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Arsenic on the Hands of Children

Kwon et al. (2004) reported significantly elevated dislodgeable soluble arsenic loads on (one or both?) hands of children following play on structures treated with chromated copper arsenate (CCA) but then concluded that the observed difference is unimportant:

> With a safe conservative assumption that all the arsenic on children's hands is ingested, the measured value is below the estimated average daily intake of inorganic arsenic from water and food ….

However, Kwon et al.'s analysis is not conservative for at least two reasons. First, it is likely that they substantially underestimated arsenic on hands. Kwon et al. reported, but apparently did not actually measure, total arsenic on hands. They washed hands, filtered the wash water, and measured soluble arsenic in the filtrate. Insoluble residue was measured as dry mass gain on the filters. They then estimated insoluble arsenic on hands as the product of the average arsenic concentration in playground sand samples (not solids recovered from hands) and filter dry weight gain. I did not arrive at this conclusion because the procedures are clearly described in the paper but because *a*) there is no discussion of extraction of filters and *b*) the ratios of minimum, mean, median, and maximum "sand arsenic" on hands to minimum, mean, median, and maximum sand mass recovered from hands are nearly constant and equivalent (in all cases but one) to the mean concentration reported for each playground.

This procedure could easily give a very poor estimate of insoluble arsenic on hands because unfractionated 0- to 6-in sand samples are likely to be a poor surrogate for adherent particles. The filter residue from the hand-wash water probably contained at least some wood particles with much higher arsenic concentrations and lower densities than the playground sand. Hemond and Solo-Gabriele (2004) reviewed studies in which (typically adult) human hands were used to deliberately wipe CCA-treated lumber and reported much higher arsenic residues on hands than found by Kwon et al. (2004). One obvious potential explanation is that the arsenic concentration in material dislodged from CCA-treated wood (Nico et al. 2004) can easily be 1,000-fold higher than the 2–3 ppm found by Kwon et al. in playground sand.

Second, the observed loads that Kwon et al. (2004) reported may be greatly influenced by the very activity they wish to assess. That is, mass recoverable at any given time reflects net accumulation and does not include material already ingested. Consider the following simplified model of mass accumulation on hands:

$$A \times \frac{dL}{dt} = G - (k_{ing} \times L \times A),$$

where A = area (in square centimeters), L = load (in milligrams per square centimeter), G = net gain in the absence of ingestion (addition minus losses other than ingestion; in milligrams per hour), and k_{ing} = a first order rate constant describing ingestion (per hour).

At steady state,

$$0 = G_{ss} - k_{ing} \times A \times L_{ss}$$

and

$$A \times L_{ss} = G_{ss} \div k_{ing}.$$

Assuming reasonable efficiency of washing, Kwon et al. (2004) provided a measure of the product of the two variables on the left hand side (for soluble arsenic). They have not measured either of the variables on the right hand side. In the absence of knowledge of k_{ing}, they guessed. Because an infinite number of paired values of G and k_{ing} can be selected to match the available data, large values of k_{ing} are not excluded. Hence any reassuring conclusion based on this work is a reflection of the assumed rate at which hand residues are orally harvested and not of the reported measurements.

Kwon et al. (2004) further concluded that

> Most of the arsenic on children's hands is water soluble and is readily washed off with water. We recommend that children wash their hands after playing to reduce their potential exposure to arsenic.

Again, this conclusion is not supported by evidence presented in the article. To evaluate efficiency of washing, some measure of the initial mass present is required. Kwon et al. measured removable soluble arsenic and estimated removable insoluble arsenic. They did not measure or estimate either soluble or insoluble arsenic remaining on the hands. Because insoluble arsenic bound to soil or wood is likely to be at least partially removed mechanically by washing regardless of solubilization, washing is probably a good strategy. However, that argument is merely logical rather than empirical and could have been made in the absence of Kwon et al.'s experiments.

Kwon et al. (2004) stated that the purpose of their study was to provide "direct measurement of arsenic levels on the hands of children in contact with … CCA-treated wood …." Given that arsenic is amenable to biomonitoring via urine, comparable urine samples from children who do and do not play on CCA-treated structures are what is most needed. Then perhaps we would be able to stop guessing about ingestion rates.

