

The study subjects varied widely in age, height, and weight. To compensate for this variability, Swan et al. (2005) defined a new parameter, which they termed the "anogenital index" (AGI), by dividing AGD by body weight. In the absence of validation, the significance of the AGI is not known, and variation cannot be assumed to be related to hormonal exposure. Swan et al. suggested that the AGI is proportional to the normal genital development of male infants, but

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2005). Salazar-Martinez et al. (2004) found that, in male infants, AGD correlated best with length, not weight.

Per definition, the AGD represents a one-dimensional parameter of the human anatomy. In analogy to similar anatomic parameters (e.g., length of limbs, hands, or feet), the AGD is likely to be proportional to body length and not to body weight. Therefore, Swan et al.'s use of the (body weight-related) AGI in the study has little biologic plausibility and appears to be arbitrary.

Swan et al. (2005) did not normalize maternal phthalate urinary concentrations for urine volume. This leaves open the possibility that higher urinary phthalate concentrations in individuals may have been due to lower urinary volume rather than higher phthalate exposure, and casts doubt on the maternal exposure classification categories. Phthalate levels were based on only a single sample per individual, and fetal development at the time of urine sampling was not reported.

Numerous maternal factors (alcohol consumption, medication, profession, body mass) may affect fetal development. Although it is unknown what factors, if any, would influence AGD in human infants, in the absence of these data, confounding factors cannot be excluded.

The levels of phthalates Swan et al. (2005) reported in maternal urine samples are extremely low, and the corresponding exposures are many orders of magnitude lower than the exposures at which selected phthalates have been found to have adverse reproductive effects in rodents. For example, assuming excretion of 2 L of urine/day, the reported concentration of butyl benzyl phthalate corresponds to an exposure of approximately 60 µg/day, or 1 µg/kg/day for a woman weighing 60 kg. Butyl benzyl phthalate has been shown to have only slight, hormone-like effects in rats at doses of ≥ 100 mg/kg/day (Nagao et al. 2000), or ~ 100,000-fold higher than the levels seen by Swan et al. (2005). In the case of the metabolite monoethyl phthalate, the expo-

sure level for the corresponding parent compound diethyl phthalate was on the order of 1,000,000-fold lower than a level found to have no adverse reproductive effects in rats (4,000 mg/kg/day, the highest dose tested) (Scientific Committee on Cosmetic Products and Non-food Products 2002). It is biologically and toxicologically inconceivable that such low levels of human exposure would produce the significant structural differences claimed by Swan et al. (2005).

reported by Swan et al. (2005) is lacking in biologic plausibility and remains unproven.

The authors are employed by advocacy groups that represent the interests of the cosmetic, toiletry, and fragrance industry.

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Anogenital Distance and Phthalate Exposure: Swan et al. Respond

In their letter, McEwen and Renner raise several points that we would like to discuss.

First, because all infants in our study (Swan et al. 2005) appeared normal, McEwen and Renner infer that there is no evidence of an adverse effect. However, the absence of evidence of an effect in infancy

does not preclude serious adverse effects in later life. For example, the genital cancers that were identified in young women, on average 19 years after their prenatal exposure to the drug diethylstilbestrol, were seen in females who had appeared to be completely normal until that time (Herbst et al. 1971). In this case, unlike that example, we do have some evidence of anatomical changes in young boys. Although anogenital distance (AGD) has rarely been used as a


correlated with the degree of testicular descent and penile volume, and children with smaller AGD tended to have smaller scrotums; these are all signs of reduced androgen action.

McEwen and Renner state that the range of AGD reported in our study (Swan et al. 2005) is likely to be representative of normal study subjects. In fact, this information is not yet available because this is the first population-based study that utilized this measurement. AGD has, however, been used in the diagnosis of medical conditions such as congenital adrenal hyperplasia, in which AGD in females is increased by excess androgen exposure (Callegari et al. 1987). AGD is also known to be sexually dimorphic in humans as well as rodents (Salazar-Martinez et al. 2004).

McEwen and Renner point out that one previous study [$n = 42$; (Salazar-Martinez et al. 2004)] used an alternative measure of AGD in human infants. However, as we indicated in our article (Swan et al. 2005), this alternative definition is less precise than the one we used and does not correspond to the measure of anogenital distance most frequently used in toxicologic studies of rodents. Our use of this measure of AGD emphasizes the correspondence between traditional toxicology studies and our study.

