Occupational Carcinogens: ELF MFs

Siemiatycki et al. (2004) published a list of occupational carcinogens based largely on the evaluations published by the International Agency for Research on Cancer (IARC), augmented with additional information on the extent of workplace exposure. They considered 28 agents as definite human occupational carcinogens (IARC group 1), 27 agents as probable occupational carcinogens (group 2A), and 113 agents as possible occupational carcinogens (group 2B). However, missing from their list of occupational carcinogens is magnetic fields (MFs) at extremely low frequencies (ELF; 3–3000-Hz), which were classified as group 2B by IARC (2002).

IARC's final conclusion (IARC 2002) is as follows:

> Overall, extremely low frequency magnetic fields were evaluated as possibly carcinogenic to humans (IIB), based on the statistical association of higher level residential ELF magnetic fields and increased risk for childhood leukaemia.

Thus, although the evaluation is based on epidemiologic studies of childhood leukemia, the classification applies to all human exposure to ELF MFs, and thus also to occupational exposure. This interpretation has been discussed and confirmed with an IARC representative on their ELF MF panel (Cardis E, personal communication). Because enough workers are exposed to ELF MFs to clearly meet the criteria for occupational exposures set by Siemiatycki et al. (2004), we are surprised that they did not include it in their list of possible occupational carcinogens.

Other groups and agencies have applied IARC's criteria to the evaluation of ELF MF carcinogenicity. The National Institute of Environmental Health Sciences working group (NIEHS 1998) evaluated the research in that era and classified ELF EMFs (electric and magnetic fields) as possibly carcinogenic (group 2B); this classification was based on the occurrence of chronic lymphocytic leukemia (CLL) associated with occupational exposure. The California Department of Health Services also evaluated the cancer risks of EMF in 2002, and their reviewers classified it as at least group 2B, including childhood leukemia and adult brain cancer (Neutra et al. 2002).

Since the IARC evaluation, several relevant studies have been published—both *in vitro* and *in vivo* work, as well as epidemiologic studies, including the following examples. Tynes et al. (2003) reported an association between exposure to calculated residential MFs and cutaneous malignant melanoma. In a cohort including all female workers, Weiderpass et al. (2003) found an association between exposure to electromagnetic fields and stomach and pancreatic cancer; Villeneuve et al. (2002) found that occupational MF exposure increased the risk of glioblastoma multiforme; Håkansson et al. (2002) investigated cancer incidence in resistance welding workers exposed to high levels of MF and found that men in the very high exposure group showed an increased incidence of tumors of the kidney, pituitary gland, biliary passages, and liver; an exposure–response relationship was indicated for these cancer sites. Women in the very high exposure group showed an increased incidence of astrocytoma I–IV, with a clear exposure–response pattern.

Ivancsits et al. (2002, 2003a, 2003b) have shown that human lymphocytes exposed to ELF MFs can generate DNA single and double strand breaks from a flux density as low as 35 µT and with a strong correlation between both the intensity and duration of the MF exposure.

The IARC evaluation (IARC 2002) ruled out a probable carcinogen classification (group 2A) because the expert panel found the animal studies were "inadequate evidence of carcinogenicity." This judgment was due to many conflicting results in the repetition of long-term animal experiments. In particular, Löscher and Mevissen (1995) reported that MF exposure to Sprague-Dawley (SD) rats after 7,12-dimethylbenz[*a*]anthracene (DMBA) initiation increased breast tumors in the exposed animals at 50 µT compared with the control group (see also Thun-Battersby et al. 1999). However, in a similar study Anderson et al. (1999) found no evidence for a cocarcinogenic or tumor-promoting effect of MF exposure, but the study used different substrains of SD rats than used in the original study. Anderson et al. (2000) stated that "the U.S. rats were more susceptible to DMBA than the European rats"; diet and DMBA were from different sources, and there were differences in environmental conditions and in MF exposure metrics. Fedrowitz et al. (2004) compared two substrains of SD outbred rats; MF exposure significantly increased mammary tumor development and growth in one of the strains of rats but not in the other. These data suggest that genetic background may play a pivotal role in effects of MF exposure; this which might explain the difficulties in replicating the original animal studies of breast tumor promotion.

According to the criteria used by Siemiatycki et al. (2004), a complete list of occupational agents classified as possible human carcinogens would include ELF MFs.

