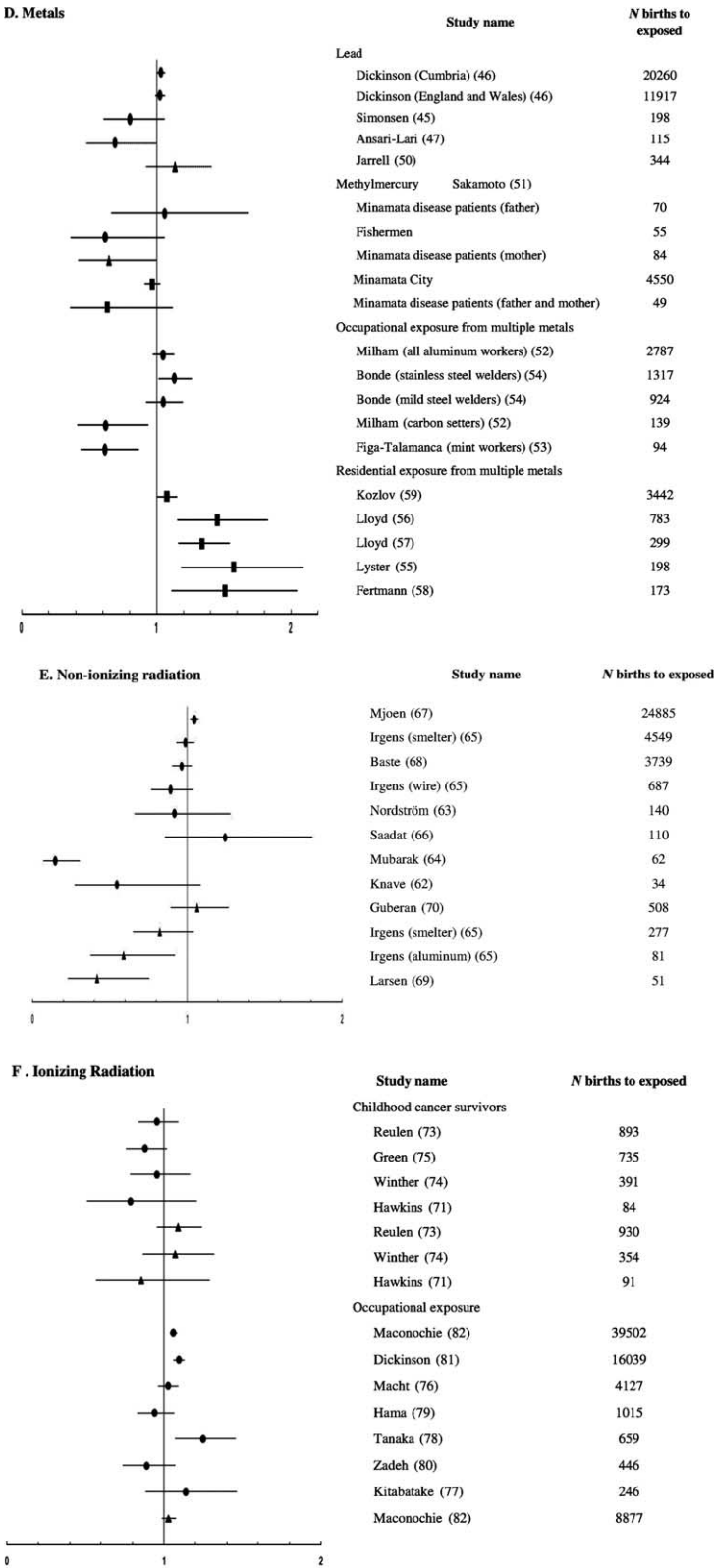


Fig. 2. (A) The sex ratio and 95% confidence intervals from studies of dioxin exposures: paternal (●), maternal (▲), or both (■). (B) The sex ratio and 95% confidence intervals from studies of PCB exposures: paternal (●), maternal (▲), or both (■). (C) The sex ratio and 95% confidence intervals from studies of pesticide exposures: paternal (●) or maternal (▲). (D) The sex ratio and 95% confidence intervals from studies of metal exposures: paternal (●), maternal (▲), or both (■). (E) The sex ratio and 95% confidence intervals from studies of non-ionizing radiation exposures: paternal (●) or maternal (▲). (F) The sex ratio and 95% confidence intervals from studies of ionizing radiation exposures: paternal (●) or maternal (▲).

offspring of fathers with TCDD levels ≥ 20 ppt (SR = 1.29) compared to fathers with TCDD levels < 20 ppt (SR = 1.03) and compared to non-exposed fathers (SR = 1.19) (20). The studies of Vietnam veterans have found little effect of dioxin exposure on the sex ratio (21, 22). Similarly, the Yucheng, Taiwan, and the Yusho, Japan incidents where residents consumed rice oils contaminated with polychlorinated dibenzofurans (PCDFs) and PCBs did not find significant differences in the sex ratio of offspring from potentially exposed residents (23, 24). Del Rio Gomez and researchers (25) examined a larger number of births to Yucheng residents over a longer time period than the Rogan et al. study (23). When assessing the offspring sex ratio by paternal age groups, they found a significantly lower sex ratio for offspring to fathers < 20 years at exposure (SR = 0.85) compared to unexposed offspring (SR = 1.18), similar to the Mocarelli et al. study (16).

