Arsenic on the Hands of Children

Kwon et al. (2004) reported significantly elevated dislodgable 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 concentration in playground sand. 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 concentration.

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:

\[ A \times \frac{dL_{ss}}{dt} = G - (k_{ing} \times L \times A), \]

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

\[ A \times L_{ss} = G_{ss} + k_{ing} \times L_{ss}. \]

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.

The author declares he has no competing financial interests.

John C. Kissel

Department of Occupational and Environmental Health Sciences
University of Washington
Seattle, Washington
E-mail: jkissel@u.washington.edu

REFERENCES

Hemond HF, Solo-Gabriele HM. 2004. Children’s exposure to arsenic from CCA-treated wooden decks and playground structures. Risk Anal 24(1):51–64.
Kwon E, Zhang N, Wang Z, Jiangni GS, Lu X, Fok N, et al. 2004. Arsenic on the hands of children after playing in playgrounds. Environ Health Perspect 112:1375–1380.
Nico PS, Fendorf SE, Lowney YW, Holm SE, Ruby MV. 2004. Chemical structure of arsenic and chromium in CCA-treated wood: implications of environmental weathering. Environ Sci Technol 38(19):5253–5260.

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.

The authors declare they have no competing financial interests.

Zhongwen Wang, Elena Kwon, Hongquan Zhang, Gian S. Jhangri, Xiufen Lu, Xing-Fang Li, and X. Chris Le
Department of Public Health Sciences
University of Alberta
Edmonton, Alberta, Canada
E-mail: xc.le@ualberta.ca

Nelson Fok
Environmental Health
Capital Health
Edmonton, Alberta, Canada

Stephan Gabos
Health Surveillance Branch
Alberta Health and Wellness
Edmonton, Alberta, Canada

REFERENCES

Dabeka RW, McKenzie AD, Lacrocq GM, Cleroux C, Bowe S, Graham RA, et al. 1993. Survey of arsenic in total diet food composites and estimation of the dietary intake of arsenic by Canadian adults and children. J. Environ. Monit. 5:16–25.

Dick GL, Hughes JT, Mitchell JW, Davidson F. 1978. Survey of trace elements and pesticide residues in the New Zealand diet. 1. Trace element content. NZ J Sci 21:57–69.

Food Additives and Contaminants Committee. 1984. Report on the Review of the Arsenic in Food Regulations. Ministry of Agriculture, Fisheries and Foods, FAC/REP/39.

London: Her Majesty’s Stationery Office.

Gartrell MJ, Graun JC, Podrebarac DS, Gunderson EL. 1985. Pesticides, selected elements, and other chemicals in adult total diet samples, October 1979-September 1980. J Assoc Off Food Chem 38:1184–1197.

Kwon E, Zhang H, Wang Z, Li X, Jhangri GS, Fok N, et al. 2004. Arsenic on the hands of children after playing in playgrounds. Environ Health Perspect 112:1375–1380.

Le XC, Lu X, Li X-F. 2004. Arsenic speciation. Anal Chem 76:26A–33A.

Reed KJ, Jimenez M, Freeman NCG, Lioy PJ. 1999. Quantification of children’s hand and mouth activities through a videotaping methodology. J Environ Health 61:132–136.

Schoof RA, Yost LJ, Creecius E, Ingrigo K, Goessler W, Guo HR, et al. 1998. Dietary arsenic intake in Taiwanese districts with elevated arsenic in drinking water. Human Ecol Risk Assess 4:117–125.

Tulve NS, Suiga JC, McCurdy T, Cohen Hulat EA, Moya J. 2000. Frequency of mouthing behavior in young children. J Environ Health 63:125–128.

Tsuda T, Inoue T, Kojima M, Aoki S. 1995. Market basket and duplicate portion estimation of dietary intakes of cadmium, mercury, arsenic, copper, manganese, and zinc by Japanese adults. J. Environ Monit. 7:1363–1368.

Yost LJ, Schoof RA, Aucoin R. 1998. Intake of inorganic arsenic in the North American diet. Hum Ecol Risk Assess 4:137–152.

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 scenario, 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...
Correspondence

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).

D.R.F. is a current employee of Monsanto. J.F.A. is retired from Monsanto, and T.L.L. works as a consultant to Monsanto.