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ELF MFs: Straif et al. Respond

Mild et al. suggest that we should have included magnetic fields at extremely low frequencies (ELF MFs) in our listing of occupational carcinogens (Siemiatycki et al. 2004). We acknowledge that ELF MFs have been classified as "possibly carcinogenic to humans" (Group 2B) by the Monographs Programme of the International Agency for Research on Cancer (IARC 2002) and that there is significant occupational exposure, thereby meeting our operational criterion for inclusion as a possible occupational carcinogen. However, the nature of the evidence that led to the IARC classification complicates the designation of ELF MFs as an occupational carcinogen.

For our article (Siemiatycki et al. 2004), we drew on the evaluations of the IARC Monographs Programme. Each evaluation was based on data that were available at the time of the deliberations of the working group. We supplemented the evaluation by adding information on major occupational exposure circumstances and on the cancer sites affected. For some carcinogens, notably those evaluated recently, such information was explicitly mentioned in the published monograph, but for others it was based on our expert judgment.

For ELF MFs, the IARC evaluation of "possibly carcinogenic" was founded on a determination that there was limited evidence of carcinogenicity in humans based on its effects on childhood leukemia and "inadequate evidence" in experimental animals (IARC 2002). In contrast with an earlier evaluation [National Institute of Environmental Health Sciences (NIEHS) 1998], the IARC Working Group considered that studies conducted among adults, at work or elsewhere, did not provide consistent enough and strong enough evidence to support an evaluation of carcinogenicity. There is no clear-cut way to classify an exposure that has only been demonstrated to be carcinogenic (albeit group 2B) in children, but also occurs among workers. Although we decided not to include ELF MFs in our tables of occupational carcinogens (Siemiatycki et al. 2004), we could have done so with a footnote to explain that the evidence supporting that evaluation was based on children.

Mild et al. also discuss the evidence on the carcinogenic effects of ELF MFs that has arisen since 2002. Although we agree that some of these studies may substantially contribute to an evaluation of the carcinogenic effects of ELF MFs, it was not in the scope of our work to evaluate new information and update the evaluations on all of the agents reviewed. The World Health Organization (WHO) will be holding a meeting of an Environmental Health Criteria Task Group in October 2005; this task group will evaluate the health effects of ELF MFs (including cancer and noncancer outcomes). We anticipate that they will review the recent evidence in conjunction with the evaluation of the 2002 *IARC Monograph*. The WHO Environmental Health Criteria document on ELF MFs should be published shortly after this meeting.

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The NAS Perchlorate Review: Second-Guessing the Experts

The Committee to Assess the Health Implications of Perchlorate Ingestion [National Academy of Sciences (NAS)] released its final report [National Research Council (NRC) 2005] in January 2005, recommending a reference dose (RfD) for perchlorate of 0.0007 mg/kg-day. In a commentary published online on 25 May 2005, Ginsberg and Rice (2005) criticized the adequacy of the NAS committee's scientific deliberations, mischaracterizing the studies reviewed by the committee and second-guessing its conclusions. Ginsberg and Rice (2005) implied that the U.S. Environmental Protections Agency's (EPA's) previous draft RfD of 0.00003 mg/kg-day (U. S. EPA 2002)—and by inference the Massachusetts perchlorate risk assessment [Massachusetts Department of Environmental Protection (Mass DEP) 2004] that mirrored the U.S. EPA's approach and which Ginsberg and Rice peer reviewed—is more scientifically defensible.

The NAS committee was composed of 15 leading physicians and scientists with combined range of expertise to evaluate every scientific aspect of the perchlorate database and of the U.S. EPA's assessment of that database. The makeup of this committee and its credentials are available on the NAS website (NAS 2004). The NAS committee studied and deliberated for more than 15 months before issuing its report. Those deliberations included three public meetings during which it accepted verbal and/or written comments from the U.S. EPA, other government agencies, industry, states, environmental groups, and attorneys. After careful study and consideration of the scientific studies that formed the basis for the U.S. EPA's 2002 draft RfD as well as the 2004 Massachusetts risk assessment (Mass DEP 2004), the NAS committee considered

> several of the animal studies … to be flawed in their design and execution. Conclusions based on those studies, particularly the neurodevelopmental studies, were not supported by the results of the studies.

