While the dose of 50 mg Al/kg bw/d is an estimation of the lower end of a broad range of LOELs observed under different experimental conditions, it is not considered to be an overly conservative estimate of the effect level of concern. As previously discussed, there are two sources of bias against consideration of lower values of LOEL in the above characterization: (a) low-dose studies were not considered if the administered dose was less than the probable base diet dose; and (b) LOELs from single-dose studies may be overestimates of the actual effect levels. The dose of 50 mg Al/kg bw/d has, however, produced neurotoxic, reproductive and developmental effects in laboratory animals more consistently under a wide range of experimental conditions, as compared to lower doses. This exposure level is therefore retained for the purpose of the characterization of human health risks as the level of concern for neurotoxic, neurodevelopmental and reproductive effects.
Figure 3.1 Compilation of the LOEL values from the two major subsets of studies (Adult exposure > 90 days and Reproductive/developmental) considered in the exposure-response analysis.
The numbers represent the 38 studies in which LOELs were observed, as summarized in Tables C1 and C2, and listed below. Where the base diet aluminum level is quantified, the LOEL is expressed as combined dose. NOELs associated with LOELs are indicated when observed.
Study references and endpoints:

Reproductive and developmental studies:

3. Bernuzzi et al. 1989:
   a. Impaired locomotor coordination;
   b. Impaired righting reflex;
   c. Impaired grasping reflex.
4. Muller et al. 1990: Impaired negative geotaxis, impaired performance in suspension and locomotor coordination tests.
5. Gomez et al. 1991: Reduced fetal body weight, increase in skeletal variations.
13. Llansola et al. 1999: Decrease in pup body weight, decreased number of cells in cerebellum, disaggregation of microtubules and neuronal death in cerebellar neuron cultures.
17. Golub and Germann (2001b):
   a. Impaired performance in rotarod test (males);
   b. Decreased weight gain in pups, impaired learning of maze with respect to cue utilization (females).
18. Wang et al. 2002a: Reduced body weight, deficits in synaptic plasticity in dentate gyrus of hippocampus.
21. Cololina et al. 2005:
   a. Reduced forelimb strength in males;
   b. Increased number of days to sexual maturation.
22. Sharma and Mishra 2006: Decreased number of corpora lutea, number of implantation sites, placental and fetal weight, increased skeletal malformations, increased oxidative stress in brains of mothers/fetuses and sucklings.

> 90 days exposure studies in adults:
23. **Commissaris et al. 1982**: Reduced motor activity, impaired learning (shuttle box).
24. **Johnson et al. 1992**: Decreased levels of microtubule associated protein-2 and spectrin in hippocampus.
26. **Lal et al. 1993**: Reduced spontaneous motor activity; impaired learning (shuttle box, maze), increased brain lipid peroxidation, reduced Mg$^{2+}$ and Na$^{+}$/K$^{+}$-ATPase activities.
27. **Florence et al. 1994**: Cytoplasmic vacuolization in astrocytes and neurons.
29. **Zatta et al. 2002**: Increased acetylcholinesterase activity.
30. **Silva et al. 2002**: Increased synaptosomal membrane fluidity, decreased cholesterol/phospholipid ratio in synaptosomes.
31. **Flora et al. 2003**: Evidence of increased lipid peroxidation in brain.
32. **Jing et al. 2004**: Impaired performance in Morris water maze, altered synapses in hippocampus and frontal cortex.
33. **Gong et al. 2005**: Impaired performance in Morris water maze.
34. **Shi-Lei et al. 2005**: Impaired performance in Morris water maze, decrease in long-term potentiation in hippocampal slices.
36. **Huh et al. 2005**: Induced apoptosis in brain, increased efficiency of monoamine oxidases and increased level of caspase 3 and 12 in brain.
37. **Rodella et al. 2006**: Decreased nitrergic neurons in the somatosensory cortex.
38. **Mameli et al. 2006**: Impaired vestibulo-ocular reflex.
3.2.4 Human health risk characterization for aluminum sulphate, aluminum chloride, and aluminum nitrate

As noted in the Introduction (section 1) three aluminum salts are specifically named for assessment on the PSL2: chloride, nitrate and sulphate. Although the data available for the assessment do not allow for accurate quantification of exposure associated with specific salts, it is possible to qualitatively estimate their relative contribution to different environmental media (see Table 3.2).

Based on the use pattern of these three salts, described in section 2.2.1, the major use of sulphate and chloride salts is in water treatment, therefore exposure to these particular salts would be expected via drinking water. Aluminum sulphate has a minor use as a food additive; other aluminum-containing additives are much more widely used. Aluminum nitrate use is limited in comparison to the sulphate and chloride salts. It is used in fertilizers and as a chemical reagent in various industries and is not expected to contribute significantly to aluminum in food and soil, the principal media of total aluminum exposure.

Based on these use patterns, the only media in which the mean concentration is significantly affected by the use of these salts is drinking water. Although the contribution of aluminum via these salts cannot be accurately quantified, in order to quantitatively compare the exposure level of concern with potential exposure to aluminum from the three salts, as a surrogate for exposure it is assumed that all aluminum in drinking water is derived from aluminum chloride and aluminum sulphate.