PCBs

PCBs are made up of over 200 congeners, some of which exhibit dioxin-like activity. The primary route of exposure to PCBs in the general population is through diet, mostly fish consumption. All three studies of paternal PCB exposure in relation to offspring sex ratio have reported increases in the sex ratio. The Michigan Fish Eaters Study reported a sex ratio of 1.33 in offspring to fathers with serum PCB levels > 8.1 ppb (26); the Michigan Long-Term PBB Study reported a sex ratio of 1.24 in offspring to fathers with serum PCB levels ≥ 8 ppb (27); and the Great Lakes Fish Consortium reported a sex ratio of 1.10 in the offspring to fathers with serum PCB levels ≥ 6.2 ppb (28).

In the six studies of maternal PCB exposures, there were conflicting findings. Three studies have reported decreases in the sex ratio (26, 28, 29) and three studies have reported very small increases in the sex ratio (27, 30, 31). When PCBs were grouped into estrogenic and anti-estrogenic congeners, Taylor and colleagues (30) found opposite effects, suggesting that PCB congener groupings may be important in understanding the influence exposure can have on the sex ratio. Only the Michigan Long-Term PBB Study has suggested an increase in the sex ratio when both parents were exposed (27).

From this body of literature, there is some evidence to suggest a decrease in the sex ratio with high levels of paternal dioxin exposure. Although the specific PCB congeners vary by study, there is some evidence to suggest an increase in the sex ratio with high levels of paternal PCB exposure (Table 1).

Pesticides

DBCP exposure

Potashnik and colleagues (32) proposed that a low sex ratio might be an early indicator of damage to the male

reproductive system. The researchers described a dramatically lower sex ratio in 26 men who worked in an Israeli chemical plant that produced dibromochloropropane (DBCP), a nematocide that severely reduced sperm count and motility. Thirteen were azoospermic (no sperm in the ejaculate), eight were oligozoospermic (sperm concentration of < 20 million per ml), and five were normal. The sex ratio for infants conceived before the fathers worked at the plant was 1.12, compared to 0.55 for the 17 offspring conceived during exposure. The men who were diagnosed azoospermic or oligozoospermic in 1977 fathered 12 offspring while working at the plant, only two of whom were boys (SR = 0.20). The researchers hypothesized that the declining sex ratio may have been an early warning sign of DBCP's gonadotoxicity.

Exposure to DBCP left some of the workers permanently sterile, but three out of nine azoospermic men and three out of six oligozoospermic men in the Israeli cohort recovered some testicular function and were eventually able to father healthy offspring. Potashnik and Porath published another paper on the same cohort (33), and found that the sex ratio seemed to recover in tandem with the men's fertility (in 41 offspring conceived after exposure, SR = 0.71).

Other pesticide exposures

Once the most widely used pesticide, DDT has revealed little if any association with the sex ratio. In an occupational study, Salazar-Garcia and colleagues (34) assessed the sex ratio among men who were sprayers of DDT for at least 1 year during 1956–1990 in the Malaria Control Program in the Pacific area of Mexico. The sex ratio was 1.04 in the offspring born after the father's exposure. The other occupational study was limited by small numbers and relied on registrar data to retrospectively identify men who worked during the 1946–1950 anti-malaria campaign in Sardinia, Italy, and who were still living 50 years after the campaign ended. The sex ratio among the 75 offspring to ever-exposed fathers was 0.94 compared to a sex ratio of 1.20 in the 34 unexposed offspring (35).

Several other studies have reported null findings for DDE exposure among Great Lakes anglers (26) and Great Lakes sport-caught fish consumers (28); and DDT exposure among residents of Sardinia during the anti-malaria campaign (36). Two studies of the fungicide hexachlorobenzene (HCB) have reported similar null findings (37, 38).

Zober and colleagues (39) did not find hormonal effects in 67 men who synthesized and processed the fungicide vinclozolin. The sex ratio in the 95 offspring born to exposed workers was low at 0.86, but was not different from the expected sex ratio.

Multiple pesticide exposures

Garry and colleagues (40) found significant changes in the sex ratio among applicators of some pesticides and proposed that changes in hormone levels might be responsible. In a cross-sectional study of 1,532 births to applicators registered in Minnesota, they found a sex ratio of 0.91 in applicators that used fungicides, and a sex ratio of 1.13 in those who did not (40). In a smaller study published in 2003 (41), Garry and colleagues tested blood samples from 91 pesticide applicators for levels of testosterone and thyroid hormones. Overall, they reported a sex ratio of 0.95. When they stratified by testosterone levels, they found that the pesticide applicators with lower levels of testosterone had more female births (1st quartile, SR = 0.83; 4th quartile, SR = 1.67). However, the sex ratio of offspring in the second quartile was even lower than the first (2nd quartile, SR = 0.64). The authors also found evidence that hormone levels varied by season in pesticide applicators, a trend that they did not see in 49 urban controls matched to the applicators on age, health, and smoking status.

Milham and Osslander (42) found a lower sex ratio in 59 births to Washington State flour mill workers potentially exposed to fumigants used to kill insects in stored grain (exposed workers, SR = 0.59; referent group, SR = 1.05). However, the exposure assessment was imprecise; the researchers considered a father exposed if the child's birth certificate listed his occupation as flour mill worker.

Other studies have found effects only among subsets of workers who may have been exposed at higher doses. Savitz and colleagues (43) did not find a lower sex ratio associated with any chemical in their analysis of men in the Ontario Farm Family Health Study. The researchers asked men to report which chemicals they had used in the previous 5 years, and then focused on applications in the 3 months before the birth of each child. The researchers did not find any significant changes in the sex ratio for crop herbicides, insecticides, fungicides, livestock chemicals, yard herbicides, or building pesticides. However, the sex ratio was lower across all categories of chemicals in men who said they did not use protective equipment (SR = 0.84).