Although Ginsberg and Rice (2005) implied that the NAS committee should have considered the threshold for measurable iodine uptake inhibition "adverse" and that the NAS inadvertently left out the "A" in NOAEL (no observed adverse effect level), the committee decisively stated that "inhibition of iodide uptake by the thyroid clearly is not an adverse effect." The committee carefully considered the issue of a NOEL (no observed effect level) and a NOAEL. Based

on a clinical study of patients receiving perchlorate long term, the NAS established the NOAEL as 0.4 mg/kg-day (57 times higher than its identified NOEL).

Ginsberg and Rice (2005) further expressed concerns regarding perchlorate in breast milk and the subsequent possibility of decreased breast milk iodine, citing Kirk et al. (2005) and Gibbs (2004). Kirk et al. (2005) reported perchlorate and iodide levels in breast milk samples and noted that "if we take all the available data, there is no meaningful correlation between the perchlorate and iodide levels in breast milk." The study from Chile that Ginsberg and Rice refer to as Gibbs (2004) is now published as Tellez et al. (2005). The study found that iodine nutrition of pregnant women in Chile is very similar to that in the United States. Tellez et al. (2005) found no maternal or neonatal perchlorate-related thyroid effects or decreases in breast milk iodine with perchlorate doses spanning the 0.0007–0.007 mg/kg-day range.

Ginsberg and Rice (2005) argued that perchlorate database deficiencies require an additional uncertainty factor of 3–10 because of key data gaps, citing breast milk concerns and the extrapolation from a 14-day exposure study to chronic exposure. The NAS committee (NRC 2005) considered this and concluded that

> if inhibition of iodide uptake by the thyroid is duration-dependent, the effect should decrease rather than increase with time, because compensation would increase the activity of the sodium-iodide symporter and therefore increase iodide transport into the thyroid.

Evidence has subsequently shown this to be the case (Braverman et al. 2005).

The California EPA perchlorate risk assessment (California EPA 2004) relied on the same studies as the NRC report (NRC 2005). The "point of departure" was based on iodine uptake inhibition by Greer et al. (2002), and a total uncertainty factor of 10 was applied to account for interindividual variability. After reviewing the NRC report (NRC 2005), the California EPA elected not to change its risk assessment or public health goal (California EPA 2005).

In summary, the concerns presented by Ginsberg and Rice (2005) have already been addressed thoroughly by experts on perchlorate and thyroid toxicology and were found to be unsubstantiated. The NAS committee and other experts came to this conclusion based on a comprehensive review of the science in the field, not based entirely on an individual study, which has been mischaracterized by Ginsberg and Rice.

Kerr-McGee Chemical LLC previously manufactured ammonium perchlorate at Henderson, Nevada, and currently is remediating perchlo-

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The NAS Perchlorate Review: Adverse Effects?

Ginsberg and Rice (2005) argued that the reference dose for perchlorate of 0.0007 mg/kg per day recommended by the National Academy of Sciences (NAS) Committee to Assess the Health Implications of Perchlorate Ingestion is not adequately protective. As members of the committee, we disagree.

Ginsberg and Rice (2005) based their conclusion on three points. The first involves the designation of the point of departure as a NOEL (no observed effect level) versus a LOAEL (lowest observed adverse effect level). The committee chose as its point of departure a dose of perchlorate (0.007 mg/kg per day) that, when given for 14 days to seven normal subjects, did not cause a statistically significant decrease in the group mean thyroid iodide uptake (Greer et al. 2002). Accordingly, the committee considered it a NOEL. Ginsberg and Rice (2005) focused on the fact that only seven subjects were given that dose; they seem to say that attention should be paid only to the results in those subjects in whom there was a decrease in thyroid iodide uptake and that the results in those in whom there was no decrease or an increase should be ignored. They considered the dose to be a LOAEL because of the decrease in uptake in those few subjects. It is important to note that a statistically significant decrease of, for example, 5% or even 10% would not be biologically important and, more important, would not be sustained. For example, in another study (Braverman et al. 2004), administration of 0.04 mg/kg per day to normal subjects for 6 months had no effect on thyroid iodide uptake when measured at 3 and 6 months, and no effect on serum thyroid hormone or thyrotropin concentrations measured monthly. [Inspection of Figure 5A in Greer et al. (2002) suggests that this dose would inhibit thyroid iodide uptake by about 25% if measured at 2 weeks.]