Therefore, the human health risk characterization for the three salts is based on the comparison of the exposure level of concern of 50 mg/kg bw/d, identified in the exposure-response analysis of section 3.2.3, and the age-group with the highest average daily intake of total aluminum from drinking water (10.8 μg/kg bw/d in non-breastfed infants, see Table 3.1). The ratio of these two levels, generally referred to as the margin of exposure (MOE), is greater than 4000. This margin of exposure is considered adequate, taking into account the fact that aluminum exposure from the three salts is overestimated in this calculation, and the following considerations.

To account for toxicokinetic and toxicodynamic variability and uncertainty, a factor of at least 100 within the MOE is considered appropriate. As there is little consensus as to the mode of action, and multiple mechanisms are likely involved, the delineation of chemical-specific adjustment factors is not possible here. Effects at the lower-bound were generally small changes in performance in motor activity and learning tests identified across a range of studies, and the MOE is considered adequate to account for uncertainties in the identification of this lower-bound.

The adequacy of the collective database for the neurotoxicity and reproductive/developmental toxicity of orally-administered aluminum was reviewed in section 3.2.2.2. As discussed, there
is a clear need for further investigation in experimental animals, in which studies are designed to provide a basis for determining a critical dose for risk assessment. The existing database is nonetheless extensive, providing a basis for the determination of the lower range of LOELs observed in the different studies, carried out under different experimental conditions and for an array of aluminum salts. The neurobehavioural and neurodevelopmental effects most frequently associated with the range of LOELs may be characterized as small but statistically significant changes in performance in motor activity and learning tests.

Collectively the limited aluminum bioavailability data do not indicate that the relative bioavailabilities of aluminum in drinking water, soil and different types of food are significantly different (see section 2.3.3.1). Therefore, it is not anticipated that aluminum from drinking water would contribute relatively more bioavailable aluminum, in proportion to its external dose, as compared with other sources. In addition there is no evidence to suggest that there are differences in relative bioavailability between humans and experimental animals.

3.2.5 Uncertainties and degree of confidence in human health risk characterization

There is a moderately high degree of confidence in the deterministic exposure assessment for aluminum, as it relates to the average external dose associated with food, drinking water, soil and air, due to a large database of experimental information for most media. There is more uncertainty with respect to the maximum or high-end exposures in the population for the different media due to the variability in measured levels.

For total aluminum, food is the principal source of exposure, followed by soil, while exposure via drinking water and air combined is less than 2% of total aluminum intake. Based on their use pattern, the three aluminum salts on the PSL2 are not significant contributors to the principal media of total aluminum exposure. Given the importance of food in the total exposure to aluminum, a probabilistic analysis of the exposure to aluminum from foods accounting for intakes by different subsets of the Canadian population is warranted. In addition, such an analysis should distinguish aluminum originating from food additives from natural aluminum sources in foods.

The greatest uncertainty with respect to the exposure assessment is the uncertainty and variability relating to the extent to which different aluminum salts are absorbed from the different media. Although some experimental bioavailability data are available for food and water, collectively the limited aluminum bioavailability data do not indicate that the relative bioavailabilities of aluminum in drinking water, soil and different types of food are significantly different. However, further research in this area, particularly in regard to soil, could provide evidence for significant differences that would in turn influence the human health risk characterization.

3.2.6 Recommendations for research

Areas for further research are described briefly below, in order to identify the main avenues for reducing the uncertainties associated with the human health database for aluminum.
3.2.6.1 Exposure assessment

Consideration of bioavailability is important to the characterization of human health risks of aluminum if relative bioavailabilities for different exposure media and different species (i.e., humans and experimental animals) differ from unity. This hypothesis could be explored through the determination of bioaccessibilities of aluminum in aluminum-treated drinking water, different soil and dust samples, in selected food items (e.g., processed cheese and packaged bakery items), and in laboratory animal chow, followed by the comparison of these in vitro bioaccessibilities with the in vivo bioavailability of aluminum determined in experimental studies for a given media.

In light of the wide use of aluminum-containing products applied to the skin, the dermal absorption of aluminum in humans should be more adequately characterized.

3.2.6.2 Exposure-response assessment

Further epidemiological study of aluminum exposure in the Canadian population is called for, to the extent that such research addresses the limitations of previous studies, including the characterization of aluminum exposure by dietary and other sources.

Additional experimental animal studies on toxicokinetics of different salts, including aluminum fluoride as well as the neurological and neurodevelopmental effects of aluminum, is necessary to provide information for better characterizing the exposure-response relationship. Following OECD guidelines for neurotoxicity and neurodevelopmental toxicity, these studies would include adequate numbers of animals, multiple doses, and examination of a standard array of neurological and neurodevelopmental endpoints. Note that one such study is currently underway in Canada.

