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PAH Exposure

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We were very interested to read the article by Choi et al. (2008). The difference between maternal exposure and our own data on actual concentrations of polycyclic aromatic hydrocarbons (PAHs) in the human male fetal liver (Fowler et al. 2008) was striking. Eight of the PAH exposures measured by Choi et al. were also on our list of PAHs measured in the human fetal liver during the second trimester.

Assuming that the 48-hr samples of airborne PAH exposure used by Choi et al. (2008) truly reflect longer-term exposure more relevant to the outcomes under consideration (which is contentious because the measurements may either overestimate or underestimate true exposure), then we can approximate a comparison between the two studies. Therefore, we calculated the fold-difference between the maximal second trimester exposures (nanograms per cubic meter) reported by Choi et al. in their Table 2 and the mean male fetal liver values presented in our Table 3 [(Fowler et al. 2008), corrected to nanograms per kilogram dry weight]. We calculated values separately for fetuses from mothers who smoked cigarettes and for those who did not (Table 1). The smallest difference was 5-fold for benzo[*a*]pyrene (BaP), whereas the largest difference was 8,340-fold for benz[*a*]anthracene (BaA), in all cases representing accumulation in the fetal liver considerably above personal maternal exposure to airborne PAHs. Of course there are other sources of exposure to PAHs, such as air pollution and occupational sources, but these data very clearly suggest that large quantities of PAHs are crossing the placenta and accumulating in the fetus. Perhaps even more interesting was the very different relative proportions of these eight PAHs in the air compared with in fetal livers: BaA comprised 11% in air but 94–96% in the livers, whereas pyrene was 17% in the air but below detection in the livers. This suggests that very different proportions of PAHs are accumulating in fetal tissues and it also underscores the fundamental principle that to really understand health risks we cannot afford to ignore the actual tissue levels in favor of exposure estimates alone.

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Fowler PA, Cassie S, Rhind SM, Brewer MJ, Collinson JM, Lea RG, et al. 2008. Maternal smoking during pregnancy specifically reduces human fetal desert hedgehog gene expression during testis development. J Clin Endocrinol Metab 93:619–626.

Table 1. Maximum air PAH exposure (ng/m^3) compared with mean human male fetal liver PAH levels (ng/kg dry weight) from mothers who did and did not smoke, during the second trimester.

	PAH concentration			Relative proportion of PAH		
	Maximum air	Liver mean		Maximum air	Liver mean	
PAH	(ng/m^3)	Nonsmoker	Smoker	(ng/m^3)	Nonsmoker	Smoker
BaA	39.69	331,000	195,000	11.14	95.47	93.80
Benzo[*b*]fluoranthene	67.47	1,300	1,800	18.93	0.38	0.87
Benzo[*k*]fluoranthene	20.33	500	1,000	5.71	0.14	0.48
Benzo[*ghi*]perylene	32.26	800	200	9.14	0.23	0.10
BaP	42.23	500	200	11.85	0.14	0.09
Chrysene	31.13	11,000	9,000	8.73	3.17	4.33
Dibenzo[*a,h*]anthracene	10.76	800	200	3.02	0.24	0.09
Indeno[1,2,3-*cd*]pyrene	50.20	800	500	14.09	0.23	0.24
Pyrene	61.96	0[a]	0	17.39	0	0

[a]Below detection in human fetal livers.

PAHs: Choi et al. Respond

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We appreciate the comments of Fowler et al. In their letter, they compared the maximal maternal inhalation level of polycyclic aromatic hydrocarbons (PAHs) in Krakow, Poland (Choi et al. 2008), with the mean fetal liver dose in Aberdeen, United Kingdom (Fowler et al. 2008). The goal of this comparison seems to have been to examine whether the fetal exposure concentration following transplacental transfer of the PAHs is higher than the airborne concentration for the mother. This is an important question because in epidemiologic investigations of developmental and health consequences of prenatal PAH exposure, researchers often assume comparability in maternal exposure level and fetal exposure dose. Fowler et al. propose two inferences in their comments: *a*) the fetal liver exposure concentration resulting from transplacental transfer of the PAHs is higher than the maternal exposure concentration of airborne PAHs; and *b*) the relative proportion of individual PAHs for the fetal liver might be different from those experienced by the mothers. However, the two studies differ in several important aspects. Direct fetal–maternal comparison based on combining the data from the two studies as proposed by Fowler et al. is problematic for the following reasons.