The second issue involves database uncertainty. In clinical studies, perchlorate has been administered prospectively to 68 normal subjects for 2 weeks to 6 months. In one study (Brabant et al. 1992), a dose of 9.2 mg/kg per day for 4 weeks had no effect on thyroid function. In occupational studies, doses as high as 0.5 mg/kg per day had no effect on thyroid hormone or thyrotropin production in workers. In epidemiologic studies, there were no abnormalities in growth or thyroid function in children exposed life-long to 100–120 µg perchlorate per liter of drinking water, or in pregnant women and newborn infants similarly exposed. Given the choice of a nonadverse effect (inhibition of iodide uptake by the thyroid) as the point of departure and the multiple studies in which doses of perchlorate much higher than 0.007 mg/kg per day had no effect on any aspect of thyroid function, the committee did not apply a database uncertainty factor.

Finally, Ginsberg and Rice (2005) argued that inhibition of thyroid iodide uptake is adverse. That conclusion assumes that any acute inhibition would be sustained, so thyroid hormone production would decrease. That is not the case. There is remarkable compensation for even substantial reductions in thyroid iodide uptake—and thyroid hormone production. As noted above, subjects given 0.04 mg/kg per day for 6 months and 9.2 mg/kg per day for 4 weeks—doses that certainly would inhibit thyroid iodide uptake for a few weeks—had no decrease in serum thyroid hormone or increase in serum thyrotropin concentrations (the hallmark of even mild hypothyroidism). Short-term inhibition of thyroid iodide uptake is not an adverse effect; it has no adverse consequences because there is rapid compensation mediated by several independent processes. One of these processes is up-regulation of the thyroid sodium-iodide transport system, as a result of intrathyroidal iodide deficiency. The second, should there be even a very small decrease in thyroid hormone production, is an increase in thyrotropin secretion, resulting in overall stimulation of the thyroid gland. Analyses of the effects of any substance on thyroid function must take these compensatory processes into account, particularly the fact that the effect of any substance that inhibits thyroid function will diminish with time. Only if all of these mechanisms fail will there be hypothyroidism, the first adverse effect in the continuum of effects resulting from perchlorate ingestion. If there is no inhibition of iodide uptake to begin with, there will be no other changes in thyroid function at any time.

We believe that the committee's recommended reference dose of 0.0007 mg/kg per day provides a wide margin of safety for all subjects of all ages.

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The NAS Perchlorate Review: Is the RfD Acceptable?

Risk assessors should always carefully evaluate whether a given reference dose (RfD) is the most appropriate choice for assessing risk. In the case of perchlorate, Ginsberg and Rice (2005) suggested that the RfD proposed by the National Research Council (NRC) is inappropriate because the NRC did not thoroughly evaluate the underlying science. However, we suggest that the NRC RfD is inappropriate because of the NRC's "unconventional" approach.

In contrast to Ginsberg and Rice (2005), we applaud the insightful and conclusive discussion of the science of perchlorate and the thyroid by the NRC (2005). The NRC concluded that human studies are the most relevant for risk assessment, and that the thyroid has a remarkable ability to compensate for iodine deficiency, so that hypothyroidism would be the first observed adverse effect. By definition, this is perchlorate's critical effect (Faustman and Omenn 2001), although U.S. Environmental Protection Agency (EPA) methods allow for the use of a known and immediate precursor (the choice of immediate precursor is based on practice of using the highest no observed adverse effect level (NOAEL) of the critical effect and is codified in several places (e.g., Barnes and Dourson 1988, p. 473). The NRC also concluded that in healthy adults the perchlorate dose required to cause hypothyroidism would be > 0.4 mg/kg-day.

In risk assessment parlance, this dose would be a NOAEL of the critical effect. The practice of risk assessment allows us to draw conclusions about public health in the absence of observable data and in the presence of scientific uncertainty. The traditional practice of developing RfD, a dose–response part of risk assessment (Barnes and Dourson 1988), would suggest two possible approaches to developing an RfD from the perchlorate data. The first would be to use the NOAEL of the critical effect from an adult population and apply uncertainty factors to account for sensitive populations and for lack of precision in defining a NOAEL. The second approach would be to use the NOAEL of an immediate precursor effect in a sensitive population and apply appropriate uncertainty factors.

Using the first approach with the NRC NOAEL, the RfD would lie in the range of 0.04–0.004 mg/kg-day depending on the choice of uncertainty factor. Using the second approach, a NOAEL of 0.005 mg/kg-day (Gibbs et al. 2004) can be identified from thyroid hormone and goiter data in a sensitive population. The RfD based on this approach would lie near the value of 0.002 mg/kg-day proposed by Strawson et al. (2004).