3.3 Conclusion

CEPA 1999 64(a) and 64 (b): Based on the available data, it is proposed that the three aluminum salts, aluminum chloride, aluminum nitrate and aluminum sulphate, are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

CEPA 1999 64(c): Based on available data concerning the exposure of the Canadian population to aluminum chloride, aluminum nitrate and aluminum sulphate, and in consideration of the health effects observed in humans and in experimental animals, it is proposed that these aluminum salts are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.
It is therefore proposed that the three aluminum salts, aluminum chloride, aluminum nitrate and aluminum sulphate, do not meet the definition of “toxic” as set out in section 64 of CEPA 1999.
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<th>Author(s)</th>
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<th>Title</th>
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<td>Su C, Evans LJ</td>
<td>1996</td>
<td>Soil solution chemistry and alfalfa response to CaCO₃ and MgCO₃ on an acidic gleysol</td>
<td>Canadian Journal of Soil Science 76: 41–47</td>
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<tr>
<td>Szerdahelyi P, Kasa P</td>
<td>1988</td>
<td>Intraventricular administration of the cholinotoxin AF64A increases the accumulation of aluminum in the rat parietal cortex and hippocampus, but not in the frontal cortex</td>
<td>Brain Res 444: 356-360</td>
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<td>Talbot RJ, Newton D, Priest ND, Austin JG, Day JP</td>
<td>1995</td>
<td>Inter-subject variability in the metabolism of aluminium following intravenous injection as citrate</td>
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<td>1986a</td>
<td>Effects of aluminum on the growth, development, and nutrient composition of honeylocust (Gleditsia triacanthos L.) seedlings</td>
<td>Tree Physiol 2: 307–316</td>
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APPENDICES

Appendix A

Search methodology for aluminum PSL2 draft assessment

Appendix B

Table B1 Epidemiological Investigations into neurological disease and aluminum in drinking water

Appendix C

Table C1 Subset of experimental animal studies for consideration in the exposure-response analysis: neurotoxic effects in exposed adults.

Table C2 Subset of experimental animal studies for consideration in the exposure-response analysis: developmental neurotoxicity or reproductive effects (prenatal exposure and/or exposure during lactation).
Appendix A

Search Methodology, PSL2 Draft Assessment, Aluminum Salts

Toxicological and Epidemiological Data

A comprehensive search of the toxicological and epidemiological literature in relation to the health effects of aluminum was carried out in preparation of the SOS report published in 2000 (Environment Canada and Health Canada 2000). Since publication of this report, literature searches were conducted using the databases Toxline, Pubmed, and Current Contents as well as the organizational Web sites from the standard Existing Substances Division literature search list (ATSDR, ECETOC, IPCS, NICNAS, Health Canada, National Toxicology Program, WHO/Air, WHO/Water). The keywords (in truncated forms) included “aluminum” plus “toxicity”, “neurotoxicity”, “epidemiology”, “bioavailability”, “mode of action”, “reproductive” and “developmental”. For databases functioning on the basis of CAS registration numbers, the CAS RN of aluminum chloride (7446-70-0), aluminum nitrate (13473-90-0) and aluminum sulphate (10043-01-3) were used.

The comprehensive literature search was conducted through 2007. Some articles published in 2008 may also be included.

In addition to evaluating original study reports in the peer-reviewed literature, Health Canada consulted four recent comprehensive reviews of the literature on the toxic effects of aluminum: ATSDR (2006); InVS-Afssa-Afssaps (2003); JECFA (2006); and Krewski et al. (2007). These reviews were used primarily to supplement the literature search and are also cited as sources for some toxicological and exposure information, where appropriate. However, for all issues central to Health Canada’s evaluation of human health risks, the original articles were consulted and cited.

Exposure Data (see text for sources of data for exposure estimates).

Environmental evaluation

As well as retrieving references from literature database searches, direct contacts were made with researchers, academics and other government agencies. In addition, a survey of Canadian industry was carried out under authority of section 16 of CEPA (Environment Canada 1997b), and a second review aimed at identifying changes in use trends and quantities was conducted in 2007 (Cheminfo Services Inc. 2008). Companies were required to provide information on uses, releases, environmental concentrations, effects or other data that were available to them and related to aluminum salts. Ongoing scans were conducted of the open literature, conference proceedings and the Internet for relevant information. Data obtained to August 2008 were considered in this assessment report.
### Table B1 Epidemiological investigations into neurological disease and aluminum in drinking water

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<th>Collection period</th>
<th>References</th>
<th>Study type</th>
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<th>Exposure measure</th>
<th>Results</th>
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<td>Ontario</td>
<td>1981–1991</td>
<td>McLachlan et al. (1996)</td>
<td>Case-control study</td>
<td>Cases and controls based on brains donated to Canadian Brain Tissue Bank.</td>
<td>Cases: a1—296 AD based on clinical history of dementia and histopathology criteria (neuritic plaques and NFTs in specific brain regions); a2—89 AD as above coexisting with other neuropathologic process. Controls: c1—125 with no brain histopathology; c2—170 with other neurodegenerative diseases.</td>
<td>Total Al in drinking water based on the data of the Water Quality Surveillance Programme of the Ontario Ministry of the Environment for municipal supplies serving place of residence and residential history (1981–1991).</td>
<td>Not weighted for residential history: a1 vs c1 + c2: Al≥100 vs &lt;100 µg/L, OR = 1.7 (95% CI 1.2–2.6) Al≥125 vs &lt;125 µg/L, OR = 3.6 (95% CI 1.4–9.9) Al≥150 vs &lt;150 µg/L, OR = 4.4 (95% CI 0.98–20) Al≥175 vs &lt;175 µg/L, OR = 7.6 (95% CI 0.98–61) a1 + a2 vs c1 + c2: Al≥100 vs &lt;100 µg/L, OR = 1.7 (95% CI 1.2–2.5)</td>
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<td>Ontario</td>
<td>1984–1991</td>
<td>Forbes et al. (1995b)</td>
<td>Cross-sectional study</td>
<td>AD or presenile dementia based on death certificate data (ICD-9 331.0 and ICD-9 290.1) from LSA cohort.</td>
<td>Forbes et al. (1995b): ≈3,000 death certificates reporting dementia (AD and presenile dementia).</td>
<td>Total Al in drinking water based on the data of the Water Quality Surveillance Programme of the Ontario Ministry of the Environment for municipal supplies serving place of residence at time of death.</td>
<td>Forbes et al. (1995b): For individuals of ≥75 years of age with AD: For Al alone: Al≤67 µg/L, RR = 1.00 Al = 68–200 µg/L, RR = 0.91 (95% CI 0.82–1.01) Al≥336 µg/L, RR = 3.15 (95% CI 1.85–5.36) Adjustment for pH: Al≤67 µg/L, pH&lt;7.85, RR = 1.00 Al = 68–200 µg/L, pH = 7.85–7.95, RR = 0.91 (95% CI 0.82–1.00) Al≥336 µg/L, pH≥7.95, RR = 3.27 (95% CI 1.92–5.57) Adjustment for F: Al≤67 µg/L, RR = 1.00</td>
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**Table B1 Epidemiological investigations into neurological disease and aluminum in drinking water**