First, in our study (Choi et al. 2008) we targeted nonsmoking pregnant women with no known risks of adverse birth outcomes in Krakow, Poland. To preclude the possibility of confounding by heavy environmental tobacco smoke (ETS) exposure or unreported maternal cigarette smoking, we further restricted the mother–newborn pairs to those with umbilical cord cotinine concentrations < 25 ng/mL in our analysis of the birth outcomes. Within our Polish cohort, mean (± SD) newborn and maternal plasma cotinine levels were 0.32 ± 0.88 and 0.28 ± 0.24 ng/mL, respectively (Choi et al. 2006). Fetal cotinine levels reported by Fowler et al. (2008) for the smoking mothers (45.2 ± 2.5 ng/mL, mean ± SE) were about 75-fold higher than those for the nonsmoking mothers (0.6 ± 1.9 ng/mL). In contrast, the fetal liver concentrations of benz[*a*]anthracene, benzo[*ghi*]perylene, benzo[*a*]pyrene (BaP), chrysene, dibenzo[*a,h*]anthracene, and indeno[1,2,-*cd*]pyrene for the smoking mothers are lower than those of the nonsmoking mothers by to 18–75% [Table 3 of Fowler et al. (2008)]. Lack of correlation between cotinine and PAH levels in the nonsmoking women raise doubt about the appropriateness of the comparison based on their control group.

Second, major sources of the PAHs in Krakow were coal- and diesel-combustion (Choi et al. 2008). In contrast, the relative

proportions of the fetal liver PAHs from the smoking and the nonsmoking women reported by Fowler et al.(2008) are almost identical. This suggests that major sources of PAHs in this study are maternal smoking or intensive ETS exposure. In their letter, Fowler et al. observed that the relative proportion of the maternal airborne exposure (from our study) is very different from the similar proportions in the fetal liver. They interpret this as very different proportions of PAHs accumulating in the liver following the maternal inhalation. However, we suspect that the difference in relative proportions of maternal air and fetal liver PAHs is likely due to the differences in the sources of the PAHs between the two studies, as well as to differential accumulation.

Third, it is unknown whether the demographic and socioeconomic characteristics of the maternal cohorts of the two studies are similar enough to support the comparison of the maternal airborne concentration with the fetal liver level. The maternal cohort of Fowler et al. (2008) elected medical abortion; about half of these women smoked intensively during their pregnancy. In contrast, the women in our cohort (Choi et al. 2008) successfully carried their pregnancies and were more likely to engage in healthy behaviors. Therefore, residual confounding by the maternal behaviors (such as micronutrient intake during pregnancy), socioeconomic status, and genetic polymorphisms might have further contributed to the differences in maternal air and fetal liver dose.

A substantial body of evidence suggests that fetuses are much more susceptible to PAH-induced carcinogenesis than are adults (Rice 1982; Soyka 1980), despite the likelihood that the transplacental dose of PAHs to the fetus is at least an order of magnitude lower than the maternal tissue levels (Neubert and Tapken 1988; Withey et al. 1993). Perera et al. (2004) reported that fetal PAH–DNA adduct levels were generally similar to those in the mothers; among ETS exposed mother–newborn pairs, the mean (± SD) maternal BaP–DNA adduct level was 0.23 ± 0.16 per 10^8 nucleotides, and the fetal level was 0.24 ± 0.15 per 10^8 nucleotides. Among the non-ETS exposed pairs, the mean maternal BaP–DNA adduct level was 0.21 ± 0.12 per 10^8 nucleotides, and the fetal level was 0.24 ± 0.15 per 10^8 nucleotides (Perera et al. 2004).

The issue raised by Fowler et al. in their letter is important because little is known about the actual concentration or type of PAHs that reach the fetus following maternal inhalation. Determining the actual fetal tissue dose is critical in understanding the sources of fetal vulnerability as well as the health effects of their exposure. However, the lack of comparability in maternal populations of the two studies does not allow valid estimation of the magnitude of maternal–fetal level difference. We believe the concentration of fetal tissue accumulation in humans following maternal inhalation of the PAHs needs further investigation.

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Linear Low-Dose Extrapolation for Noncancer Responses Is Not Generally Appropriate

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I disagree with the assertion of White et al. (2009) that linear low-dose extrapolation is generally appropriate as a default for noncancer, as well as cancer, end points. Such a stance would radically alter a basic tenet of toxicology and risk analysis, and any such course should be considered only after rigorous and broadly based examination of the scientific principles involved.