Donna R. Farmer
Product Safety Center
Monsanto Company
St. Louis, Missouri
E-mail: donna.r.farmer@monsanto.com

Timothy L. Lash
Boston University School of Public Health
Boston University
Boston, Massachusetts

John F. Acquavella
Product Safety Center, Retired
Monsanto Company
St. Louis, Missouri

REFERENCES

Acquavella JF, Alexander BH, Mandel JS, Gustin C, Baker B, Chapman P, et al. 2004. Glyphosate biomonitoring for farmer-applicators and their families: results from the Farm Family Exposure Study. Environ Health Perspect 112:321–326.

Acquavella JF, Dee J, Tomenson J, Chester G, Cowell J, Bloemen L. 2003. Epidemiologic studies of occupational pesticide exposure and cancer: regulatory risk assessments and biologic plausibility. Ann Epidemiol 13:1–7.

De Roos AJ, Blair A, Riusicki JA, Hoppin JA, Svec M, Dozmeci M, et al. 2005. Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. Environ Health Perspect 113:49–54; doi:10.1289/ehp.7340 [Online 4 November 2004].

European Commission. 2002. Report for the Active Substance Glyphosate. Available: http://europa.eu.int/comm/food/ plant/protection/evaluation/exsactive/list_glyphosate_en.pdf [accessed 25 January 2002].

Greenland S, Schwartzbaum JA, Finkle WD. 2000. Problems due to small samples and sparse data in conditional logistic regression. Am J Epidemiol 151:531–538.

U.S. EPA. 1993. Glyphosate Reregistration Eligibility Decision (RED). EPA-738-R-93-014. Washington, DC: U.S. Environmental Protection Agency.

Williams GM, Krouse R, Munro IC. 2000. Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans. Regul Toxicol Pharmacol 31:117–165.

WHO. 1994. Glyphosate. Environmental Health Criteria 159. Geneva: World Health Organization.

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.

The authors declare they have no competing financial interests.

Anneclaire J. De Roos and Megan A. Svec
Program in Epidemiology
Fred Hutchinson Cancer Research Center
and the Department of Epidemiology,
University of Washington
Seattle, Washington
E-mail: deroos@u.washington.edu

Aaron Blair, Jennifer A. Rusiecki, Mustafa Dosemeci, and Michael C. Alavanja
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
Department of Health and Human Services
Bethesda, Maryland

Jane A. Hoppin and Dale P. Sandler
Epidemiology Branch
National Institute of Environmental Health Sciences
National Institutes of Health
Department of Health and Human Services
Research Triangle Park, North Carolina

REFERENCES
Aquavella JF, Alexander BH, Mandel JS, Gustin C, Baker B, Chapman P, et al. 2004. Glyphosate biomonitoring for farmers and their families: results from the Farm Family Exposure Study. Environ Health Perspect 112:321–326.

CLIA. 2005. Clinical Laboratory Improvement Amendments Homepage. Available: http://www.cms.hhs.gov/clia/ [accessed 27 April 2005].

De Roos AJ, Blair A, Rusiecki J, Hoppin JA, Svec M, Dosemeci M, et al. 2005. Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study cohort. Environ Health Perspect 113:49–54.

Greenland S, Schwartzbaum JA, Finkle WD. 2000. Problems due to small samples and sparse data in conditional logistic regression. Am J Epidemiol 151:531–539.

Marc J, Mulner-Lorillon O, Durand G, Bellé R. 2002. Pesticide Roundup provokes cell division dysfunction at the level of CDK1/cyclin B activation. Chem Res Toxicol 15:326–331.

Marc J, Mulner-Lorillon O, Bellé R. 2004. Glyphosate-based pesticides affect cell cycle regulation. Biol Cell 96:245–249.

U.S. EPA. 1993. Reregistration Eligibility Decision (RED). Glyphosate. EPA-738-R-93-014. Washington, DC: U.S. Environmental Protection Agency.

Williams GM, Kroes R, Munro IC. 2000. Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans. Regul Toxicol Pharmacol 31:117–165.

World Health Organization. 1994. Glyphosate. Environmental Health Criteria 199. Geneva:World Health Organization.
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).