Forbes and McLachlan (1996):
For individuals ≥85 years of age:
For AI alone:
AI = 68–250 µg/L vs ≤67 µg/L, RR = 0.85, p<0.05
AI>250 µg/L vs ≤67 µg/L, RR = 4.76, p<0.05

Adjustment for water source:
AI = 68–250 µg/L vs ≤67 µg/L, RR = 0.88, p>0.05
AI>250 µg/L vs ≤67 µg/L, RR = 4.93, p<0.05

RR corresponds to rate ratio where the population reference was from Ontario Longitudinal Study of Aging.
Table B1  Epidemiological investigations into neurological disease and aluminum in drinking water

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<td>Ontario</td>
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<td>Cross-sectional study</td>
<td>Males with cognitive impairment based on interview/questionnaire with modified mental status test for subjects from the LSA cohort. For deceased persons, the questionnaires were administered to survivors or proxy respondents. Forsyth et al. (1992): 485 males. Forsyth et al. (1994): 290 males for analysis restricted to treated surface drinking water and 485 males for other analysis.</td>
<td>Total Al in drinking water based on the data of the Water Quality Surveillance Programme of the Ontario Ministry of the Environment for municipal supplies serving place of residence and residential history. Medians of Al and F</td>
<td>Forbes et al. (1992): Based on treated water: Al≥84.7 µg/L vs Al&lt;84.7 µg/L OR = 1.14 (p&lt;0.05) Al&lt;84.7 µg/L, F≥880 µg/L OR = 1.00 Al&lt;84.7 µg/L, F&lt;880 µg/L OR = 1.69 (p&lt;0.05) Al&lt;84.7 µg/L, F&lt;880 µg/L OR = 2.21 (p&lt;0.05) Al&lt;84.7 µg/L, F&lt;880 µg/L OR = 2.72 (p&lt;0.01) Al&lt;84.7 µg/L, F&lt;880 µg/L OR = 1.00 Al&lt;84.7 µg/L, F&lt;880 µg/L OR = 0.45 (p&lt;0.05) Al&lt;84.7 µg/L, F&lt;880 µg/L OR = 1.23 (p&lt;0.05) Al&lt;84.7 µg/L, F&lt;880 µg/L OR = 1.00 other combinations of Al and F, OR=0.61 (p&gt;0.05) Al&lt;84.7 µg/L, F&lt;880 µg/L OR = 1.00 Al&lt;84.7 µg/L, F&lt;880 µg/L OR = 1.69 (p&gt;0.05) other combinations of Al and F, OR = 1.95 (p&lt;0.05) Similar analyses with raw water concentrations were presented but no significant association was reported.</td>
<td>Forbes et al. (1992), Forbes et al. (1994), Forbes and Agwani, (1994), Forbes et al. (1995a): Exposure not weighted for residential history. Cognitive impairments generally slight. Forbes et al. (1992), Forbes and Agwani, (1994): No control for age, education, occupation, etc.</td>
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<td></td>
<td>Forbes et al. (1994): 290 males for analysis restricted to treated surface drinking water and 485 males for other analysis.</td>
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</table>

Adjustment for water source, Si:
Al = 68–250 µg/L vs ≤ 67 µg/L, RR = 0.91, p>0.05
Al>250 µg/L vs ≤ 67 µg/L, RR = 5.07, p<0.05

Adjustment for water source, Si, Fe:
Al = 68–250 µg/L vs ≤ 67 µg/L, RR = 0.89, p>0.05
Al>250 µg/L vs ≤ 67 µg/L, RR = 6.27, p<0.05

Adjustment for water source, Si, Fe, pH:
Al = 68–250 µg/L vs ≤ 67 µg/L, RR = 0.90, p>0.05
Al>250 µg/L vs ≤ 67 µg/L, RR = 7.38, p<0.05

