Parental Exposure to Dioxin and Offspring Sex Ratios

I would like to respond to the comments of Jongbloet et al. (*1*) on the data of Mocarelli et al. (*2*). Mocarelli et al. (*2*) reported on the offspring sex ratios (proportions male) following the explosion at Seveso, Italy, that released 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, dioxin) into the environment. Mocarelli et al. (*2*) categorized matings into the four possible combinations by sex and exposed versus unexposed. Their analysis yielded one unequivocal result and one equivocal one: *a*) exposed men mated to unexposed women produced offspring with a a significantly low sex ratio; and *b*) exposed women mated to unexposed men produced offspring with a nonsignificantly high sex ratio.

Jongbloet et al. (*1*) explained both of these phenomena by their hypothesis of preovulatory and postovulatory overripeness, and they claimed that it is more plausible than my hormonal hypothesis (*3*). Because I had predicted that exposed men would sire an excess of daughters (*3*), my hypothesis—at least initially—seemed preferable. However, it now seems that these theories (both theirs and mine) may be premature: paternal exposure to organochlorine compounds has been reported to be followed by significant excesses of daughters (*2,4*), a nonsignificant excess of sons (*5*), and a significant excess of sons (*6*). This disarray may be potentially explained in several ways:

- The various organochlorine compounds may actually have different effects on the offspring sex ratio of exposed men. This may not be accurate because opposite effects have been reported in respect of dioxin itself.
- The organochlorine compounds may have opposite effects on exposed mothers and exposed fathers, thus suggesting the possibility of confounding. However, both Mocarelli et al. (*2*) and Karmaus et al. (*6*) assessed paternal and maternal exposures and yet reached opposite conclusions (admittedly in one case on TCDD and in the other on polychlorinated biphenyls).
- It is possible that the different exposures may have been to different congeners and/or contaminants and that these contaminants had causal effects.

Logically, Jongbloet's hypothesis and mine are not mutually exclusive: both may be applicable, either separately or simultaneously. I subscribe to the appeal of Jongbloet et al. (*1*) for more research on the effects of organochlorine compounds on mammalian offspring sex ratios, and I welcome their predictions.

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References and Notes

1. Jongbloet PH, Roeleveld N, Groenwoud HMM. Where the boys aren't: dioxin and the sex ratio. Environ Health Perspect 110:1–3 (2002).
2. Mocarelli P, Gerthoux PM, Ferrari E, Patterson DG, Kieszak SM, Brambilla P, Vincoli N, Signorini S, Tramacere P, Carreri V, et al. Paternal concentrations of dioxin and sex ratio of offspring. Lancet 355:1858–1863 (2000).
3. James WH. Re: "Total serum testosterone and gonadotropins in workers exposed to dioxin." Am J Epidemiol 141:476–477 (1995).
4. Potashnik G, Abeliovich D. Chromosomal analysis and health status of children conceived to men during or following dibromochloropropane-induced spermatogenic depression. Andrologia 17:291–296 (1985).
5. Schnorr TM, Lawson CC, Whelan EA, Dankovic DA, Deddens JA, Piacitelli LA, Reefhuis J, Sweeney MH, Connally LB, Fingerhut MA. Spontaneous abortion, sex ratio, and paternal exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Environ Health Perspect 109:1127–1132 (2001).
6. Karmaus W, Huang S, Cameron L. Parental concentrations of dichlorodiphenyl dichloroethene and polychlorinated biphenyls in Michigan fish eaters and sex ratio in offspring. J Occup Environ Med 44:8–13 (2002).

Dioxin and Offspring Sex Ratios: Jongbloet et al.'s Response

We are very pleased with James' comments on the sex ratio shifts after the dioxin disaster in Seveso (*1*) and his appreciation of our explanation of these phenomena. He mentions the disarray of results after exposure to organochlorine compounds and concludes that our and his own hormonal hypothesis "are not mutually exclusive" and that "both may be applicable, either separately or simultaneously." We like to stress, however, the added value and the parsimony of the overripeness ovopathy concept.