In contrast, the approach the NRC actually used was a nonstandard approach for developing an RfD based on the inhibition of iodine uptake, a distant precursor to the critical effect. This nonstandard approach yields a safe dose, but it is not an RfD, by definition, because, according to the NRC's own scheme, it is not based on the critical effect or its known and immediate precursor.

We continue to advocate that the best risk assessment approach for perchlorate is to use data collected from sensitive populations such as children and, in particular, the published and ongoing work in Chile. This is consistent with the NRC's conclusion that the data from Chile could be considered in the evaluation of the U.S. experience with perchlorate in drinking water (NRC 2005). Specifically, the Chilean experience (Crump et al. 2000; Tellez et al. 2005) can be used to help frame the public debate in the United States, which suggests perchlorate water standards as low as 1 ppb. In Chile, perchlorate water concentrations of 100–120 ppb do not result in an exposure that would inhibit iodine uptake inhibition in adults. In fact, these concentrations have not caused any adverse effects in pregnant women, neonates, or older children exposed chronically. Following traditional RfD methods and using data from a sensitive human population results in an RfD that can be used with high confidence in the United States.

Toxicology Excellence for Risk Assessment (TERA) is a nonprofit organization dedicated to the best use of toxicity data for risk values.

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The NAS Perchlorate Review: Ginsberg et al. Respond

We would like to respond to the comments from several members of the NAS perchlorate panel (Johnston et al.) and from two other groups (Gibbs et al., Strawson et al.). These letters were in response to our commentary published in *EHP* (Ginsberg and Rice 2005). The letters take an opposing viewpoint but do not invalidate our main assertions that *a*) the low dose reported in the Greer et al. study (Greer et al. 2002) does in fact demonstrate a majority of subjects with the perchlorate-induced effect; *b*) there is the potential for greater perchlorate vulnerability in pregnant women and newborns than in the general population; and *c*) inhibition of iodide uptake is a key step in the perchlorate toxicodynamic pathway, with moderate levels of uptake inhibition potentially sufficient to produce adverse effects in sensitive subgroups.

The low dose reported by Greer et al. (2002) was termed a no observable effect level (NOEL) by the National Research Council (NRC 2005). We disagreed with this view in our commentary because four of seven individuals at this dose showed the characteristic perchlorate-induced suppression of iodine uptake. Johnston et al. claim that we ignored the nonresponders when we described the low dose in the Greer study (Greer et al. 2002) as an effect level. We did not disregard these subjects, but we pointed out that they segregate out as a subgroup who appear to be less sensitive to the perchlorate effect and have low baseline values. We further pointed out that, because of the small sample size (*n* = 7), there is very little statistical power to detect an effect at Greer et al.'s low dose (0.007 mg/kg/day) given the variability in response. Rather than simply relying on a weak test of significance, our closer inspection of the data indicated that the majority of low-dose subjects were responders. When the results are organized categorically into responders and nonresponders, it is evident that the low dose is part of the dose–response continuum with no evidence of a threshold: 0.5 mg/kg/day, 9 responders out of 9 subjects; 0.1 mg/kg/day, 10 responders out of 10 subjects; 0.02 mg/kg/day, 6 responders out of 10 subjects; and 0.007 mg/kg/day, 4 responders out of 7 subjects. The lack of statistical significance should not be used as grounds for disqualifying what appears to be a biologically significant response.

Hydrogen sulfide provides a good example for illustrating biologic versus statistical significance. In a key study, Jappinen et al. (1990) found that an inhaled dose of hydrogen sulfide did not cause a statistically significant effect on airway parameters in a group of 10 subjects with asthma. However, when these data were used by the Agency for Toxic Substances and Disease Registry (ATSDR) to set a public health benchmark (the acute minimum risk level), the fact that 2 of the 10 asthmatics were responders was sufficient for this dose to be considered a critical effect level (ATSDR 1999). The perchlorate low-dose responders should not be ignored, just as the hydrogen sulfide low-dose responders were not ignored.