Adjustment for water source, Si, Fe, pH, F:
Al = 68–250 µg/L vs ≤ 67 µg/L, RR = 0.90, p>0.05
Al>250 µg/L vs ≤ 67 µg/L, RR = 9.95, p<0.05
<table>
<thead>
<tr>
<th>Location Collection period</th>
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<tr>
<td></td>
<td>Forbes and Agwani (1994): 530 males.</td>
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<td>concentrations are the cut-off values.</td>
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<td>Forbes et al. (1995a): 494–541 males for each analysis.</td>
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<td>Forbes et al. (1994): Increased ORs when analysis restricted to subjects residing &gt;5 years at current address.</td>
<td>Analyses based on all treated drinking water (N = 485):</td>
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<td>pH&lt;7.85 (N = 68)</td>
<td>Al≥84.7 vs &lt;84.7 µg/L, OR = 0.76 (95% CI 0.28–2.06)</td>
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<td>Al≥84.7 vs &lt;84.7 µg/L with F&lt;880 µg/L, OR = 0.91 (95% CI 0.30–2.74)</td>
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<td>pH = 7.85–8.05 (N = 54)</td>
<td>Al≥84.7 vs &lt;84.7 µg/L, OR = 0.68 (95% CI 0.21–2.19)</td>
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<td>Al≥84.7 vs &lt;84.7 µg/L with F&lt;880 µg/L, OR = 0.67 (95% CI 0.07–6.41)</td>
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<td>pH&gt;8.05 (N = 363)</td>
<td>Al≥84.7 vs &lt;84.7 µg/L, OR = 1.30 (95% CI 0.85–2.04)</td>
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<td>Al≥84.7 vs &lt;84.7 µg/L with F&lt;880 µg/L, OR = 1.36 (95% CI 0.55–3.39)</td>
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<td></td>
<td></td>
<td>Al≥84.7 vs &lt;84.7 µg/L, F≥880 vs &lt;880 µg/L, OR = 0.87 (95% CI 0.50–1.52)</td>
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<td></td>
<td>Al&lt;84.7 µg/L, F≥880 vs &lt;880 µg/L, OR = 0.47 (95% CI 0.23–0.97)</td>
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<tr>
<td></td>
<td></td>
<td>Logistic regression adjusted for F, pH, water source, age, education, health, income and number of moves:</td>
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<tr>
<td></td>
<td></td>
<td>Al≥84.7 vs &lt;84.7 µg/L, OR = 1.72 (95% CI 1.08–2.75)</td>
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</table>
**Table B1 Epidemiological investigations into neurological disease and aluminum in drinking water**