White et al. (2009) offered only a cursory summary of arguments that were discussed in a 2007 workshop, but any fuller discussion that may have occurred in that workshop was not recounted. Continual revisiting of the scientific thinking underlying risk assessment policies is valuable, but a change of this nature—which would depart from decades of well-established practice—needs to be carefully and critically examined.

I believe that most observers would find fault with all of the proffered lines of reasoning that White et al. (2009) cited in advocating that noncancer dose–response relationships should be treated as linear. Although harmonization of cancer and noncancer toxicity assessment holds some value (regarding commonality of pharmacokinetics and, potentially, elements of modes of action), there are still fundamental differences between carcinogenicity on the one hand, in which the probability of constellations of rare events (that get rarer with lower doses) drives the dose–response function, and most noncancer responses on the other, in which the dose–response function hinges on the degree of perturbation of physiologic and homeostatic processes (which becomes less pronounced and less efficacious with lower doses) (Rhomberg 2004).

The argument of White et al. (2009) that epidemiologic studies often show no thresholds, even for end points having thresholds in animal studies, is readily attributable to the small range of exposure levels and the approximate nature of exposure measurements in most human studies; these artifically flatten apparent dose–response curves and tend to make any dose-related effect (even those that are truly threshold in nature) look more or less linear as an artifact of the analysis.

Heterogeneity in sensitivity and in modifying factors among people in the target population may tend to broaden the dose–response relationship, but it does not linearize it, as White et al. (2009) asserted; indeed, the logic they invoked (the combined effect of variation in many modifying factors) leads to the expectation of a cumulative log-normal dose–response function, which is always nonlinear, rather than a linear one.

Similarly, when examined rigorously, the invocation by White et al. (2009) of the principle of additivity to background fails to support general linearity; unless it is framed in the discussion of a specific mode of action, the additivity-to-background argument amounts to begging the question—assuming the hypothetical existence of an underlying and rate-limiting no-threshold mechanistic effect to argue for linearity of the end result caused by that process. In fact, many biological processes—notably homeostasis and switch

mechanisms—are inherently nonlinear, with threshold effects for their perturbation to a degree sufficient to have health consequences. A rigorous examination of how additivity to background affects dose response for different modes of action should be undertaken before its general applicability is assumed.

The approach taken when extrapolating dose–response relationships to low doses has profound impact on risk-management decision making. If a change is proposed that is to be justified by invoking general principles, then the bearing of those principles needs to be rigorously articulated, well understood, and evaluated through broad discussion and debate. At present, this discussion has yet to occur.

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Linear Low-Dose Extrapolation for Non-Cancer Responses: Burke et al. Respond

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In his letter, Rhomberg raises several issues concerning recommendations in our report of the workshop "Issues and Approaches to Low Dose–Response Extrapolation for Environmental Health Risk Assessment" (White et al. 2009). One recommendation of the workshop was to set aside the generally held presumption that dose–response functions should follow a threshold model when extrapolating from higher dose studies of noncarcinogenic responses to lower dose levels typical for environmental exposures to chemicals. Workshop participants generally concluded that the selection of population-level low-dose extrapolation models should be informed by population factors such as interindividual variability in susceptibility and coexposures, as well as by categorization of mechanisms of toxicity. As indicated in the meeting report (White et al. 2009), most workshop participants preferred a linear, no-threshold approach to low-dose extrapolation modeling, combined with modeled estimates of the low range of observed data, for noncancer, as well as cancer, outcomes in the absence of convincing evidence to indicate that an alternative model is more appropriate. We recognize that this recommendation represents a departure from current generally accepted practice.

On a nonsubstantive point, Rhomberg's comment that we did not include additional information regarding "fuller discussions" at the workshop on this and other issues reflects the constraints imposed by *EHP*'s article length limits and changes made to accommodate reviewer comments encouraging emphasis on workshop findings and recommendations rather than on workshop discussions.

We disagree with Rhomberg's assertion that the finding of a linear, no-threshold exposure–response relationship in many epidemiologic studies of the effect of environmental pollutants, such as particulate matter and ozone air pollution, can be attributed entirely to a small range of exposures and measurement error. Although these factors need to be considered in evaluating epidemiologic study results, modeling techniques such as nonparametric smoothing methods have demonstrated the capacity to identify potential threshold relationships even in the context of relatively extreme measurement error (Cakmak et al. 1999; Schwartz and Zanobetti 2000).

