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Letter to the Editor

Response to "Urinary Excretion of Chromium Following Ingestion of Chromite-Ore Processing Residues in Humans: Implications for Biomonitoring" by Gargas et al.

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In their recent paper,[1] Gargas et al. fed soil contaminated with chromate production waste to human volunteers and on the basis of their findings, claimed that human exposure to chromate production waste does not result in an increase in urinary chromium concentration. The purpose of Gargas et al. appears to be to cast doubt on previous investigations of environmental exposure to chromate production waste in Hudson County, New Jersey, employing population-based biomonitoring of urine chromium.[2,3] While Gargas et al. found no significant increase in urinary chromium excretion, we believe that their study does not accurately reflect conditions of exposure to chromate production waste in Hudson County and that their findings therefore do not, in fact, invalidate the conclusions of previous studies of chromium (Cr) exposure in Hudson County. We base our conclusion on the presence of three major flaws in the Gargas et al. study: 1) The assumption of Gargas et al. that measured levels of Cr in Hudson County air are insufficient to result in a measurable increase in urinary Cr due to inhalation exposure is based on a misunderstanding of the existing literature; 2) The chromate production waste ingested by the volunteers in their study was not representative of the resuspended residential dust addressed in previous investigations, either in particle size, or Cr concentration and; 3) Gargas et al. mischaracterize two previous New Jersey Cr biomonitoring studies which they assert support their conclusions, one of which is, however, not relevant to residential exposure and the other of which is clearly inconsistent with their conclusions.

Gargas et al. assume that ingestion is the only route of exposure which could result in elevation of urine chromium levels among Hudson County residents. They base this assumption on a comparison between measured levels of Cr in air at Hudson County waste sites[4] and an assumed air concentration of Cr necessary to cause elevated urinary Cr levels. Mean levels of chromium at the Hudson County sites under all weather conditions in the referenced study ranged as high as 0.25 $\mu g/m^3$ (± 0.30 $\mu g/m^3$) for total Cr and 0.11 $\mu g/m^3$ (± 0.20 $\mu g/m^3$) for Cr VI. Under dry soil conditions, mean levels of Cr ranged as high as 0.66 $\mu g/m^3$ for total Cr and 0.16 $\mu g/m^3$ for Cr VI. Gargas et al. cite several references to support their assertion that the Cr concentration in air must be at least 20 $\mu g/m^3$ to observe an increase in urinary Cr.[5–7] However, none of these references, in fact, provides support for that assumption. In one of these studies,[7] the lowest level of airborne exposure was 2–23 $\mu g/m^3$. This was associated with a mean urine Cr level of 24.7 $\mu g/m^3$. Neither pre-shift, nor background urinary Cr levels are reported, so a "threshold" air concentration for this study cannot be deduced. Nonetheless, compared to a population mean background urine Cr concentration of about 0.2 $\mu g/l$,[8] it seems clear that this exposure resulted in an increase in urinary Cr. In another of these studies,[6] which was conducted nearly twenty years ago and which did not report a minimum detection limit for urine Cr, the stated conclusion was that no increase in urinary excretion of Cr was observed after a single working period when the airborne Cr concentration was *lower than* 0.01 mg/m^3 (i.e., 10 $\mu g/m^3$). Again, no response "threshold" for this study can be deduced from these data. The last of the studies cited by Gargas et al.,[5] also nearly twenty years old, reported a practical detection limit for urine Cr of 2 $\mu g/l$, ten times the mean background urine Cr in the non-occupationally exposed population. In fact, that paper suggests that about 30 $\mu g/l$ be used as a benchmark indicating an elevation in urine Cr. Given our current knowledge that the mean non-occupational background urine Cr is 0.2 $\mu g/l$, this reference clearly has no relevance to the evaluation of population exposure using currently acceptable methodology. In contrast, Angerer et al.[9] reported that work-