Although the NRC considered Greer et al.'s (2002) low dose a NOEL, like us, the U.S. Environmental Protection Agency (EPA) draft assessment (U.S. EPA 2002) and a risk assessment by the Massachusetts Department of Environmental Protection (Mass DEP 2004) considered this dose to be a LOAEL (lowest observed adverse effect level). The California EPA conducted a benchmark dose analysis on the data published by Greer et al. (2002), finding 0.0037 mg/kg/day (approximately 2-fold below Greer et al.'s low dose) the critical point of departure for standard setting (California EPA 2004).

Strawson et al. make the argument that the critical adverse effect of perchlorate is hypothyroidism. It is important to understand that clinical hypothyroidism is not the critical end point for derivation of the perchlorate RfD. Subclinical hypothyroidism in pregnant women can result in adverse nervous system effects in offspring (Zoeller et al. 2002), including decreased IQ (Haddow et al. 1999). Perchlorate's inhibition of iodine uptake increases the risk for hypothyroidism, which even if subclinical, may still be associated with neurodevelopmental effects.

The rebuttal letters (Gibbs et al., Johnston et al., and Strawson et al.) consider inhibition of iodine uptake a nonadverse effect because it is only temporary and because compensatory homeostatic mechanisms would not allow actual declines in thyroid hormone to occur. They cite an abstract by Braverman et al. (2004) to demonstrate that the perchlorate effects seen by Greer et al. (2002) disappear upon longer-term (6 month) exposure. As we pointed out in our commentary (Ginsberg and Rice 2005), the study by Braverman et al. (2004) has not been published or peer reviewed and involves small numbers of subjects. It is unclear whether there was sufficient statistical power to see the perchlorate effect. Since the publication of our commentary we became aware of a different study by this same group (Braverman et al. 2005). Gibbs et al. also mentioned this study. In contrast to their abstract (Braverman et al. 2004), Braverman et al. (2005) show iodine uptake inhibition in relatively young male Caucasian workers who had a median perchlorate exposure period of 5.9 years. The dose response for these long-term perchlorate workers was similar to that shown for subjects exposed to perchlorate for 2 weeks (Greer et al. 2002). This suggests that, contrary to the NRC report (NRC 2005) and Braverman et al. (2004), perchlorate does not lose its potency to inhibit iodide uptake under conditions of long-term exposure.

The fact that the workers in the study by Braverman et al. (2005) did not have indications of thyroid deficiency suggests that healthy workers can compensate for this type of biochemical impairment. This is likely due to several factors, including sufficient iodide and hormone reserves in these workers. However, it is uncertain that perchlorate-induced impairment of iodine uptake would be compensated for in all members of the population. In particular, a substantial percentage of the general public has low iodine intake [Centers for Disease Control and Prevention (CDC) 2000; Hollowell et al. 1998], pregnant women can be at greater risk for iodine deficiency (Azizi et al. 2003), and the neonate appears to have minimal stores of thyroid

hormone (Delange 1998; van den Hove et al. 1999). In addition, the data of Braverman et al. (2005) suggest up-regulation of the iodide symporter in these workers, a protective mechanism that may not exist in the fetus or neonate. Infants have added susceptibility because perchlorate is excreted into breast milk and appears to inhibit iodine secretion into breast milk (Kirk et al. 2005).

On this last point, the letter by Gibbs et al. casts doubt on the relationship between perchlorate and iodine levels in breast milk by quoting from Kirk et al. (2005): "If we take all the available data, there is no meaningful correlation between the perchlorate and iodide levels in breast milk." This is a case of selective quoting, as the very next sentence states, "On the other hand, for breast milk that contained ≥ 10 μg/L perchlorate, the iodide concentration expressed in milk is linearly related to the reciprocal of perchlorate concentration." Although we would agree that the findings of Kirk et al. (2005) need to be further explored, Gibbs et al.'s dismissal of these findings—on the basis of an out-of-context quote—is misleading.

Strawson et al. claim in their letter that the NRC used a nonstandard approach in deriving the perchlorate RfD. Citing an article by Barnes and Dourson (1988), they state that there are two possible approaches to developing an RfD: the use of a NOAEL of a critical effect from an adult population, or the use of the NOAEL of a precursor effect in a sensitive population. Barnes and Dourson (1988) did not discuss such a dichotomy of approaches, nor did more recent U.S. EPA guidance (e.g., U.S. EPA 1991, 2002). In fact, IRIS (the Intergrated Risk Information System; IRIS 2005) defines "critical effect" as "[T]he first adverse effect, or its known precursor, that occurs to the most sensitive species." There is no distinction in any of these documents made for critical end point being chosen based on sensitive population, nor is there discussion of "immediate precursor" versus other precursors, a distinction made by Strawson et al. Therefore, the assertion that the NRC used a nonstandard approach in using a precursor event in a nonsensitive population (adults) is not supported in U.S. EPA guidance (U.S. EPA 1991, 2002).