We agree that both hypotheses are concerned with the hormonal concentrations around the time of conception and that the antiestrogenic effects of the organochlorine compounds affect both paternal and maternal reproductive pathways. The increase of male-biased fetuses and subsequently (after having reached a critical threshold) the decrease due to loss of them, however, can only be understood by a dose–response fallacy. Nonoptimally matured oocytes—preferentially inseminated by Y-bearing spermatocytes and preferential loss of male fetuses—are supposed to be the key for elucidating this dose–response fallacy in mammals, including humans (*1,2*).This explains *a*) the mentioned disarray of varying and controversial results (either more sons or more daughters); *b*) the difficulties in reaching statistically significant results; *c*) the analogy with other high-risk conception categories in which the maturation of the oocyte is at stake (e.g., in very young and premenopausal mothers, in very short or unintendedly long interpregnancy intervals, in transitional stages between ovulatory and anovulatory seasons, etc.) (*1,2*); and *d*) the reduced quality of cumulus expansion, impaired maturation, fertilization, and embryonic development of porcine oocytes (*3*), besides the wide spectrum of reproductive disorders from menstrual disturbances, subfecundity, spontaneous abortions, stillbirths, and congenital malformations up to neurologic deficits in human progeny (*4*). This cluster of phenomena is not explained either by the prevailing theories or by James' hormonal hypothesis.

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References and Notes

1. Jongbloet PH, Roeleveld N, Groenewoud HMM. Where the boys aren't: dioxin and the sex ratio. Environ Health Perspect 110:1–3 (2002).
2. Jongbloet PH, Zielhuis GA, Groenewoud HMM, Pasker-de Jong PCM. The secular trends in male:female ratio at birth in postwar industrialized countries. Environ Health Perspect 109:749–752 (2001).
3. Campagna C, Sirard M-A, Ayotte P, Bailey JL. Impaired maturation, fertilization, and embryonic development of porcine oocytes following exposure to an environmentally relevant organochlorine mixture. Biol Reprod 65:554–560 (2001).
4. Ribas-Fitó N, Sala M, Kogevinas M, Sunyer J. Polychlorinated biphenyls (PCBs) and neurological development in children: a systematic review. J Epidemiol Community Health 55:537–546 (2001).

Mechanistic and Epidemiologic Data: When Is Enough Enough?

In the current draft of the U.S. Environmental Protection Agency's (EPA) Guidelines for Cancer Risk Assessment (*1*), animal carcinogens are considered "likely to be carcinogenic to humans" if the weight of experimental evidence indicates a mode of action (MOA) that can be assumed to be, or is known to be, relevant to humans. The wording of this guideline begs the question, "Who is assessing the relevance for humans of the experimental MOA?" Similarly, the category of "not likely to be carcinogenic to humans" requires "extensive experimental evidence showing that the only carcinogenic effects observed in animals are not considered relevant to humans" (*1*). The criteria for judging data places emphasis on "the degree

of consensus and general acceptance among scientists" (*1*). However, experience demonstrates that such consensus is rare, primarily due to the healthy tendency of scientists to present constructive challenge to the reasoning of their peers. Even when an MOA is accepted by a majority, some will still call for more data. For example, Melnick of the National Institute of Environmental Health Sciences appears to accept, albeit tentatively, the proposed MOA for the rodent hepatocarcinogenicity of the peroxisome proliferators, but he also suggested that this knowledge is inadequate to judge human relevance (*2*). Thus, as long as some investigators assume that the rodent cancer data for a chemical are relevant to humans, implementation of the guidelines would require a subjective decision by the agency. This issue is also illustrated by the near, but imperfect, "consensus" on the α2μ-globulin mechanism of male rat renal carcinogenesis induced by *d*-limonene and its lack of relevance for humans. The extent of the data set addressing rodent MOA and human relevance underpins the view of many, including the International Agency for Research on Cancer (IARC), that the MOA for *d*-limonene is "through an α2μ-globulin associated response which is not relevant to humans" (*3*–*5*). Nonetheless, in this context, some still call for the unobtainable goal of "incontrovertible proof [in] … our rightful quest to identify mechanisms of chemical carcinogenesis" (*6*). The question is "When does negative data constitute incontrovertible proof?"