<table>
<thead>
<tr>
<th>Location</th>
<th>Collection period</th>
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<th>Study type</th>
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<th>Results</th>
<th>Comments</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Neri and Hewitt (1991)</td>
<td>Case-control</td>
<td>Cases: AD and presenile dementia based on ICD criteria from individuals’ hospital discharge data. Controls: other diagnoses (not psychiatric or neurological) matched to the Ontario Water Quality Surveillance Programme of the Ontario</td>
<td>carbon and water source: Al≥84.7 vs &lt;84.7 µg/L, OR = 1.97 (95% CI 1.21–3.22)</td>
<td>Logistic regression adjusted for F, pH, turbidity, dissolved organic carbon, water source and detailed source: Al≥84.7 vs &lt;84.7 µg/L, OR = 2.27 (95% CI 1.27–4.07)</td>
<td>Neri and Hewitt (1991); Neri et al. (1992): Significant dose-response between AD and concentrations ≥10 µg/L (p&lt;0.05). Neri and Hewitt (1991): &lt;10 µg/L, RR = 1.0 10–99 µg/L, RR = 1.13 100–199 µg/L, RR = 1.26</td>
</tr>
<tr>
<td>Location</td>
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<td>Quebec (Saguenay-Lac-Saint-Jean)</td>
<td>Gauthier et al. (2000)</td>
<td>Cases: 68 probable and possible AD based on a three-step procedure: (1) MMS examination, (2) DSM-IV criteria, (3) NINCDS-ADRDA and ICD-10. Controls: 68 free of cognitive impairment, matched with cases for age and sex. ≥70 years of age.</td>
<td>Ministry of the Environment for municipal supplies serving place of current residence.</td>
<td>&gt;200 µg/L, RR = 1.46 95% CI or p value are not mentioned</td>
<td>the history of exposure. Possible inaccuracies in death certificate data due to the different certification practices of local doctors.</td>
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<td>Neri et al. (1992): &lt;10 µg/L, RR = 1.00 10–99 µg/L, RR = 1.15 100–199 µg/L, RR = 1.45 &gt;200 µg/L, RR = 1.46 95% CI or p value are not mentioned</td>
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<td>For long-term exposure to Al (1945 to onset): No significant association for any Al species.</td>
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<td>For exposure estimated at onset (vs &lt;fourth quartile): Total (&gt;77.2 µg/L): OR = 2.10 (95% CI 0.83–5.35) Total dissolved (&gt;38.9 µg/L): OR = 1.93 (95% CI 0.79–4.67) Monomeric organic (&gt;12.2 µg/L): OR = 2.67 (95% CI 1.04–6.90) Monomeric inorganic (&gt;8.4 µg/L): OR = 0.71 (95% CI 0.29–1.72) Al-OH (&gt;8 µg/L): OR = 0.53 (95% CI 0.20–1.42) Al-F (&gt;0.3 µg/L): OR = 0.67 (95% CI 0.26–1.67) Al-Si (&gt;0.4 µg/L): OR = 0.67 (95% CI 0.26–1.69) Polymeric (&gt;14.6 µg/L): OR = 1.98 (95% CI 0.79–4.98)</td>
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<tr>
<td>France (southwestern: Gironde and Dordogne)</td>
<td>Jacqmin et al. (1994) Jacqmin-Gadda et al. (1996)</td>
<td>Cognitive impairment based on the MMS examinations of individuals ≥65 years of age from the PAQUID cohort. Jacqmin et al. (1994): 3,469 individuals.</td>
<td>Total Al in drinking water based on data from treatment plant or distribution system serving</td>
<td>No significant association with Al without adjustment for pH; association positive for pH≤7.3, association negative for pH≥7.3 (p values not mentioned).</td>
<td>Control for age, sex, education levels, principal lifetime occupation and calcium.</td>
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<td>Logistic regression adjusted for age, sex, education, occupation, calcium, pH.</td>
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Table B1: Epidemiological investigations into neurological disease and aluminum in drinking water
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<tbody>
<tr>
<td>France</td>
<td>(southwestern: Gironde and Dordogne)</td>
<td>1988–1989 to 1997</td>
<td>Longitudinal study (follow-up analysis in eight years)</td>
<td>Dementia and AD based on a two-step procedure: (1) DSM-III criteria, (2) for those with positive DSM results or decline of MMS score (&gt;2 points), NINCDS-ADRDA criteria for AD and Hachinski score for vascular dementia. Re-evaluation of the subjects one, three, five and eight years after the initial visit (the subjects from Dordogne were not re-evaluated after one</td>
<td>Total Al in drinking water based on data from treatment plant or distribution system serving place of residence (from two analysis surveys). Data from distribution system were weighted to take into account the period length of use of each treatment plant over the previous 10 years (1981–1991) and the hourly flow or the relative contribution of the treatment plant.</td>
<td>OR = 5.2 (95% CI 1.1–25.1), with increase of logarithm of the Al concentration (1 mg Al/L) OR = 0.80 (95% CI 0.65–0.98), with increase of logarithm of the Al concentration (1 mg Al/L) with the pH/Al interaction term No significant association (p&gt;0.05) when adjusted for education and occupation.</td>
<td>weighted for residential history.</td>
</tr>
<tr>
<td>France</td>
<td>(southwestern: Gironde and Dordogne)</td>
<td>1988–1989 to 1997</td>
<td>Longitudinal study (follow-up analysis in eight years)</td>
<td>Dementia and AD based on a two-step procedure: (1) DSM-III criteria, (2) for those with positive DSM results or decline of MMS score (&gt;2 points), NINCDS-ADRDA criteria for AD and Hachinski score for vascular dementia. Re-evaluation of the subjects one, three, five and eight years after the initial visit (the subjects from Dordogne were not re-evaluated after one</td>
<td>Total Al in drinking water based on data from treatment plant or distribution system serving place of residence (from two analysis surveys). Data from distribution system were weighted to take into account the period length of use of each treatment plant over the previous 10 years (1981–1991) and the hourly flow or the relative contribution of the treatment plant.</td>
<td>Logistic regression adjusted for age, sex, education, occupation, calcium, pH, Si: Only significant association (p&lt;0.05) with Al when the cutpoint was the first quartile of Al (vs median and third quartile): Al≥3.5 µg/L vs &lt;3.5 µg/L: OR = 1.65 (95% CI 0.80–3.39) (without Al/Si interaction term) OR = 3.94 (95% CI 1.39–11.2) (with Al/Si interaction term)</td>
<td>Logistic regression adjusted for personal characteristics and calcium: Al&lt;3.5 µg/L, pH&lt;7.35, Si&lt;10.4 mg/L, OR = 1.00 Al≥3.5 µg/L: pH≥7.35, Si≥10.4 mg/L, OR = 0.75 (95% CI 0.59–0.96) pH≥7.35, Si&lt;10.4 mg/L, OR = 0.89 (95% CI 0.64–1.22) pH&lt;7.35, Si≥10.4 mg/L, OR = 0.74 (95% CI 0.53–1.02) pH &lt; 7.35, Si &lt; 10.4 mg/L, OR = 1.30 (95% CI 0.75–2.24)</td>
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**Table B1 Epidemiological investigations into neurological disease and aluminum in drinking water**

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Table B1 Epidemiological investigations into neurological disease and aluminum in drinking water

<table>
<thead>
<tr>
<th>Location</th>
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<tbody>
<tr>
<td>Eight regions of England and Wales 1986–1992</td>
<td>Martyn et al. (1997)</td>
<td>Cases: 106 with clinical diagnosis of AD or normal computer tomography (CT) scan or cerebral atrophy, with a progressive deterioration of cognition in the absence of other causes for dementia. Controls: 99 patients with other types of dementia</td>
<td>AI in drinking water based on data from treatment plant or distribution system serving place of residence and residential history from age</td>
<td>No significant association between AD and drinking water concentrations based on several OR (27 OR were presented and were not significant p&gt;0.05): AI = 15–44, AI = 45–109 and AI ≥110 µg/L in comparison to AI&lt;15 µg/L. When: AI concentrations were averaged over 10 years before diagnosis AI concentrations were averaged from age 25 to 10 years before</td>
<td>Control for age, neuroradiology centre where diagnosis was made and distance of residence from neuroradiology centre. AD clinical</td>
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<tr>
<td>France (southwestern: Gironde and Dordogne) 1988–1989</td>
<td>Michel et al. (1991)</td>
<td>Possible and probable AD based on a two-step procedure: (1) DSM-III, (2) NINCDS-ADRDA criteria in 2,731 individuals ≥65 years of age from the PAQUID cohort.</td>
<td>Total Al in drinking water based on data from treatment plant or distribution system serving place of residence (years of collection not mentioned).</td>
<td>Spearman rank correlation between Al concentration and AD was significantly different from zero (p&lt;0.05). Logistic regression adjusted for age, education and place of residence: Increase of 10 µg/L, RR = 1.16, p = 0.0014 Increase of 100 µg/L, RR = 4.53 (95% CI 3.36–6.10)</td>
<td>Control for age, education, rural and urban residence. Relationship between Al and AD discounted based on updated analyses of water Al levels post-publication (Smith 1995; WHO 1997).</td>
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### Table B1 Epidemiological investigations into neurological disease and aluminum in drinking water