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Arsenic on the Hands of Children: Wang et al. Respond

In our study of arsenic on children's hands (Kwon et al. 2004), we measured arsenic in water samples in which participating children washed both hands after playing on selected playgrounds. The hand-washing water was filtered, and the soluble arsenic concentration in the filtrate was determined by inductively coupled plasma mass spectrometry. In response to Kissel's comment that we did not measure insoluble arsenic, we analyzed the arsenic levels in the insoluble residue collected on the filter and summarized the unpublished data here. Results from the analysis of 64 samples from the CCA playgrounds and another 63 samples from the non-CCA playgrounds are available upon request. The total amount of arsenic in the insoluble residue collected in the hand-washing water of 64 children from the eight CCA playgrounds was 418 ± 601 ng (mean ±SD), compared to 172 ± 278 ng in the hand-washing water of 63 children from the eight non-CCA playgrounds. The total arsenic collected in the hand-washing water (insoluble arsenic on the filter plus water-soluble arsenic in the filtrate) was

934 ± 940 ng for the CCA playground and 265 ± 311 ng for the non-CCA playgrounds. The maximum amount of total arsenic collected from children's hands was 4,743 ng (4.7 µg). This is compared with the 3.9 µg that we reported previously (Kwon et al. 2004).

To provide a perspective of relative contribution of this amount of arsenic to the overall exposure to arsenic, in our article (Kwon et al. 2004) we included references for the average daily dietary ingestion of total arsenic:

> 38 µg (15 µg for children 1–4 years of age) for Canada (Dabeka et al. 1993), 62 µg for the United States (Gartrell et al. [1985]), 89 µg for the United Kingdom (Food Additives and Contaminants Committee 1984), 55 µg for New Zealand (Dick et al. 1978), and 160–280 µg for Japan (Tsuda et al. 1995). A range of arsenic species that have different toxicities may be present in food (Le et al. 2004). Estimated daily dietary intake of inorganic arsenic was 8.3–14 µg in the United States (Yost et al. 1998), 4.8–12.7 µg in Canada (Yost et al. 1998), and 15–211 µg in Taiwan (Schoof et al. 1998).

We did not monitor children's hand-to-mouth activity because this behavior has already been documented in the literature (Reed et al. 1999; Tulve et al. 2002). Our intent was to provide direct measurements of the amount of arsenic on children's hands. We recognize the importance of these other studies, as we pointed out in our "Conclusions" (Kwon et al. 2004):

> The results—along with other information, such as the frequency and habit of hand-to-mouth activity, efficiency of transfer of arsenic from hands to mouth, and repeated contact of hands with CCA-treated wood surface after hand-to-mouth activity—are useful for assessing children's exposure to arsenic.

We have measured arsenic in sequential hand-washings and found that most arsenic was present in the first hand-washing (unpublished data). Results of arsenic in hand-washings of three children before and after playing on a CCA playground are available upon request. The amount of arsenic in the second washing was < 10% of that in the first washing, suggesting that the arsenic on children's hands is readily washed off with water. Therefore, we conclude that children should "wash their hands after playing to reduce their potential exposure to arsenic" (Kwon et al. 2004).

Biomonitoring of arsenic species in urine samples from children who play on CCA-treated structures and children who do not could be useful if the ingestion of arsenic from dietary sources would not be a major confounder.

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Glyphosate Results Revisited

With respect to the recent article by De Roos et al. (2005), we would like to *a*) comment on the authors' incomplete genotoxicity review, which is inconsistent with conclusions reached by regulatory agencies; *b*) estimate the likely range of systemic doses and margins of exposure for farmers based on comprehensive glyphosate biomonitoring data published in 2004; and *c*) request further evaluation of confounding and selection bias in their analyses for multiple myeloma.

In their discussion of genotoxicity, De Roos et al. focused on selected studies that conflict with the weight of evidence for glyphosate and Roundup brand (Monsanto Company, St. Louis, MO) agricultural herbicides containing glyphosate. They cited Williams et al. (2000) regarding the lack of a carcinogenic effect in rodent feeding studies with glyphosate but neglected to cite the extensive genotoxicity review in the same article in which Williams et al. concluded that Roundup and its components do not pose a risk for heritable or somatic mutations. This conclusion is in agreement with findings by the U.S. Environmental Protection Agency (U.S. EPA 1993), the World Health Organization (WHO 1994), the European Commission (2002), and regulatory agencies worldwide. None of the studies cited by De Roos et al. (2005) as presumptive evidence of genotoxicity were conducted under Good Laboratory Practices or according to international guidelines. Additionally, many of these studies used toxic dose levels and/or irrelevant routes of exposure.