Similar issues are raised by the U.S. EPA requirement for "extensive human epidemiology that demonstrates lack of carcinogenic effect" when considering the category "not likely to be carcinogenic to humans" (*1*). Practical implementation of this guideline would require the registrant to prove a negative result with respect to epidemiology data. It may be that such language is intended to allow the U.S. EPA freedom of interpretation, but this language seems to imply rigidity rather than adaptability. This is in contrast to the implementation of the Bradford Hill criteria, cited by the U.S. EPA (*1*), which were devised to assess the strength of an association between exposure and cancer in humans, not to prove a negative result. When no association is found in relevant, adequately powered, and well-conducted epidemiologic studies, the only valid conclusion is that there is no effect. A lack of definition of the required nature and power of epidemiology studies opens the door to individuals who will always call for more data before the issue can be resolved. An example of this is the hypolipidemic drug and rodent hepatocarcinogen clofibrate. IARC (*7*) concluded that "the mechanism of liver carcinogenesis in clofibrate treated rats would not be operative in humans." This was based on the observation that clofibrate causes peroxisome proliferation and cell proliferation in rodent but not human hepatocytes and on the results of extensive epidemiologic studies (*7*), particularly the World Health Organization trial on clofibrate including 208,000 man-years of observation (*8,9*). Further, in a meta-analysis of the results from six clinical trials on clofibrate, Law et al. (*10*) found no excess cancer mortality. Despite this weight of evidence, Melnick (*2*) has suggested that these epidemiologic data are "insufficient to permit a definite conclusion on the presence or absence of a causal association between exposure to lipid lowering drugs and cancer." The lack of definition of the required nature and power of epidemiology studies would require individuals in the U.S. EPA to either set their own standards or to use default procedures in order to implement the guideline. This is in marked contrast to IARC, where clear guidance is given concerning the types of epidemiology studies that can be considered, the required quality of those studies, and the criteria for causality. Without refinement, there remains the possibility that the U.S. EPA might dismiss from the hazard assessment process epidemiologic data that fail to identify an association between chemical exposure and cancer, even when these studies show sufficient power to detect a cancer increase. A more meaningful use of such data would be to conclude that there is no evidence of carcinogenicity in humans based on epidemiology studies with a given resolving power.

To provide impetus to continuing mechanistic and epidemiologic studies, regulatory agencies need to give precise guidance on the extent of data required to influence the categorization of a chemical.

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References and Notes

1. U.S. EPA. Guidelines for Carcinogen Risk Assessment. Draft. Washington, DC:U.S. Environmental Protection Agency, 1999. Available: http://www.epa.gov/ncea/raf/pdfs/cancer_gls.pdf [cited 12 July 2002].
2. Melnick R. Peroxisome proliferators: response. Environ Health Perspect 109:A463–A464 (2001).
3. Whysner J, Williams GM. *d*-Limonene mechanistic data and risk assessment: absolute species-specific cytotoxicity, enhanced cell proliferation, and tumor promotion. Pharmacol Ther 71:127–136. (1996).
4. Hard GC, Whysner J. Risk assessment of *d*-limonene: an example of male rat-specific renal tumorigens. Criti Rev Toxicol 24:231–254 (1994).
5. IARC. Some Chemicals that Cause Tumours of the Kidney or Urinary Bladder in Rodents and Some Other Substances. IARC Monogr Eval Carcinog Risks Hum 73 (1999).
6. Huff J. Response: α2μ-globulin nephropathy, posed mechanisms, and white ravens. Environ Health Perspect 104:1264–1267 (1996).
7. IARC. Clofibrate. IARC Monogr Eval Carcinog Risks Hum 66:391–426 (1996).
8. WHO cooperative trial on primary prevention of ischaemic heart disease using clofibrate to lower serum cholesterol: mortality follow-up. Lancet 2:379–385 (1980).
9. WHO cooperative trial on primary prevention of ischaemic heart disease with clofibrate to lower serum cholesterol: final mortality follow-up. Report of the Committee of Principal Investigators. Lancet 2:600–604 (1984).
10. Law M, Thompson S, Wald N. Assessing possible hazards of reducing serum cholesterol. Br J Med 308:373–379 (1994).

Duration of Breast-Feeding and PBBs

Thomas et al. (*1*) report that polybrominated biphenyl (PBB) exposure has no effect on duration of lactation. Their data come from interviews in 1997 or later with women who were exposed to PBBs in the mid-1970s and who had a child since then. In a study contemporary with the exposure, however, Weil (*2*) found that unexposed women breast-fed about twice as long as exposed women (30 weeks vs. 15 weeks). This might have been because of the warnings about breast-feeding with PBB-contaminated milk (*3*), which we recall as being more ominous than reported by Thomas (*1*), or because of some biological effect of PBB. In any event, the presence of the finding then and its absence now causes us to speculate that there may be poor recall or other reasons why duration of lactation does not work well as a recalled outcome. Consistent with that speculation, cigarette smoking by the mother (*4*) and infant's gestional age < 37 weeks (*5*), for example, are usually associated with early weaning, but the hazard ratios for these characteristics in the report by Thomas et al. (*1*) are small and nonsignificant. It is disappointing to think that PBB did interfere with lactation but that the effect cannot be detected in data about lacation recalled years later.