As we noted in our meeting report (White et al. 2009), for the limited number of chemicals and agents for which robust low-dose response data exists (e.g., epidemiologic studies of large populations with exposures to particulate matter and ozone air pollution extending from relatively high to low ambient levels), thresholds have not been observed for noncancer or cancer outcomes [U.S. Environmental Protection Agency (EPA) 2006a, 2006b]. Additionally, for some of the exposures considered, the mechanisms of action thought to underlie the observed effects have been characterized by some as threshold mechanisms (e.g., the disruption of the homeostatic conditions for reactive oxygen species). In such cases, interindividual variability, background disease processes, and coexposures may explain the observed linearity.

Although we acknowledge that there are differences in the intrinsic biological processes involved in generating cancer and noncancer outcomes, we disagree with Rhomberg's assertion that heterogeneity in intrinsic population susceptibility and additivity to background disease processes result in simply "broadening" the dose–response relationship (which we presume means making the dose–response curve shallower). The underlying concept that additivity to background disease processes and variability in population susceptibility results in a linearization of the dose–response function for populations exposed to environmentally relevant levels was originally discussed in the context of cancer outcomes [Crump et al. 1976; Lutz 1990; National Research Council (NRC) 2005], and the suggestion that this same concept applies to noncancer outcomes is not novel (Clewell and Crump 2005; Crawford and Wilson 1996). Similarly, the importance of considering interindividual variability in assessing uncertainty associated with chemical risk assessments of noncancer effects has been recognized (Hattis and Silver 1994). The significance of these factors in the selection of dose–response models for use in environmental health risk assessment was also highlighted in a recent NRC report (NRC 2008).

Regarding the assumption of additivity to background disease on low-dose extrapolation, in our meeting report (White et al. 2009) we noted the importance of assessing, to the extent possible, whether the mode or mechanism of action of the key events involved are consistent. However, current knowledge of these detailed biologic processes is still quite limited for most chemicals and pollutants, and as noted by Hoel (1997)

> [L]ow-dose linearity is speculative and it is a reasonable assumption for public health purposes in those instances where there is no scientific evidence to the contrary.

We recognize that uncertainty increases as the dose–response extrapolation extends farther below observed data. The findings regarding exposure–response relationships from large-scale epidemiologic studies of environmental pollutants suggest that when considering population-level dose–response factors, interindividual variability, additivity to background disease processes, coexposures, and mechanisms of action, warrant careful consideration. As a consequence, we continue to recommend that the approach proposed in our meeting report (White et al. 2009) is appropriate and necessary.

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Errata

In Table 1 of the article by Tarantini et al. [Environ Health Perspect 117:217–222 (2009)], the sequence for the *iNOS* forward primer should be AATGAGAGTTGTTGGGAAGTGTTT instead of AATGAGAGTTGTTGTTGGGAAGTGTTT.

The authors apologize for the error.

In the article "Diesel Exhaust Particles Activate the Matrix-Metalloproteinase-1 Gene in Human Bronchial Epithelia in a β-Arrestin–Dependent Manner via Activation of RAS" by Li et al. [Environ Health Perspect 117:400–409 (2009)], the competing financial interest declaration was incorrect. Jinju Li was not supported by the Philip Morris grant but by a Leon-Goldberg Fellowship.Therefore, the declaration should be as follows:

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In the February 2009 Focus article ["Carbon Offsets: Growing Pains in a Growing Market," Environ Health Perspect 117:A62–A68 (2009)], a quotation at the bottom of p. A64 is incorrectly attributed to David Antinioli. The quotation should actually be attributed to Bill Burtis of Clean Air-Cool Planet; Antinioli is affiliated with the Voluntary Carbon Standard Association. On p. A68 of the same article, a quotation by James Lovelock is incorrectly attributed to the 22 January 2009 issue of *New Scientist*; the quotation actually appeared in the 24 January 2009 issue.

The December 2008 Focus article ["The Yuck Factor: When Disgust Meets Discovery," Environ Health Perspect 116:A524–A527 (2008)] incorrectly stated on p. A525 that Fountain Valley, California, is north of Redwood City. Fountain Valley is actually south of Redwood City.

EHP regrets the errors.