When evaluating epidemiologic findings, it can be helpful to compare the range of likely exposure levels to the exposure levels of toxicologic significance (Acquavella et al. 2003). The cancer no-effect levels for glyphosate, based on rat and mouse lifetime feeding studies, are 1,000 and 1,500 mg/kg/day, respectively (Williams et al. 2000). Acquavella et al. (2004) reported results of a biomonitoring study in which 48 farmers collected all of their urine over 5 consecutive days (before, during, and for 3 days after a glyphosate application). In this study, the maximum systemic dose resulting from application of glyphosate to areas as large as 400 acres was 0.004 mg/kg. The geometric mean systemic dose was 0.0001 mg/kg. Accordingly, in the worst-case situation, if a farmer made a similar application every day for a lifetime, the systemic dose would be at least 250,000-fold lower than the cancer no-effect level in rodents. Indeed, this very large margin of exposure combined with the lack of evidence for genotoxicity must be factored into an assessment of biologic plausibility.

Finally, De Roos et al.'s Table 2 (De Roos et al. 2005) shows an age-adjusted relative risk (RR) of 1.1 [95% confidence interval (CI), 0.5–2.4] associating multiple myeloma and ever-use of glyphosate. The RR adjusted for selected demographic and lifestyle variables was 2.6 (95% CI, 0.7–9.4). The factors that account for the difference in these RRs are not well explained. Given the weak associations between the covariates and ever-use of glyphosate and the weak or nonexistent relation between these variables and risk of multiple myeloma, it is unlikely that the change in RR from 1.1 to 2.6 is attributable to confounding. The authors mention that only 75% of eligible subjects

were included in the fully adjusted analysis and that this reduction in analytic sample size was due to the exclusion of subjects that were missing covariate data. Further, De Roos et al. (2005) did not find an association in the complete data set without adjustment for covariates (RR = 1.1), but they did find a positive association in the restricted data set without adjustment for covariates. The difference in association due simply to restricting the data set to those with covariate information was not quantified, although such quantification would help the reader understand what proportion of the change from 1.1 to 2.6 was attributable to adjustment for candidate confounders and what proportion was due to selection of subjects with more complete data. An analysis stratified by each covariate individually should have allowed the investigators to identify covariates for which missing data and/or adjustment made the biggest impact on the estimated RR. The identity of these covariates would help the reader weigh the potential for confounding versus selection bias to explain the change in RR from 1.1 to 2.6. Given that only 32 cases of multiple myeloma were observed and as few as 19 cases were included in some of the analyses, the authors should have explored the potential for the analysis of sparse data to result in estimates biased away from the null (e.g., see Greenland et al. 2000 for an example involving conditional logistic regression).

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Glyphosate Results Revisited: De Roos et al. Respond

The reaction of Farmer et al. regarding our article on glyphosate exposure and cancer incidence in the Agricultural Health Study (AHS) (De Roos et al. 2005) is difficult to understand given the tentative nature of our conclusions. For the most part, we found no associations with the cancers we studied, and to quote from our abstract,

> Glyphosate exposure was not associated with cancer incidence overall or with most of the cancer subtypes we studied. There was a suggested association with multiple myeloma incidence that should be followed up as more cases occur in the AHS.

Despite the fact that we believe our presentation of the data was quite fair and included a lengthy discussion of possible biases affecting our results, several comments by Farmer et al. necessitate a response.

Farmer et al. had several criticisms of our review of the genotoxicity literature (De Roos et al. 2005). Although the discussion of the toxicity studies is interesting, these studies only serve as background information in our article; the epidemiologic associations between glyphosate exposure and cancer incidence we observed are the empirical result of our investigation. Criticisms of our reference to the genotoxicity literature do not, of course, alter the human data we presented. We stated in our article the conclusion of the U.S. Environmental Protection Agency (U.S. EPA 1993) and the World Health Organization (1994) that glyphosate is not mutagenic, but because that conclusion focused on the active ingredient, glyphosate, and not formulated products such as Roundup (Monsanto Company, St. Louis, MO), we also cited several studies which show potentially greater toxic effects of Roundup than glyphosate. Our article (De Roos et al. 2005) does not purport to be a comprehensive review of the toxicology literature, and because of space limitations imposed by the journal, we did not discuss several studies showing potentially toxic effects of several glyphosate-based pesticide products through disruption of cell-cycle control mechanisms, which may be relevant for cancer as well as noncancer health outcomes (Marc et al. 2002, 2004).