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References and Notes

1. Thomas AR, Marcus M, Zhang RH, Blanck HM, Tolbert PE, Hertzberg V, Henderson AK, Rubin C. Breast-feeding among women exposed to polybrominated biphenyls in Michigan. Environ Health Perspect 109:1133–1137 (2001).
2. Weil WB, Spencer M, Benjamin D, Seagull E. The effect

of polybrominated biphenyl on infants and young children. J Pediatr 98:47–51 (1981).
3. Finberg. PBBs: the ladies' milk is not for burning. J Pediatr 90:511–512 (1977).
4. Counsilman JJ, MacKay E. Cigarette smoking by pregnant women with particular reference to their past and subsequent breast feeding behavior. Aust N Z J Obstet Gynaecol 101:25–29 (1985).
5. Bereczkei T. Maternal trade-off in treating high risk children. Evol Hum Behav 22–197–212 (2001).

Breast-Feeding and PBBs: Response to Rogan and Weil

We thank Rogan and Weil for their comments. In our analyses we examined breast-feeding among infants born between 1973 and 1998. We did not find an association between PBB exposure and a decision to breast-feed or breast-feeding duration. Because the proportion of women who chose to breast-feed their infants increased during this 25-year period, we adjusted for year of birth in 5-year intervals. This notation was inadvertently left out of the footnote accompanying Table 6 of our paper (*1*). An interaction term between year of birth and PBB exposure did not contribute to any of the multivariate models of breast-feeding.

Prompted by the comments of Rogan and Weil we have now examined the possibility of an interaction between birth cohort, PBB exposure, and breast-feeding more closely. Table 1 shows the proportion of women who chose to breast-feed by PBB exposure stratified by 5-year birth cohorts. During the first 5 years after exposure (1973–1978) we found a suggestion that women with higher PBB exposure were less likely to breast-feed their infants than women with lower exposure, consistent with the findings of Weil et al. (*2*). However, the number of infants in this stratum was small and the trend was not statistically significant (p = 0.35). Multivariate analyses (adjusting for maternal education and prior history of breast-feeding) yielded similar, nonsignificant differences in breast-feeding by PBB exposure for births from 1973 to 1978. Among the women who chose to breast-feed, there were no suggested differences in duration of breast-feeding by PBB exposure for any of the 5-year birth cohorts.

In summary, we found some suggestion of an association between PBB exposure and breast-feeding during the years immediately after the PBB incident; however, the association was weak and nonsignificant in contrast to the strong association found by Weil et al. (*2*). Weil et al. (*2*) found that 42% of PBB exposed women breast-fed their infants compared to 85% of control women. In their letter, Rogan and Weil suggest that inaccurate recall of breast-feeding may have led us to underestimate the difference in breast-feeding between the PBB-exposed women and unexposed women. This is a valid concern. Recall of breast-feeding behavior is likely to decrease in accuracy as the recall interval lengthens. However, we believe that differences in recall play a small role in the differences between our conclusions and those of Weil et al. (*2*). In fact, our data (*1*) and the data of Weil et al. (*2*) for breast-feeding among PBB-exposed women are remarkably similar. We found that 47% of women (27/57) enrolled in the PBB cohort (lived on quarantined farms or obtained food from quarantined farms) reported breast-feeding their infants born between 1973 and 1978. Weil et al. (*2*) found that 42% of women (14/33) who lived on quarantined farms reported breast-feeding their infants born between 1973 and 1975. These figures are also consistent with national data collected during the same period. The National Survey of Family Growth (*3*) found that 30% of women in the United States breast-fed their infants born between 1972 and 1974. That proportion increased to 48% by 1978–1980 (*3*). The Ross Laboratories Mother Survey (*4*) found breast-feeding rates of 29% in 1973 and 47% in 1978.

The major difference between Weil et al.'s study (*2*) and our own (*1*) is the choice of comparison group. Weil et al. (*2*) compared the PBB-exposed women to a control group of women obtained from two sources: "… families in which the mother's milk had been tested for PBB and had been found negative …" and "… families who were identified by the school system as having moved to Michigan since 1975." Eighty-five percent of women in this comparison group breast-fed their infants, more than double the proportion among PBB-exposed women in Michigan and more than double the proportion among U.S. women interviewed for the National Survey of Family Growth (*3*). It is possible that women who had a breast milk sample tested for PBBs had already decided to breast-feed their infants. In our study (*1*) we compared breast-feeding among women in the PBB cohort categorized by their estimated serum PBB at the time of the pregnancy.