In a study of fruit-growing families in the Netherlands, researchers (44) found a normal overall sex ratio of 1.04 in 127 births. The exposure was predominantly paternal, because the men typically applied the pesticides, but some of the women may have also been exposed through pruning or harvesting. They also found that the families with more daughters ($n=16$) had been more likely to apply pesticides and herbicides using particular types of sprayers. These 16 families with more daughters also reported more frequent application of pesticides.

While there has been a range of pesticide exposure studies examining the sex ratio, we found only limited evidence to suggest a decrease in the sex ratio with a specific pesticide, DBCP (Table 1).

Metals

Metals are ubiquitous elements that can cause a variety of adverse health effects. There is extensive literature on the adverse effects of lead exposure on reproductive health and birth outcomes, but limited studies on lead exposure and the sex ratio. Other metals including mercury, arsenic, and cadmium have been studied less extensively with respect to reproductive health effects and the sex ratio. We present the studies of lead and methylmercury exposure, following which we highlight the studies from multiple metal exposures in occupational and residential settings.

Lead exposure

Three studies have suggested a decrease in the sex ratio with paternal occupational lead exposure (45–47). Simonsen and colleagues (45) combined data from two occupational cohorts, one of Danish battery workers and a second of various occupational exposures in Belgium, Italy, England, and Finland. The sex ratio in 26 births to men with blood lead levels >60 $\mu\text{g/dL}$ was 0.86, and the sex ratio in 94 births to men with the lowest blood lead concentrations (0–20 $\mu\text{g/dL}$) was 1.24. Dickinson and Parker (46) re-analyzed data from two other studies in order to examine whether men who worked as professional drivers had a sex ratio different from expected. Data from the Parker et al. study (48) included birth records from 1950 to 1989 in Cumbria, a county in northwest England. Data from McDowall (49) was for England and Wales births during 1980–1982. The sex ratios were not different from expected (Cumbria, SR = 1.03; England and Wales, SR = 1.02). In the Ansari-Lari et al. study (47), 49 men working in filling stations in Shiraz (south of Iran) had offspring with a significantly lower sex ratio (SR = 0.69) compared to unexposed offspring from men in the general population (SR = 1.07).

Only one study examined maternal exposure to lead and the sex ratio. Jarrell and colleagues (50) combined data from two Mexico City cohort studies (overall SR = 1.11). Lead was measured in maternal blood, cord blood, and bone and analyzed as quintiles of exposure. For maternal blood Pb, only the third suggested a significant increase in the sex ratio (3rd quintile, SR = 1.42; referent: 1st quintile, SR = 0.94). The sex ratio in the 5th quintile was 1.14. No trends were seen for any of the measured matrices.

Methylmercury exposure

Residents of Minamata City, Japan were exposed to methylmercury pollution released from a chemical plant in the 1950s. Local fishermen had the highest occupational exposure and local residents were exposed through consumption of contaminated fish. There were 2,200 residents with what was recognized as the 'Minamata disease' who experienced symptoms including neurological deficits

following exposure. From birth record data, Sakamoto and colleagues (51) determined the sex ratio of 20,487 offspring born in Minamata City during 1950–1969. During the most severe years of the disease (1955–1959), there was a low sex ratio in Minamata City ($SR = 0.97$) and Minamata Bay ($SR = 0.85$). For the Minamata diseased patients, there was a low sex ratio for offspring where only the mother was a patient ($SR = 0.65$) and both parents were patients ($SR = 0.63$), but not where only the father was a patient ($SR = 1.06$). The lowest sex ratio was seen for the offspring of the highly exposed fishermen ($SR = 0.62$).

Occupational exposure from multiple metals

Milham (52) published a brief report on aluminum industry workers from Washington State. In particular, researchers were interested in whether the low sex ratio found for offspring of carbon setters would be similar to the sex ratio of offspring born to any aluminum worker as determined by the father's occupation on birth records from 1980 to 1990. Carbon setters were considered to be most highly exposed to air pollutants, heat, and strong magnetic fields. Researchers did not find a low sex ratio in the offspring of any aluminum workers ($SR = 1.05$) as they did for carbon setters ($SR = 0.62$), which was significantly different from the general population sex ratio of 1.05.

In a brief letter, Figa-Talamanca and Petrelli (53) reported the sex ratio of offspring born to Italian mint workers exposed to chromium and nickel. Workers were classified by job titles, and there appeared to be a trend of lower sex ratio with increasing exposure. The sex ratio in the offspring of the highly exposed founders was 0.50 and the sex ratio in the non-exposed administrative workers was 1.40. However, even for these highly exposed founders, blood nickel levels were reportedly near the reference value.

In a Danish cohort of welders, Bonde and researchers (54) ascertained self-reported paternal welding exposure. Welders were known to be exposed to high levels of hexavalent chromium and nickel in stainless steel. There was no difference in the sex ratio of offspring to stainless steel welding workers ($SR = 1.13$) or mild steel welding workers ($SR = 1.05$) compared to non-exposed offspring ($SR = 0.98$).

Residential exposure from multiple metals

Four population-based studies of residents presumed to be exposed to various metals reported significant increases in the sex ratio of offspring born to residents in areas of Australia (55), Scotland (56, 57), and Germany (58). A fifth study (59), reported a non-significant increase in a Russian town. These studies lacked detailed exposure assessments.