<table>
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<tr>
<th>Location</th>
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<tbody>
<tr>
<td>Northern England</td>
<td>1990–1992</td>
<td>Forster et al. (1995)</td>
<td>Case-control study</td>
<td>Cases: 109 AD-type presenile dementia diagnosed before 65 years of age based on a three-step procedure: (1) hospital case notes (NINCDS-ADRDA and DSM criteria), (2) MMS examination, (3) geriatric mental state examination. Controls: 109 from general population paired for age and sex with exclusion of potentially dementia.</td>
<td>Al in drinking water based on data from water treatment plant serving place of residence, and residential history for longest residence in the 10 years before disease onset. Consumption of tea and of antacid based on interview data.</td>
<td>Al in drinking water 10 years before dementia onset: Al&lt;50 vs &gt;50 µg/L, OR = 1.2 (95% CI 0.67–2.37) Al&gt;50 vs &lt;50 µg/L, OR = 0.8 (95% CI 0.42–1.50) Al&gt;99 vs &lt;99 µg/L, OR = 0.8 (95% CI 0.44–1.49) Al&gt;149 vs &lt;149 µg/L, OR = 1.0 (95% CI 0.41–2.43)</td>
<td>Same conclusions when the exposure is based on Al in drinking water at birthplace (N = 80 cases/control).&gt;4 cups tea/day, OR = 1.4 (95% CI 0.81–2.63) Prolonged antacids used, OR = 1.6 (95% CI 0.77–3.51)</td>
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<tr>
<td>Northern England (three districts: North Tyneside, Sunderland and Durham)</td>
<td>1982–1985</td>
<td>Wood et al. (1988)</td>
<td>Cross-sectional study</td>
<td>Dementia in 386 patients with hip fracture &gt;55 years of age (no information about the mental test).</td>
<td>Al in drinking water based on data from water treatment plants either in two districts where water is not treated with aluminum coagulants (low Al) or in a district where water is treated</td>
<td>No significant difference in mental test scores between the residents from district with high-Al level (180–250 µg/L) and those from districts with low-Al levels (≤50 µg/L).</td>
<td>Control for age and sex. Primary focus of study was bone mass/hip fracture. No information on the history of exposure. Details of mental test scores not stated.</td>
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</table>
Table B1 Epidemiological investigations into neurological disease and aluminum in drinking water

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<tbody>
<tr>
<td>Switzerland (Zurich) ≈1989</td>
<td>Wettstein et al. (1991)</td>
<td>Cross-sectional study</td>
<td>Cognitive impairment based on MMS scores in 805 residents of two districts aged 81–85 years (400/district) and residing in each district &gt;15 years.</td>
<td>Al in drinking water based on data from water treatment plants either in a district where water is not treated with aluminum coagulants (low Al) or in a district where water is treated with alum (high Al), and place of residence.</td>
<td>No significant difference in MMS scores between the residents from the district with low mean Al level (4 µg/L) and those from the district with high mean Al level (98 µg/L).</td>
<td>Control for socioeconomic status, age and education. No significant differences in Al serum, Al urine or Al urine/creatinine ratio in 20 patients with probable AD in comparison to 20 control patients.</td>
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Notes:
AD = Alzheimer’s disease
Al = Aluminium
F = Fluoride
LSA = Ontario Longitudinal Study of Aging
NFT = neurofibrillary tangles
OR = Odds ratio
PAQUID = Principle Lifetime Occupation and Cognitive Impairment in a French Elderly Cohort study (≥65 years old)
RR = Relative risk
Si = Silicon
Criteria for Alzheimers or dementia diseases:
ADRDA = Alzheimer’s Disease and Related Disorders Associations
DSM = Diagnostic and Statistical Manual of Mental Disorders
ICD = International Classification of Diseases (World Health Organization)
MMS = mini-mental state examination
NINCDS = National Institute of Neurological and Communicative Disorders and Stroke