Table 1. Number and percent of infants breast-fed by year of birth and PBB exposure status of mother in the Michigan Female Health Study.

Year of birth	No.	PBB exposure		
		Low (≤ 1 ppb)	Medium (1–7 ppb)	High (> 7 ppb)
July 1973–June 1978	57	11/20 (55)	13/29 (45)	3/8 (38)
July 1978–June 1983	137	42/63 (67)	38/59 (64)	10/15 (67)
July 1983–June 1988	114	48/69 (70)	25/38 (66)	6/7 (86)
July 1988–June 1993	96	50/72 (69)	7/13 (54)	6/11 (55)
July 1993–June 1998	42	26/34 (76)	4/4 (100)	4/4 (100)

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References and Notes

1. Thomas AR, Marcus M, Zhang RH, Blanck HM, Tolbert PE, Hertzberg V, Henderson AK, Rubin C. Breast-feeding among women exposed to polybrominated biphenyls in Michigan. Environ Health Perspect 109:1133–1137 (2001).
2. Weil WB, Spencer M, Benjamin D, Seagull E. The effect of polybrominated biphenyl on infants and young children. J Pediatr 98:47–51 (1981).
3. CDC, NCHS, Division of Vital Statistics. Data from the National Survey of Family Growth, Cycle 4 1988.
4. Martinez GA, Nalezienski JP. The recent trend in breast-feeding. Pediatrics 64:686–692 (1979).

Chevron v. Echazabal: A Sobering Decision for Environmental Health Research

A recent Supreme Court decision (*Chevron v. Echazabal*) may have important implications for environmental health research (*1*). Risk-factor research has made important contributions to workplace health and safety. Systematic evaluation of the impact of chemical and physical agents on disease occurrence has provided information for the development of policies for controlling injury and disease. Research has focused predominantly on the impact of external risk factors on workers. With the advancement of molecular genetic methods, researchers have begun to identify individual risk factors believed to affect the occurrence of disease. Considerable attention has been given to identifying biological markers—markers of susceptibility, exposure, or effect—that enable better

characterization of disease risk resulting from exposure. Studies investigating gene–environment interactions have identified DNA markers (e.g., polymorphisms in metabolic enzymes and allelic variation associated with hypersensitivity) associated with elevated risk for occupational disease.

In *Chevron v. Echazabal,* the court addressed issues central to the Americans with Disabilities Act (ADA). The ADA is cited by some commentators as offering individuals protection from genetic discrimination (*2,3*). Others have questioned whether regulations promulgated under the ADA by the Equal Employment Opportunity Commission offer such protection (*4,5*). The recent decision addresses the case of a refinery worker who was denied employment due to chronic liver disease, which was eventually identified as hepatitis C. Chevron sought to exclude the individual based on the rationale that his liver function was impaired and would be subject to further damage if he experienced chemical exposures characteristic of refinery work. Conceptually, a preplacement examination using a liver function assay resulted in the identification of a biological marker that the employer interpreted to suggest a heightened susceptibility to disability from workplace exposure.

At the heart of this ruling is the court's interpretation of the direct threat provision of the ADA. A direct threat is defined as a significant risk of substantial harm that cannot be eliminated by reasonable accommodation (*6*). An individual may be refused employment if a direct threat can be established. Historically, there has been ambiguity over the scope of the direct threat defense (*5*). In a previous ruling [*Echazabal v. Chevron* (*7*)], the Ninth Circuit Court held that the direct threat defense was not available to Chevron because Echazabal only presented a risk to himself. The court reasoned that a direct threat only applies when the individual's condition poses a direct threat to others. In other words, the circuit court affirmed the notion of health as a discretionary right in which the individual may chose to assume certain risks so long at they do not have the potential to harm others. The recent Supreme Court decision rejects this reasoning and reverses the circuit court's judgment. Individuals who pose a risk exclusively to themselves may be excluded from a job as long the employer relies on reasonable medical judgment and accounts for the duration of the risk and the nature, severity, likelihood, and imminence of the potential harm (*6*).