The limitations present in the metal exposure studies include exposure misclassification, temporality issues, and small sample sizes. Of the 13 studies, only three (45, 50, 53) had an individual measure of exposure. In the Jarrell et al. study (50), the median maternal blood Pb was $7.3 \mu\text{g/dL}$, which was higher than the general US population around the same time ($1.7 \mu\text{g/dL}$) (60). Blood levels in the Simonsen et al. report (45) were much higher, with a median of $38.8 \mu\text{g/dL}$ in Danish battery workers and $33.0 \mu\text{g/dL}$ in men with other occupational exposures. The blood nickel levels of workers in the Figa-Talamanca and Petrelli report (53) were around $0.5 \mu\text{g/dL}$, the reference value. In the occupational studies, there is likely considerable heterogeneity of exposures to professional drivers (46), as well as to filling station (47), aluminum industry (52), welding (54), mint (53), and battery workers (45). Temporal details such as when the offspring births occurred in relation to the fathers' exposure were not specified or were unclear in several studies (46, 47, 52, 53), making it difficult to evaluate their results.

There appears to be limited evidence for a decrease in the sex ratio for paternal occupational exposure to specific metals, lead or methylmercury (Table 1). There is insufficient evidence for other metal exposures, mainly due to limited exposure assessments.

Non-ionizing radiation

Concern about possible adverse reproductive health effects of exposure to non-ionizing radiation has prompted a relatively small body of literature on non-ionizing electromagnetic field exposures and the sex ratio (reviewed in Shaw and Croen (61)). There was a decrease in the sex ratio found in the three studies of male workers exposed to high-voltage electricity (62–64). The lowest sex ratio was a case series reported in a letter of 62 offspring born to 18 high-voltage power station workers in Baghdad ($SR = 0.15$) (64). The other two studies included workers from power plants in Sweden. Nordström and colleagues (63) reported a sex ratio of 0.92 in switchyard workers (400 kV) and a sex ratio of 1.16 in a referent group of workers. Knave and colleagues (62) found an overall sex ratio of 0.93 in substation workers (400 kV) and a sex ratio of 1.27 in low voltage distribution control workers (220/380 V). When considering only the offspring born after exposure, the sex ratio in the substation workers was even lower (substation workers $SR = 0.55$; distribution workers $SR = 1.11$) (62).

In workers exposed to extremely low-frequency electromagnetic fields, Irgens and researchers (65) found a slight decrease in the sex ratio for offspring to workers in smelter industries in Norway ($SR = 0.99$) compared to unexposed workers ($SR = 1.06$). Saadat (66) reported a higher sex ratio in power linesman exposed to electromagnetic fields

in Shiraz (SR = 1.24) compared to general population controls (SR = 1.04).

There have been inconsistent findings reported for the sex ratio among offspring to workers exposed to radio-frequency fields. Mjoen and colleagues (67) found no difference in the sex ratio of offspring born to what they defined as 'probably exposed' fathers (SR = 1.05). Baste and colleagues (68) found a decrease in the sex ratio for very high exposure and high-frequency aerials work (closer than 10 m: very high exposed, SR = 0.91) compared to the non-exposed (SR = 1.09) and a significant linear trend of lower sex ratios and higher degrees of exposure.

For maternal exposures, there are two studies of physiotherapists (69, 70). Of 229 Danish physiotherapists, the Larsen et al. study (69) found a low sex ratio among the offspring of exposed physiotherapists (SR = 0.42) compared to non-exposed physiotherapists (SR = 1.51). Guberman and colleagues (70) attempted to replicate the findings of Larsen et al. (69) but did not find an effect in the sex ratio of offspring to 1030 Swiss physiotherapists (exposed SR = 1.07; unexposed SR = 1.01). The one study of maternal exposure to extremely low-frequency electromagnetic fields found significant decreases in the sex ratio for women working in the aluminum (SR = 0.59) and smelter industries (SR = 0.82) (65).

In summary, there is limited evidence for a decrease in the sex ratio as a result of paternal exposure to high-voltage electricity (Table 1). The variability in the findings may be explained by the heterogeneity and poor characterization of exposure, and possibly inappropriate consideration of births that occurred prior to exposure. Several studies used a crude assessment of occupational exposure from employment records, census data or birth registries, where the length of employment was vague or not available.

Ionizing radiation

Treatment for childhood cancers

Several recent studies have focused on whether radiation treatment for childhood cancer might cause lasting damage to the germ cells, altering the sex ratio of survivors' offspring years later. The results thus far have been reassuring, with only limited evidence for a decrease in sex ratio after paternal exposure (Table 1).

Hawkins (71) found low sex ratios in births to cancer survivors who had been treated with radiotherapy or an alkylating agent as children (exposed fathers SR = 0.79; exposed mothers SR = 0.86). Byrne and colleagues (72) found normal sex ratios overall, though they did find a somewhat lower than normal sex ratio of 0.84 in offspring of female survivors exposed to potentially mutagenic forms of therapy (radiotherapy below the diaphragm and above the knees or chemotherapy with an alkylating agent), but this subgroup of women was

small. Reulen and colleagues (73) also found little effect in offspring to patients in the British Childhood Cancer Survivor Study who had been treated with radiation therapy (male survivors SR = 0.95; female survivors SR = 1.09), which was not different than the 1.05 sex ratio in the general population. In a nationwide cohort in Denmark, Winther and colleagues (74) found a decrease in the sex ratio of offspring born to male survivors with radiation exposure (SR = 0.96), but not for female survivors (SR = 1.07). The age at cancer diagnosis differed by cohort—before age 21 in the Green et al. study (75), before age 15 in Hawkins (71), and before age 20 in Byrne et al. (72) and Winther et al. (74). Green and researchers (75) reported a significantly lower sex ratio in offspring fathered by men in the Childhood Cancer Survivor study (underwent radiotherapy SR = 0.88; no radiotherapy SR = 1.13).