The fact the some of the studies we cited did not use Good Laboratory Practices is irrelevant, because this system is used primarily in analytical chemistry and contract laboratories for routine support of pesticide regulation, and is not required by any of the principal funding agencies for research studies. Studies that are submitted to the U.S. EPA to support applications for licensing pesticides are required to meet specified guidelines for record keeping, data reporting, and protocol development. These Good Laboratory Practices provide some assurance that regulators can rely on the data they review and give them the ability to perform audits as needed. Investigators who perform studies for research purposes are not required to follow these structured practices, but many may do so. Furthermore, it does not follow that work done in labs that do not strictly adhere to the U.S. EPA's testing and reporting requirements follow "bad" laboratory practices. Quality assurance for research studies is provided by the peer-review process and by replication. This is analogous to the distinction between clinical laboratory tests performed in the context of human research and tests performed for diagnostic purposes. In order for these tests to be covered by insurers, they must be performed in laboratories approved by the Clinical Laboratory Improvement Amendments (CLIA 2005). CLIA approval assures that the test results are valid but does not address the underlying science that led to the development of the test.

In their letter, Farmer et al. used exposure information from a study by Acquavella et al. (2004) in which biomonitoring of farmers who applied glyphosate was used to determine a maximum dose calculation. The dose thresholds Farmer et al. cite as relevant for carcinogenicity are from mouse and rat models in which the active ingredient, glyphosate, was tested in feeding studies (Williams et al. 2000). Lower relevant doses may apply for Roundup and other formulated products containing glyphosate, or for glyphosate products used in combination with other active ingredients. In addition, epidemiology can provide direct information on the question of what happens in humans from more relevant routes of exposure.

Some questions were raised about the possible associations we observed between glyphosate and multiple myeloma concerning the discrepancy between the age-adjusted relative risk of 1.1 [95% confidence interval (CI), 0.5–2.4] and the relative risk adjusted for selected demographic and lifestyle variables of 2.6 (95% CI, 0.7–9.4) (De Roos et al. 2005).

Farmer et al. question whether the discrepancy may be due to confounding or the selection of subjects into the more restricted analysis. This is plausible, and we discussed these issues at length in our article. The association only appeared within the subgroup with complete data on all the covariates; even without any adjustment, there was a 2-fold increased risk of multiple myeloma associated with glyphosate use among the smaller subgroup with covariate data. We acknowledged that this could be due to selection bias, effect modification, or confounding within this subgroup. We would point out, however, that confounding can be both positive and negative. The type of analysis suggested by Farmer et al., in which the data are stratified by each covariate individually in order to identify covariates for which missing data and/or adjustment made the biggest impact on the estimated relative risk, would be unreliable for such a small number of cases. Each estimate would be subject to small sample bias (Greenland 2000), which was cited by Farmer et al. as an issue with our overall estimate for myeloma. The most reliable approach will be to reanalyze the data after more cases accumulate, both to assess whether the association with myeloma persists and to further evaluate confounding and selection bias using a larger case group to support analyses. Following up initial observations with more comprehensive epidemiologic data from the AHS has been our plan since the inception of the study.

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Erratum

In Figures 1, 2, and 3 of "Altered Profiles of Spontaneous Novelty Seeking, Impulsive Behavior, and Response to D-Amphetamine in Rats Perinatally Exposed to Bisphenol A" by Adriani et al. [Environ Health Perspect 111:395-401 (2003)], results for oil controls and bisphenol A (BPA)-treated rats were labeled incorrectly. The corrected figures are shown below. *EHP* apologizes for the errors.