In this example, Chevron produced evidence identifying a severe disease in a prospective employee and concluded that Echazabal's liver function was subject to further damage under job conditions in the refinery. Conceptually, Chevron based its position, and the court concurred unanimously, on the identification of biological evidence of clinical disease. Basing workplace exclusion on evidence of clinical disease is substantively different from the identification of DNA markers associated with elevated risk for occupational illness, and perhaps the court would recognize such a difference and rule differently in the later example. However, the difference between a DNA marker of disease and susceptibility is not always clear. It is conceivable that if the DNA marker was sufficiently predictive of an individual's risk of a severe disease, then the basis for a direct threat exclusion may exist (*8*). Although this scenario is speculative, the Supreme Court has unanimously stated that a direct threat to self may serve as the basis for workplace exclusion.

This is a sobering decision for researchers involved in risk factor research, some of whom have articulated the belief that assumption of risk is a discretionary right of workers. Researchers and institutional review boards should be mindful of this decision when considering future research into individual risk factors, particularly for occupational disease.

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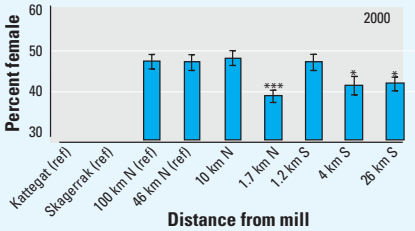
References and Notes

1. Chevron U.S.A. Inc. *v.* Echzabal. Case No. 00-1406, U.S. Supreme Court, Washington, DC, 2002.
2. Natowicz MR, Alper JK, Alper JS. Genetic discrimination and the law. Am J Hum Genet 50(3):465–475 (1992).
3. Miller PS. Genetic discrimination in the workplace. J Law Med Ethics 26(3):189–197 (1998).
4. Holtzman NA, Rothstein M. Reply to Natowicz et al. [Letter] Am J Hum Genet 51:897 (1992).
5. Rothstein MA. Genetics and the Work Force of the Next Hundred Years. Columbia Business Law Review (3):371-402 (2000).
6. Equal Employment Opportunity Commission. Regulations to Implement the Equal Employment Provisions of the Americans with Disabilities Act. 29CFR1630.2(r) (2001).
7. Echazabal *v.* Chevron U.S.A. Inc. Case No. 98-55551, U.S. Court of Appeals for the Ninth Circuit, Pasadena, CA, 2000.
8. Rothstein M. Personal communication.

Corrections

In Figure 1 of the paper by Larsson et al. [*EHP* 110:739–742 (2002)], the embryonic sex ratios of eelpout broods (mean ± SEM) for year 2000 were incorrect. The corrected figure appears below. Values for 1997–1999 were correct.



In "Cadmium and Lead in Blood in Relation to Low Bone Mineral Density and Tubular Proteinuria" by Alfvén et al. [*EHP* 110:699–702 (2002)], the values for smoking in Table 2 and several of the 95% confidence intervals in Table 3 were incorrect. The corrected tables appear below. *EHP* regrets the errors.

Table 2. Multiple linear regression analysis for log transformed protein HC (mg/mmol creatinine) as a function of age, blood-cadmium, blood-lead, and smoking.

Characteristics	Men[a] (*n* = 460)		Women[b] (*n* = 521)	
	Regression coefficient	95% CI	Regression coefficient	95% CI
Age (years)	0.023	0.019–0.028	0.017	0.013–0.020
Blood Cd (nmol/L)	0.016	0.0099–0.023	0.015	0.0049–0.025
Blood Pb (μmol/L)	0.015	−0.80–0.83	−0.19	−0.99–0.60
Smoking (never or former/current)	−0.042	−0.18–0.096	0.028	−0.090–0.15

[a]R^2 = 0.26. [b]R^2 = 0.17.

Table 3. Multiple linear regression analysis of BMD for the subgroup ages 60 years and older, as a function of age, weight, blood cadmium, blood lead, and smoking.

Characteristics	Men (*n* = 172)[a]		Women (*n* = 176)[b]	
	Regression coefficient	95% CI	Regression coefficient	95% CI
Age (years)	−0.0035	−0.0058–−0.0013	−0.0055	−0.0074–−0.0035
Weight (kg)	0.0022	0.0011–0.0032	0.0026	0.0017–0.0035
Blood Cd (nmol/L)	−0.00044	−0.0012–0.00035	−0.0030	−0.0054–−0.00066
Blood Pb (μmol/L)	−0.048	−0.20–0.10	0.078	−0.057–0.21
Smoking (never or former/current)	−0.020	−0.044–0.0035	0.019	−0.0077–0.045

[a]R^2 = 0.21. [b]R^2 = 0.28.