Occupational ionizing radiation

Studies of the sex ratio among those occupationally exposed to ionizing radiation have yielded conflicting and inconclusive results (Table 1). In a cross-sectional study of births to US radiologists, Macht and Lawrence (76) found a sex ratio of 1.03 in 4,127 exposed births, which was not different from 3,390 unexposed births (SR = 1.09). Kitabatake (77) found a higher sex ratio among offspring of Japanese radiologists and X-ray technicians, but had a sample size of only 246 births to exposed men (exposed, SR = 1.14; referent group, SR = 1.04). Tanaka and Ohkura (78) found similar results in their study of radiological technicians in Japan, with a sex ratio of 1.25 for offspring born after the father was exposed, compared to the referent Japanese national sex ratio of 1.05.

Hama and colleagues (79) found a sex ratio of 0.94 in 1,015 births to irradiated men, and 0.53 in a subset of 87 births to the men who received the highest doses. They were the only researchers who were able to use dosimetry to verify exposure, but still had to rely on recall in some cases because radiologists did not always wear the film badges designed to measure radiation dose. Zadeh and Briggs (80) similarly found a lower sex ratio of 0.89 in their study of births to male orthopedic surgeons in Britain, who are routinely exposed to X-rays.

Dickinson and colleagues (81) found a higher sex ratio in men exposed to ionizing radiation at the Sellafield nuclear plant in Cumbria, England. The sex ratio among offspring of men employed at Sellafield at any time was 1.09, compared to a referent sex ratio of 1.06 in the Cumbria region. The sex ratio was even higher (1.40) in the 345 offspring whose fathers' exposures were estimated from annual dose summaries and who had reportedly received more than 10 mSv of external radiation in the 3 months before conception. However, Maconochie and colleagues (82) did not find an association between exposure and the sex ratio in a larger study

of more than 46,000 workers in the UK nuclear industry between 1937 and 1996. The researchers estimated cumulative lifetime pre-conceptual doses from the parents' individual dosimetry records. The sex ratio of offspring born to male workers was 1.06, exactly the same as in the general population. The sex ratio of 1.03 in offspring to female workers also did not differ from expected.

Finally, a study of laboratory workers in Sweden found paternal exposure to radioactive isotopes associated with a marginal increase in the sex ratio. Magnusson and researchers (83) found a relative risk of 1.2 (95% CI: 1.0–1.4) for the sex ratio in men who had worked with isotopes pre or peri-conceptually, according to employment records.

Nuclear ionizing radiation

Studies on radioactive fallout have yielded insufficient evidence for an effect on the sex ratio (Table 1). Schull and Neel (84) analyzed births to survivors of the atomic bombings in Hiroshima and Nagasaki and concluded in a 1958 paper that there may have been a change in sex ratio. However, Schull and Neel (85) reconsidered their initial findings in a 1966 paper, after analyzing additional births and finding no significant association with either maternal or paternal exposure.

Two sets of researchers conducted population-based studies after the meltdown at the Chernobyl nuclear power plant, which released a plume of fallout over much of Europe. Peterka and colleagues (86) analyzed 50 years of birth records in the Czech Republic, finding that the number of males outnumbered females in 599 out of 600 months. In November 1986, only 6 months after the accident, did the sex ratio drop below one (SR for November 1986 = 0.97, $p < 0.05$ for decrease in number of boys). Scherb and Voigt (87) analyzed births in eight neighboring countries and found the opposite effect—an extremely small but significant jump in the sex ratio in 1987 (odds ratio for a male birth: 1.0047; 95% CI: 1.0013–1.0081; $p = 0.0061$).

Mudie and colleagues (88), however, found a normal sex ratio of 1.07 in a study of 11,464 births to mothers exposed to above-ground nuclear tests conducted by the former Soviet Union in Kazakhstan in 1949–1956.

Other ionizing radiation

The historical use of radiation to treat women with infertility raised concerns about possible long-term damage to the oocytes. Between 1924 and 1958, a New York radiologist administered a tissue dose of 90r to the pituitary and 60–65r to each ovary of more than 700 patients who were unable to conceive. A total of 308 women eventually gave birth to 540 offspring with a sex ratio of 0.96 (89), which was not different from expected.

Saadat (90) also found a typical sex ratio at birth in an Iranian town with naturally occurring levels of ionizing radiation estimated at 260 mSv annually (SR = 1.04; unexposed urban areas in the same province SR = 1.04).

In summary, there is little consistent evidence that ionizing radiation affects the sex ratio. There is limited evidence that treatment for childhood cancer causes long-term changes in the sex ratio after paternal exposure and, if there is an effect, it is likely to be small. It is difficult to draw solid conclusions from the nuclear studies. Researchers designing future occupational studies should rely on dosimetry records rather than workers' recall.

G-forces

Speculation among military pilots that they tend to father girls led to five studies of the secondary sex ratio, of which three found a significantly higher proportion of daughters born to pilots who were exposed to high g-forces. Jet fighter pilots are often exposed to rapid acceleration that can cause disorientation, blackouts, and temporary loss of peripheral vision. Other possible exposures include ionizing radiation at high altitudes.