Also at issue are the uncertainty factors that need to be applied to the data of Greer et al. (2002) to derive a health-protective RfD. The NRC risk assessment included a total 10-fold uncertainty factor (NRC 2005). This factor is expected to cover a lot of ground: variability in toxicokinetics and toxicodynamics among healthy adults, variability caused by low iodine uptake, pregnancy, neonatal vulnerabilities described above, and the data gaps and temporal uncertainties described in our commentary (Ginsberg and Rice 2005). Because of these factors, our scientific judgment is that a 10-fold uncertainty factor is insufficient, which is the same judgment arrived at in the U.S. EPA draft assessment (U.S. EPA 2002) and in the Massachusetts risk assessment (Mass DEP 2004).

The letters of Gibbs et al. and Strawson et al. allude to the Chilean data set (Crump et al. 2000; Tellez et al. 2005) as documenting that early life stages are not especially affected by relatively high exposure to perchlorate in drinking water. If this were the case, it would decrease the level of uncertainty contained in the risk assessment. However, in our commentary (Ginsberg and Rice 2005), we pointed out the limitations of the Chilean data. It requires extrapolation from an iodine-enriched population in Chile to the United States, which has considerably less iodine intake. Further, nearly 5% of school-age children and 15% of women of childbearing age in the United States have low iodine intake (CDC 2000; Hollowell et al. 1998) these individuals are likely not well represented by the Chilean data set. Crump et al. (2000) show an association between high perchlorate in drinking water and family history of thyroid disease. The fact that this association did not extend to altered thyroid status in the children studied raises the possibility that iodine supplementation efforts in recent decades in Chile prevented the perchlorate effect in current-day children (Crump et al. 2000). This leaves open the question of perchlorate-induced effects in children in the United States whose iodine intake is suboptimal. A follow-up study by Tellez et al. (2005) reproduces some of the earlier Chilean findings but shows that in spite of very recent reductions in the iodide content of salt in Chile, iodine levels are still approximately 2-fold higher there than in the United States. The Chilean studies do not remove the uncertainties present in the perchlorate database.

Our disagreement with the NAS perchlorate document (NRC 2005) and with these letters centers around how a no effect level is defined and how vulnerable life stages are factored into a risk assessment. These authors recommend stretching the definition of NOEL to include a dose level in which the majority of the subjects demonstrate the perchlorate effect. Gibbs et al., Johnston et al., and Strawson et al. also recommend using studies of healthy adults and a poorly matched Chilean population to dismiss the adverse nature of perchlorate-induced iodide uptake inhibition for vulnerable subgroups. As state risk assessors, we strive to keep methods and judgment consistent across all chemicals. Applying that to perchlorate leads us to a different analysis than what was presented by the NAS and what is promoted in the letters responding to our commentary (Ginsberg and Rice 2005).

The authors declare they have no competing financial interests.

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ERRATUM

In Figure 2D of Greer et al. [Environ Health Perspect 110:927–937 (2002)], there should have been seven subjects in the 0.007 mg/kg-day group, but *EHP* erroneously included an extra line (without symbols), indicating a nonexistent eighth subject. This error was reproduced in the commentary of Ginsberg and Rice [Environ Health Perspect 113:1117–1119 (2005)] and was included in their argument that there was an inhibitory effect overall in that dose group.
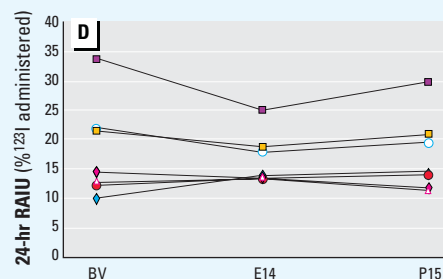
EHP regrets the error.

Figure 2D. The 24-hr thyroid radioiodine uptake (RAIU) at the baseline visit (BV) and on exposure day 14 (E14) and postexposure day 15 (P15) for each subject in the 0.007-mg/kg-day dose group.