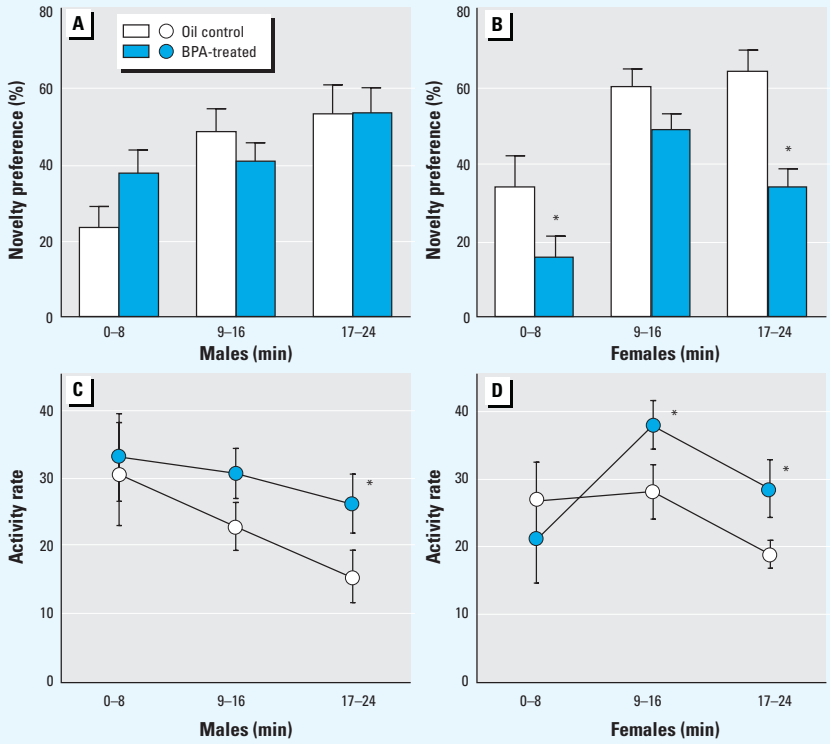

Figure 1. (*A,B*) Mean (± SE) percentage of time spent in the novel compartment by subjects of both sexes on testing day (experiment 1). (*C,D*) Mean (± SE) activity rate, measured as number of line crossings per minute, shown by subjects of both sexes in the novel compartment on testing day. During the pretreatment period (days 1–3), subjects were familiarized to one compartment. On testing day, animals were placed in the familiar compartment. After 5 min, a partition was removed and subjects were allowed free access to a novel compartment of the apparatus for a 24-min session.
*$p < 0.05$ in comparisons between BPA and control perinatal treatments ($n = 9$).

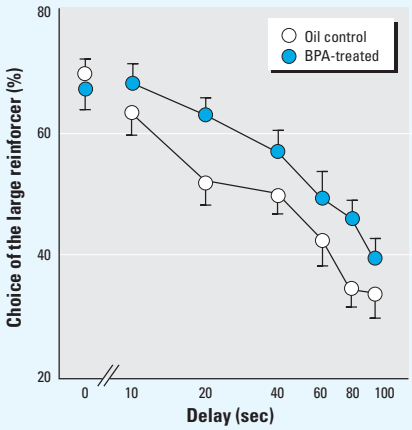

Figure 2. Mean (± SE) choice (%) of the large reinforcer, demanded by nose poking at the LAD hole, shown by rats during the test for impulsivity (experiment 2). These data reveal that, as the length of the delay increased, animals increased demanding the small but immediate reinforcement and decreased demanding the larger but delayed one. A shift to the right of the whole curve (i.e., a profile of reduced impulsivity) was evident in BPA-exposed rats compared with controls. In the absence of significant differences, data from the two sexes were collapsed ($n = 18$).

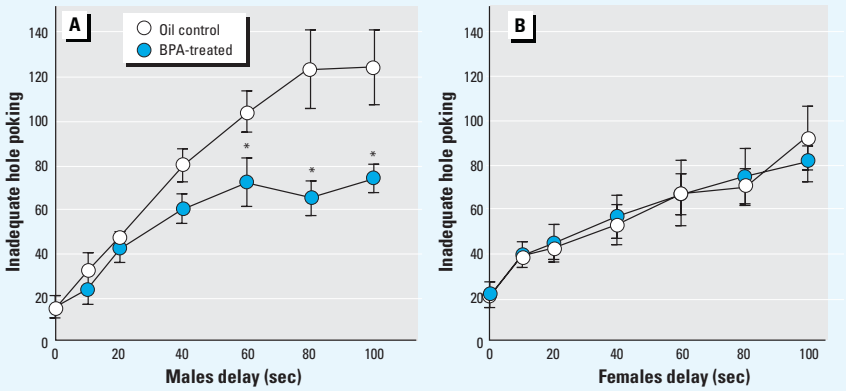

Figure 3. Mean (± SE) frequency of inadequate responding at the IAS hole (i.e., nose poking during the length of the delay, when it was without any consequence) shown by rats during the test for impulsivity (experiment 2). These data reveal that, when animals were waiting for the delivery of the large reinforcer, they failed to rest and were demanding the immediate one. A clear-cut demasculinization in the restlessness profile was evident.
*$p < 0.05$ in multiple comparisons between BPA and control perinatal treatments ($n = 9$).