Snyder (91) was the only researcher who used detailed military flight logs to calculate the number of flight hours for each pilot, and the only author to focus on flights during the critical window of spermatogenesis. Japanese and American men who flew fighter planes in the 3 months prior to conception fathered 59 girls and 35 boys (fighter pilots SR = 0.59; US population SR = 1.05; $p < 0.01$). Little and colleagues (92) also found a lower sex ratio in births to 44 US tactical pilots, as well as to 18 US astronauts, who experience similar g-forces during takeoff of the shuttle (tactical pilots and astronauts, $n = 166$ offspring, SR = 0.66; military officers not exposed to high g-forces, $n = 582$ offspring, SR = 1.03). Irgens and Irgens (93) similarly found a sex ratio of 0.59 in a small sample of 65 offspring born to military pilots in Norway. The fathers' occupations were identified using census records taken every 10 years, making it unclear whether the fathers were exposed in the months prior to conception.

Goerres and Gerbert (94) analyzed 1,613 births to jet, cargo, and helicopter pilots in Germany. A higher proportion of boys were born to jet pilots who had amassed fewer than 1,000 hours of cumulative flying time ($n = 471$ offspring, SR = 1.31), while more girls were born to those flying between 1,000 and 2,000 hours ($n = 264$ offspring, SR = 0.73). However, there was no trend of decreasing sex ratio with flying time above 2,000 hours, and this isolated finding may have been due to chance. Fujita and colleagues (95) attempted to replicate Goerres and Gerbert's (94) results in their study of Japanese fighter pilots. The researchers did find more girls born to fighter pilots overall, but the study size was small and the difference was not significant ($n = 90$ offspring, SR = 0.91; Japanese population SR = 1.06).

While there appears to be limited evidence to suggest a decrease in the sex ratio of offspring and paternal g-force exposures, larger sample sizes and studies focusing on paternal exposures in the 3 months prior to conception are needed to establish whether exposure to g-forces is associated with a decrease in the sex ratio in offspring of military pilots.

Boron

Boron, an element mined for uses including detergents, fire retardants, and pesticides has been associated with decreases in sperm production and histologic changes to the testes in rats (96). However, there is little evidence that boron affects fertility at typical human doses.

Five studies on boron have reported sex ratios slightly below the expected sex ratio. Sayli (97) found a slightly lower sex ratio in a study of three generations of offspring born to families living near a large borate deposit in Turkey. Some of the families lived near open or underground mines; others lived farther away but worked in the mines. Among the families' 2,438 offspring, the sex ratio was 0.99. In an occupational study in 2003, Sayli (98) found no fertility problems in borate plant workers and a sex ratio of 1.01 in their 307 offspring.

Whorton and colleagues (99) found a sex ratio of 0.90 in offspring born to 542 male workers at a borax plant in California. Boron did not appear to impair overall fertility; the men had more offspring at least 9 months after they began work at the plant than the US population as a whole. A study of boron mining and processing workers in China (5) found a sex ratio of 1.10 in births to 936 exposed workers, compared to 1.19 in a control group of 251 men who lived in a nearby village.

Yazbeck and colleagues (100) found a sex ratio of 1.04 in a sample of French municipalities with drinking water boron concentrations greater than 0.30 mg/L, compared with 1.05 in areas with drinking water that contained only trace amounts of boron. Individual exposures, however, could not be measured and about half of the residents sampled said they drink only mineral water. The findings are limited with respect to boron exposures and the sex ratio. Additional studies with individual exposure measurements are needed to determine whether boron is associated with a lower or higher than expected sex ratio.

Other exposures studied

There is limited evidence that other occupational and environmental exposures may affect the sex ratio. Table 2 gives the exposures with three or fewer studies. Additional research is needed to determine whether any of these exposures are associated with a lower or higher sex ratio.

Biological mechanisms

The periods of intense cellular division during spermatogenesis and early fetal development are particularly

sensitive to environmental threats. An altered sex ratio at birth could suggest an environment more favorable to the development or survival of X- or Y-bearing sperm or preferential survival of male or female embryos. From our review of the literature, we found little evidence that pollutants other than PCBs cause an increase in male births. Many studies of other environmental and occupational hazards, however, have shown fewer male offspring born to men exposed to potentially toxic chemicals.

Although the exact mechanism is unclear, some animal studies have linked the production of sons with fertility. In a study of red deer, Gomendio and researchers (101) found that male animals with higher fertility produced more male offspring. More males were similarly born to deer with a higher percentage of morphologically normal spermatozoa. Studies in humans have similarly shown that factors that reduce male fertility, such as higher scrotal temperatures (102) and older paternal age (8), are also associated with a reduction in the proportion of male births.

Lead has been shown to cause male-mediated reproductive effects. Occupational studies have associated blood lead levels to reductions in sperm count, sperm motility, and abnormal sperm morphology (reviewed in Wirth and Mijal (103)). Similarly, pesticide exposures have been associated with deficits in male reproductive parameters. The potential mechanisms behind other exposures, such as non-ionizing radiation or g-forces and the sex ratio are less clear.

There are several mechanisms by which environmental or occupational hazards might reduce the sex ratio in men. Paternal exposures could lower the proportion of Y-bearing spermatozoa in the ejaculate or reduce the ability of Y-bearing sperm to reach or fertilize the oocyte. One recent study found that mice with deletions in the Y-chromosome produce a higher proportion of morphologically abnormal spermatozoa, resulting in more female offspring (104).