In our study (Swan et al. 2005) we did not have data that would allow us to consider parental phenotype (e.g. parental height or father's AGD), as McEwen and Renner suggest should be done. If AGD was affected by parental stature (through infant body size), this association should be controlled for by adjusting for body size. Moreover, in order for a phenotypic variable to explain the observed association, it too would have to be related to maternal phthalate levels. This, too, would be an interesting finding.

McEwen and Renner question the use of normalizing AGD by dividing by weight (AGI) at examination. We examined several alternative measures of body size and, as discussed in our article (Swan et al. 2005), AGI provided the best fit to the data (independent

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of phthalates). Vanderbergh and Huggett (1995) found the same to be true in rodents. The fact that there was some variation of AGI with age is to be expected; not all 1-year-olds have the same length, either.

McEwen and Renner point out potential sources of “exposure misclassification” which, we agree, may have been present (and we stated so) (Swan et al. 2005). However, unless these sources of measurement error were related to AGD, their presence would lead to underestimates of the strength of the associations we presented.

We examined a number of potential confounders, such as maternal smoking and alcohol consumption; the prevalence of both was quite low (Swan et al. 2005). None affected results appreciably. Of course, the phantom “unmeasured confounder” always lurks in the wings of any observational study, can never be ruled out, and is a favorite of critics of epidemiologic studies. Any constructive suggestions for alternatives to observational studies would be appreciated; the only alternative we know of, randomizing pregnant women to receive phthalates (or not), hardly seems ethical.

Rodent studies test only one phthalate at a time. As we demonstrated (Swan et al. 2005), women were exposed to measurable levels of multiple phthalates, many known to be reproductively toxic. Until we have data on the toxicology of this complex mixture, we do not have the information to draw conclusions about the relative toxicity of these compounds in rodents versus humans. Furthermore, although doses in rodent studies of specific phthalates are high, effects have been demonstrated at lower doses used in recent studies (Lehmann et al.). Unfortunately no toxicologic study has yet examined effects of phthalates at environmental levels. Because we did find a significant association with phthalates at such levels, we can only conclude that environmental levels, however low, are associated with somatic alterations in humans.

Our study (Swan et al. 2005) is relatively small and must be replicated; subsequent studies will undoubtedly eliminate many of the sources of potential exposure and outcome misclassification. Nonetheless, in this first study of its kind, we set out to test the hypothesis, suggested by a large toxicologic literature (Gray et al. 2000), that prenatal phthalate exposure is associated with several measures in humans that reflect the antiandrogenic action of these chemicals. Using similar outcome measures to those utilized in these toxicologic studies, that is what we found.

The authors declare they have no competing financial interests.

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ERRATA

In the October articles “Children’s Centers Study Kids and Chemicals” [*Environ Health Perspect* 113:A664–A668 (2005)] and “Are EDCs Blurring Issues of Gender?” [*Environ Health Perspect* 113:A670–A677 (2005)], photographs and their captions erroneously imply that plastic drink bottles contain *ortho*-phthalates. Plastic drink bottles sold in the United States are made from polyethylene terephthalate and do not contain *ortho*-phthalates. Also, at the end of the EDCs article, references are made to plastic wrap and Saran Wrap. For clarification, neither plastic wrap nor Saran Wrap contains *ortho*-phthalates. *EHP* regrets these errors.

EHP regrets the incorrect and unintentional inference in “Paving Paradise: The Peril of Impervious Surfaces” [*Environ Health Perspect* 113:A456–A462 (2005)] that coal tar pitch is used in the actual hot-mix asphalt used to pave roads. Coal tar pitch is instead used in many sealcoat formulations used atop asphalt pavement. Findings published in the 1 August 2005 issue of *Environmental Science & Technology* suggest, in fact, that coal tar-based parking lot sealant may be a major contributor to stream loads of polycyclic aromatic hydrocarbons, including many known carcinogens.

In Figure 1 of the article by Chen et al. [*Environ Health Perspect* 113:1723–1729 (2005)], the legend should have read (A) PM₁₀; (B) PM_{2.5}, instead of (A) PM_{2.5}; (B) PM₁₀.

In Figure 1 of the article by Tsan et al. [*Environ Health Perspect* 113:1784–1786 (2005)], the double bond between HN and boron was incorrect. The corrected figure appears below.