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ers with a *median* exposure to Cr in air of less than 4 $\mu g/m^3$ had urine Cr levels at least 7 times background. Mutti et al.[10] reported increases of 7 and 21 times the background urine Cr level corresponding to *median* Cr air concentrations of 5 and 6 $\mu g/m^3$ respectively. The current literature does not permit the derivation of an airborne concentration of Cr corresponding to a practical threshold for elevation of urine Cr. Nonetheless, such a concentration is certainly much below the value of 20 $\mu g/m^3$ assumed by Gargas et al. If we assume that a doubling of the mean background urine Cr level of 0.2 $\mu g/l$[8] is a detectable increase, and we assume a 5% systemic absorption of inhaled Cr,[11] a daily urine volume of 1 liter,[12] and a daily inhalation volume of 20 m^3,[13] we can calculate that an airborne concentration of only 0.2 $\mu g/m^3$ would be required to achieve such an increase in the urine Cr level. This is well within the range of airborne concentrations of Cr III and Cr VI reported at Hudson County chromate production waste sites.[4] We feel it is important to put these exposures into perspective by noting that given the current U.S. EPA cancer potency for Cr VI of $1.2 \times 10^{-2}/\mu g/m^3$,[11] 0.2 $\mu g/m^3$ corresponds to a risk of greater than 2 *per thousand.* Therefore, the underlying assumption in Gargas et al., that inhalation is not a relevant route of exposure to Cr waste in Hudson County, appears to have no basis and does not bear on the ability of population-based urine monitoring of Cr to detect exposure to chromate production waste in Hudson County.

The household dust sampling investigations[17,18] (conducted in conjunction with the New Jersey Department of Environmental Protection and New Jersey Department of Health biomonitoring studies[2,3]) upon which Gargas et al. purport to base their study design, specifically employed measurement of chromium in household dust collected from elevated surfaces as the metric of residential exposure to chromate production waste. As such, the dust and the Cr it contained were resuspended material and therefore had a particle size (<30 μm in diameter) capable of being transported as an aerosol from outside locations. In contrast, the soil material administered by Gargas et al., was sieved to a maximum particle size of 500 μm in diameter. It is likely that most of the mass of Cr in this material was in large non-resuspendable particles. By analogy to lead,[14-16] it seems clear that much of the Cr in this large particle-size fraction would not be bioavailable compared to the smaller size resuspendable particles. The bioavailability of the large particle size material of Gargas et al. is all the more a consideration because of the etiology of the waste material. This material is largely the result of the high temperature roasting of Cr ore, producing refractory nodules which are resistant to digestion. The much smaller resuspendable particles resulting from the weathering and long-term environmental leaching of the waste will be more susceptible to digestion and absorption. Furthermore, the material administered by Gargas et al. had a Cr concentration of 100 ppm. In the most recent household dust sampling study,[18,21] the *mean* concentration of Cr among nine neighborhoods adjacent to a chromate production waste site was 228 ppm. The largest neighborhood mean was 457 ppm (s.d. = 421 ppm).[18] The concentration of Cr administered by Gargas et al. was therefore neither typical, nor reflective of those higher environmental concentrations most likely to result in elevated urine Cr. Thus, the material administered by Gargas et al. is not comparable to the resuspended dust in the studies they attempt to refute and their data do not bear on the conclusions from those studies.

Gargas et al. attempt to support their arguments by repeatedly mischaracterizing the results of two previous Cr biomonitoring studies conducted in New Jersey, Bukowski et al.[19] and Stern et al.[2] Both studies are cited to support the claim that "exposures to COPR (chromate production processing waste) in the environment does not result in obviously increased levels of urinary Cr." Bukowski et al. studied outdoor park employees working in an area separate from a waste site which was not being disturbed by their activity. This is not analogous to residential exposure as noted by Bukowski et al., who stated that "The results of this study cannot be extrapolated to other sites in Hudson County." Stern et al. made it clear that, indeed, there *were* statistically significant differences in mean urine Cr among their participants when examined according to household dust level. Stern et al. state that ". . . the most significant finding of this study has been the identification, based on the results of environmental sampling and urine analysis, of a subgroup of the potentially exposed population which showed statistically significant evidence of both environmental exposure to chromium and increased urine chromium levels," and concluded that "this association between elevated exposure to Cr in household dust and elevated Cr concentration in urine is consistent with environmental exposure to the Cr production waste." These results have since been confirmed in a separate study.[18,21] While not everyone residing in the vicinity of a Cr waste site had elevated urine Cr in the Stern et al. study, it was clear that only some of the individuals were effectively exposed. When an environmental metric of exposure (household dust sampling) was applied to identify those in the *potentially* exposed population with high potential for effective exposure, clear differences in

urine levels emerged. It is difficult to understand how Gargas et al. could construe the clear conclusion of Stern et al. to claim that no increase in urine Cr was observed in populations living near Cr sites.

Finally, we must raise serious reservations about the propriety of dosing human volunteers with material containing Cr VI. Cr VI is one of the few clear human carcinogens.[20] While its demonstrated carcinogenicity is via the inhalation route, no determination has been made that Cr VI is not carcinogenic by the ingestion route. Quite simply, there are insufficient data to support any evaluation of Cr VI ingestion carcinogenicity. The claim by Gargas et al. "... that the study involved no risk to the participants," thus, cannot be justified given the lack of data.

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