Some studies have linked particular exposures with a reduction in the ratio of Y:X spermatozoa. After a study in China showed a lower proportion of sons born to workers in the boron industry, Robbins and researchers (105) found a decreased Y:X sperm ratio in 63 boron workers compared to controls ($p < 0.0001$). In a study of persistent organic pollutants, Tiido and researchers (106) found an interesting interaction. Men from Sweden and Greenland with higher serum levels of persistent organohalogen pollutants, including PCB-153 and *p,p'*DDE, had higher proportions of Y-bearing sperm; the opposite was true for Polish men with higher exposures. This could be due to the genetic or environmental differences among the two populations.

James (107) has hypothesized that parental hormone levels around the time of conception may be partially responsible for changes in the sex ratio. Jongbloet (108)

Table 2. Exposures with three or fewer studies available

Study	<i>n</i> births to exposed	Exposure	Route	Sex ratio	95% CI	<i>p</i> internal referent	<i>p</i> for expected SR*
Heacock et al. (115)	18,016	chlorophenates	paternal	1.06	1.03–1.09	—	0.88
Jakobsson and Mikoczy (116)	1,763	rubber industry workers	paternal	1.10	1.00–1.21	—	0.40
Alexopoulos et al. (117)	1,012	shipyard workers	paternal	1.02	0.90–1.15	—	0.52
Pour-Jafari (118)	759	sulfur mustard	paternal	1.34	1.16–1.54	0.02	<0.01
Volk (119)	413	submariners	paternal	1.16	0.96–1.41	0.29	0.34
Saadat and Khalili (120)	340	mountain climbers	paternal	0.99	0.80–1.22	0.66	0.57
Wyatt and Wilson (121)	157	anesthetists	paternal	0.76	0.56–1.05	0.04	0.04
Lyster (122)	130	underwater divers	paternal	0.53	0.37–0.76	<0.001	<0.001
Rylander et al. (123)	6,960	hairdressers	maternal	1.07	1.02–1.12	—	0.57
Jakobsson Mikoczy (116)	721	rubber industry workers	maternal	0.96	0.83–1.11	—	0.19
Yang et al. (124)**	464	betel quid chewing	maternal	0.95	0.79–1.14	<0.01	—
Zhu et al. (125)	—	hairdressers	maternal	1.11	—	—	—
Yang et al. (126)**	208,501	petrochemicals	both	1.09	1.08–1.10	0.003	—
Yang et al. (127)**	92,600	oil refinery	both	1.07	1.06–1.09	—	—
Vassilev et al. (128)	64,538	polycyclic organic material	both	1.03	1.01–1.05	0.67	<0.001
Yang et al. (129)**	24,882	chlorine in drinking water	both	1.08	1.06–1.11	—	—
Bhopal et al. (130)	18,305	petrochemical/steel plant	both	1.05	1.02–1.08	0.81	0.5
Revich et al. (131)	11,090	chemical plant	both	1.03	0.99–1.07	—	0.16
Saadat (132)	4,246	sulfur mustard	both	1.07	1.00–1.13	0.03	0.79
Williams et al. (133)	1,025	incinerators	both	0.90	0.80–1.02	—	0.01
Saadat et al. (134)	359	natural gas	both	1.29	1.05–1.58	0.03	0.07
Mackenzie et al. (112)	347	industrial pollution	both	0.70	0.57–0.87	<0.01	<0.001
Jakobsson and Mikoczy (116)	287	rubber industry workers	both	0.83	0.66–1.04	—	0.04
Lyster (135)	253	Great London Smog	both	0.76	—	—	0.01
Lyster (135)	222	drinking water after flood	both	0.54	—	—	<0.001
Williams et al. (136)	—	industrial pollution	both	1.07	—	<0.05	—

**p*-values calculated using a binomial test with the expected = 0.514 proportion male births.

**Yang studies in Taiwan not compared to an expected value because the sex ratio varies by year and region due to sex selection.

proposed that this could occur because Y-bearing sperm are smaller and thus better able to navigate non-optimal cervical mucous. This would imply that Y-bearing sperm may also be more likely to reach and fertilize oocytes that are overripe, which could occur more often when a couple's coital rates are infrequent due to low male testosterone. Jongbloet suggested that the ability of Y-bearing sperm to reach poor-quality oocytes could result in a disproportionate loss of XY embryos and conceptuses, and pointed to the finding of many studies that fetuses with defects often have higher sex ratios (108).

Further, Jongbloet and colleagues (109) propose that the anti-androgenic effects of dioxins may perhaps alter

sperm transit time. Dioxins and PCBs, which may alter the sex ratio through the endocrine pathway, have congeners shown to exhibit estrogenic, anti-estrogenic, or anti-androgenic activity (110). Most exposures are hypothesized to have an effect during the period of spermatogenesis before ejaculation. But two studies with small sample sizes have suggested that dioxin may have longer-term effects in men exposed in their teenage years. The Mocarelli et al. study (16) found that men in Seveso who had serum concentrations of dioxin >15 ppt and were younger than 19 at the time of the accident in 1976 fathered significantly more girls for at least 15 years. Moshhammer and Neuberger (18) then analyzed a cohort

of 157 men exposed to high concentrations of dioxin while working at a chemical plant in Austria. Male workers exposed before the age of 20 fathered significantly more girls, leading the researchers to propose that dioxin might induce cellular changes in the leydig and sertoli cells that could still affect Y-bearing sperm years later.

