

Summary of Public Comments Received on the Government of Canada’s Draft Priority Substance List Assessment Report on three aluminum salts (aluminum chloride, aluminum nitrate and aluminum sulphate)

Formal comments made during the 60-day public comment period that took place from February 7, 2009, to April 8, 2009, on the draft assessment report were provided by the Aluminum Association of Canada.

Comment	Response
<p>The comments describe a number of limitations and areas of uncertainty in the experimental animal data on the effects of oral exposure to aluminum. The commenter concluded that the experimental animal studies cited in the draft PSL report are not relevant to evaluating human risk, and that “there is no evidence that aluminum poses any health risk to adults with normal kidney function.”</p>	<p>We thank the commenter for their detailed comments on key issues. The Government of Canada does consider, however, that the experimental animal studies cited in the PSL report are relevant to evaluating human risk.</p> <p>Toxicokinetic data indicate that the ranges of aluminum bioavailability in drinking water and food for humans and experimental animals largely overlap. These data do not provide evidence for a significant interspecies difference (p. 61). A given administered dose can be anticipated to result in similar blood aluminum levels in animals and humans. Experimental animals do provide a relevant model for human health risk assessment, and despite the limitations of the experimental animal studies described in this PSL assessment, the assessment concludes that “considered in its entirety, [the database] gives evidence for neurological, neurodevelopmental and reproductive toxicity in experimental animals” at the doses administered (p.115).</p> <p>The PSL assessment recognizes the limitations of both the human and experimental animal data sets, and the “clear need for further investigation, in which [experimental animal studies] are designed to provide a basis for determining a critical dose for risk assessment. (p.133)”. Nonetheless, in the absence of results from such a study or studies, a level of concern can be established for aluminum salts based on the existing experimental animal data. Risk can then be characterized by comparing this value to estimated exposure levels (i.e, derivation of a margin of exposure).</p> <p>In the PSL assessment, the focus was on three specific aluminum salts: aluminum chloride, nitrate, and sulphate. Margins of exposure were derived for exposures from drinking water alone, as aluminum sulphate and aluminum chloride contribute significantly to the total Al in drinking water, through the use of these salts in water treatment, but are minor contributors to the total Al in other media, including food. Aluminum nitrate, because of its limited use in Canada, contributes little to total Al concentrations in drinking water,</p>

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	<p>food, or soil. Although aluminum nitrate has a very minor use in the food industry, it is not permitted as a food additive and thus residues of the compound would not remain in or on the food. The magnitude of the resulting margins of exposure demonstrated that there is adequate protection in the Canadian population with respect to potential adverse health effects of aluminum estimated to be derived from these three salts.</p>
<p>The comment was made that there were two major difficulties with the mammalian studies cited in the draft assessment report:</p> <ol style="list-style-type: none"> 1. Blood aluminum levels were not monitored. 2. Indirect effects of aluminum on brain and/or behavior were not considered. 	<ol style="list-style-type: none"> 1. Although blood aluminum levels were generally not monitored in studies examining the neurological and reproductive effects of aluminum in the diet or drinking water, the toxicokinetics of aluminum have been studied in both animals and humans. These toxicokinetic data indicate that the ranges of aluminum bioavailability in drinking water and food for humans and experimental animals overlap. The data do not provide evidence for a significant interspecies difference (p. 61). A given administered dose can be anticipated to result in similar blood aluminum levels in animals and humans. <p>The toxicokinetic data also did not provide evidence for significant differences in aluminum elimination rates between humans and experimental animal species. The commenter states that “although kidney function in humans is not overly vulnerable to aluminum, the kidneys of rodents.... are exquisitely sensitive to the toxic effects of aluminum.” However, the two studies cited to support this statement are animal studies, and do not provide comparative data for human and rodent elimination rates.</p> <ol style="list-style-type: none"> 2. The proposed modes of action for aluminum neurotoxicity, discussed in section 2.4.4 of the PSL Assessment, include both direct effects on the brain and indirect effects such as the perturbation in the distribution and homeostasis of essential metals, and associated adverse metabolic effects. Greater knowledge of the mode of action of aluminum toxicity could contribute to better characterization of risk to human health, particularly through the use of chemical-specific adjustment factors that take into account species and individual differences relative to this mode of action. Nonetheless, the nature of the mode of action (direct or indirect) would not, in itself, alter the overall approach to characterization of risk. The level of concern in risk assessment is based on the observation of adverse effects, regardless of whether the mode of action is direct or indirect.
<p>The comments describe two major difficulties with the draft assessment’s discussion of human studies:</p> <ol style="list-style-type: none"> 1. Two critical studies were neither cited nor discussed 	<p>Rifat et al. 1997 is an unpublished report to the Ontario Minister of Labour. The PSL Assessment reviewed only studies from the published peer-reviewed literature. The commenter suggests that the report may not have been published because it is more difficult to publish negative results than positive ones. We cannot</p>

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<p>The comment was made in regards to the discussion of studies relating to the mode of action of aluminum:</p> <ol style="list-style-type: none"> 1. Thresholds for aluminum's effects were either unknown or physiologically high. 2. The discussion of aluminum's effects in animals was incomplete and misleading. 	<p>The commenter emphasizes the importance of determining “whether the aluminum levels at which toxic effects occur in the animal model correspond to levels seen in humans in normal and disease states.” The commenter is referring to potential differences in the bioavailability, distribution and elimination of aluminum between rodents and humans. Relevant toxicokinetic studies are covered in detail in the PSL Assessment. However there are no studies in which both animal and human serum levels are compared using the same analytical methodology. This is a limitation of the experimental animal database that is recognized in the PSL Assessment (p.63).</p> <p>The commenter limits their comments to the discussion of the relationship between aluminum exposure and Alzheimer's disease, and not the broader assessment of the extensive literature on the effects of aluminum ingestion in experimental animals.</p> <p>The relationship between aluminum exposure and Alzheimer's disease is presented on pp. 97-98. The objective of this section of the PSL Assessment was to summarize the current state of the science on this issue. However, it is important to note that the human health risk characterization presented in the assessment is based on neurological and reproductive effects observed in experimental animals.</p>