There is less evidence that maternal exposures around the time of conception or during early pregnancy affect the sex ratio. But only about a quarter of all fertilizations result in a live birth, and rates of implantation or survival of embryos may differ when the mother is exposed. After finding that an unusually low number of males were born 6 to 7 months after Chernobyl, Peterka and colleagues (86) hypothesized that a disproportionate number of male fetuses miscarried. The researchers proposed that radioactive iodine-131, which was present in high amounts after Chernobyl and has been associated with high miscarriage rates, may have been particularly hazardous to males between 8 and 12 weeks gestation.

New studies on toxic exposures such as cigarette smoking have suggested that gene-environment interaction may help to explain some differences across populations. Gloria-Bottini and colleagues (111) found a decrease in the sex ratio in most offspring born to smoking mothers, but an increase in a small group of newborns with an allele most common in European populations. The sample size was extremely small, however, and more studies are needed.

As Potashnik and Porath (33) proposed in their studies on workers who produced the nematocide DBCP, the sex ratio may be an indicator of male fertility. The sex ratio of offspring born to the DBCP workers fell in tandem with their sperm counts and did not rise again until years after the exposure, when some of the men began to recover sexual function. A precipitous drop in the number of male births may have served as a warning that DBCP was highly toxic to male reproduction. Not all of the exposures associated with a lower sex ratio in exposed men are known to impair fertility, however. Many of the studies on boron, for example, showed above-average fertility in exposed men.

Discussion

Limitations in study design and methodological issues make it difficult to draw firm conclusions from the existing sex ratio literature. One difficulty in the interpretation of sex ratio studies is that men and women share exposures. James has pointed out that environmental hazards, particularly those that affect endocrine hormones, may have opposite effects in men and women (14). In studies of pollutants such as PCBs, where both parents are exposed, the overall sex ratio may mask these different biologic reactions in the mother and father. Few studies are designed to consider all possible combinations of exposure: both parents exposed, neither parent

exposed, mother exposed and father unexposed, and father exposed and mother unexposed. Even in cohort studies with individual exposure assessments, it can be difficult to disentangle the effects exposure may have on men and women. In addition, many occupational studies have been limited to one gender.

One of the most critical limitations in sex ratio studies is the ecologic study design, where the exposure is often unmeasured and unclear. Residents of polluted areas are exposed to a variety of chemicals that may interact with each other or have opposite effects. For example, in the Mackenzie et al. study (112) of the Aamjiwnaang First Nation community, residents were exposed to more than a dozen pollutants from the nearby petrochemical industry, many in excess of Canadian national guidelines.

Timing of exposure is also poorly assessed in a large proportion of the sex ratio studies. In studies of paternal exposure, many required that the exposure preceded the birth, but few focused on exposures during the 3-month period of spermatogenesis prior to conception. It is also unclear whether women were exposed at any time prior to the pregnancy, specifically during the period of conception, or in early fetal development.

Another shortcoming of the literature is that many sex ratio studies are underpowered. The studies that assessed environmental exposures using biomarkers (usually serum or urine samples) had limited sample sizes that cannot reveal small shifts in the sex ratio.

Publication bias is a concern in any literature review. Dozens of authors have published null results, often as letters to the editor in response to published studies, but it is possible that significant findings are nonetheless over-represented in the literature. Departures from the expected sex ratio have typically been small, with more dramatic differences limited to studies with small sample sizes. We limited our review to published data and did not seek unpublished work to determine the extent of this possible bias.

Conclusions

There is some evidence that the endocrine disruptors, dioxin and PCBs, are associated with altered secondary sex ratio. Dioxin exposure is associated with a lower male:female sex ratio in offspring of exposed men, while PCB exposure is associated with a higher male:female sex ratio in offspring of exposed men.

There is insufficient evidence for lower or higher than expected sex ratios when the mother is exposed. Most of the studies with significant findings analyzed occupational or accidental exposures at doses much higher than would be experienced by the general population. Dioxins and PCBs, where the evidence for change in sex ratio is strongest, likely have endocrine effects (113, 114).

Recommendations

Although no longer manufactured, PCBs are persistent in the environment and will remain an important area of study. Little is currently known about the sex ratio in relation to chemicals such as bisphenol A, fluorochemical compounds including PFOA and PFOS, phthalates, or the brominated flame retardants, PBDEs. In future studies of these and other similar compounds, it may be useful to examine the sex ratio in addition to other reproductive outcomes.

Studies have more often found a decrease in the proportion of male births to exposed men. Although the current body of research is suggestive, more research is needed to establish if DBCP and other pesticides, lead, methylmercury and other metals, non-ionizing radiation, radiation treatment for childhood cancer, g-forces, or boron are associated with a lower sex ratio when the father is exposed prior to conception.

Instead of large-scale ecologic studies, which have yielded poor evidence, future research should measure individual exposure of each parent. Studies on gene-environment interaction may also help to explain the inconsistent findings that are common in the field. Wherever possible, researchers should examine sex ratio in combination with other outcomes such as sperm quality, Y:X sperm ratio, hormone levels, and time to pregnancy. Prospective studies with biomarkers to confirm exposures will likely yield the best evidence of whether environmental threats can alter the sex ratio at birth. These enhancements may help to shed light on the biological mechanism, as well as whether the sex ratio can serve as an indicator of overall reproductive capacity.

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The authors have no competing interests.

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***Michele Marcus**

Departments of Epidemiology and Environment Health
Rollins School of Public Health
Emory University
Atlanta, Georgia 30322
Tel: 404-727-8010
Email: mmarcus@emory.edu