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## Appendix C

### Tables

<table>
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<tr>
<th>Table C1 Subset of experimental animal studies for consideration in the exposure-response analysis: neurotoxic effects in exposed adults</th>
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<tr>
<td><strong>Species, sex, strain and number</strong></td>
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<tr>
<td><strong>Al species (number of dose levels in addition to control)</strong></td>
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<tr>
<td>RATS</td>
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<tr>
<td>Male Sprague-Dawley rats (five per group)</td>
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<tr>
<td>Al sulphate</td>
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<tr>
<td>Wistar rats (3 age groups: 3, 10, 24 months) (20 per dose per age group)</td>
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<tr>
<td>Al chloride</td>
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<tr>
<td>Male Sprague-Dawley rats (six per group)</td>
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<tr>
<td>Al maltolate</td>
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<tr>
<td>Male Wistar rats (seven per group)</td>
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<tr>
<td>Al chloride</td>
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<tr>
<td>Male Wistar rats (ten per group)</td>
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<tr>
<td>Al chloride</td>
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<tr>
<td>Sprague-Dawley rats (nine per group)</td>
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<tr>
<td>Species, sex, strain and number</td>
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<tr>
<td>Al chloride</td>
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<tr>
<td>Male rats (strain not specified) (20–40 per group) Al species not specified (indicated to be water-soluble)</td>
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<tr>
<td>Male Wistar rats (ten per group) Al nitrate</td>
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<tr>
<td>Male Lister hooded rats (11–24 per group) Al sulphate</td>
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<tr>
<td>Male Sprague-Dawley rats (ten per group) Al nitrate with citrate (two dose levels)</td>
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<tr>
<td>Male Druckrey albino rats (40 per group) Al chloride</td>
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<tr>
<td>Wistar rats (6–8 per group) Al citrate</td>
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<tr>
<td>Male Druckrey albino rats (90 per exposure group; 6 to 10 animals per test group)</td>
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<tr>
<td>Species, sex, strain and number</td>
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</tbody>
</table>
| Al species (number of dose levels in addition to control) | Dose levels in study: Dₐ (administered dose), or Dₑ (combined dose) | | Dₐ = administered dose  
Dₑ = combined dose | |
| **Al chloride** | Dₐ: 52 mg Al/kg bw/d* | Reduction in Mg²⁺- and Na⁺K⁺-ATPase activities. | **LOEL** = 420 (Dₐ) | Johnson et al. (1992) |
| Male Sprague-Dawley rats (4–6 per group) | Drinking water, for three months | Decrease in levels of microtubule associated protein-2 and spectrin in hippocampus. | **LOEL** = 50 (Dₐ) | Commissaris et al. (1982) |
| Al sulphate | One dose level: Dₐ: 420 mg Al/kg bw/d* | | | |
| Male Sprague-Dawley rats (8-14 per group) | Diet for 11 months | Reduction in motor activity; Impaired learning (shuttle box). | **LOEL** = 333 (Dₐ) | Zatta et al. (2002) |
| Al chloride | One dose level: Dₐ: 50 mg Al/kg bw/d* | | | |
| **MICE** | | | | |
| CD mice (10 per group) | Gavage, for three months | Increase in acetylcholinesterase activity. | **LOEL** = 160 (Dₑ) | Golub et al. (1992) |
| Al lactate | One dose level: Dₑ: 333 mg Al/kg bw/d* | | | |
| Swiss Webster mice (10–12 per group) | Diet for 90 days | Decrease in motor activity, hindlimp grip strength, and auditory and air puff startle responsiveness. | **LOEL** = 90 (Dₑ) | Katz et al. (1984) |
| Al lactate | One dose level: Dₑ: 160 mg Al/kg bw/d** | | | |
| **DOGS** | | | | |
| Beagle dogs (6M, 6F per dose) | Diet for 6 months | No difference in body weight; No ocular changes; No effect on haematological parameters; No change in organ weight. | **NOEL** = 90 (Dₑ) | Katz et al. (1984) |
| Acidic SALP | Three dose levels: Dₑ: 9.5, 29.0 or 90.0 mg Al/kg bw/d | | | |

* Dose calculated with Health Canada’s reference values for body weights and intakes (Health Canada 1994).
** Dose calculated with author’s reported body weights and intakes.
<table>
<thead>
<tr>
<th>Species, strain and number</th>
<th>Exposure</th>
<th>Critical effects in pups (or dams where indicated)</th>
<th>LOEL or NOEL (mg Al/kg bw/d)</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td><strong>RATS</strong></td>
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<tr>
<td>Sprague-Dawley rats (12 per group)</td>
<td>Drinking water, during gestation and lactation</td>
<td>Biphasic effect on learning: improved performance at Dₐ= 50 mg/kg bw/d, but no difference compared to controls at Dₐ= 100 mg/kg bw/d; No effect on motor activity.</td>
<td>NOEL = 103 (Dₐ)</td>
<td>Roig et al. (2006)</td>
</tr>
<tr>
<td>Al nitrate with citrate</td>
<td>Two maternal dose levels: Dₐ: 50 or 100 mg Al/kg bw/d</td>
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<tr>
<td>Wistar rats (eight per group)</td>
<td>Gavage, during gestation and lactation</td>
<td>Decrease in placental and fetal weight; Increase in number of resorptions; Increase in skeletal malformations; Increase in oxidative stress in brains of mothers/fetuses and sucklings.</td>
<td>LOEL = 70 (Dₐ)</td>
<td>Sharma and Mishra (2006);</td>
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<tr>
<td>Al chloride</td>
<td>One maternal dose level: Dₐ: 70 mg Al/kg bw/d</td>
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<tr>
<td>Sprague-Dawley rats (5–6 per group)</td>
<td>Gavage, during lactation, pups also exposed 39 days after weaning via gavage</td>
<td>Increased lipid peroxidation, decrease in superoxide dismutase and catalase activity in cerebrum and cerebellum.</td>
<td>LOEL = 100 (Dₐ)</td>
<td>Nehru and Anand (2005)</td>
</tr>
<tr>
<td>Al chloride</td>
<td>One maternal dose level: Dₐ: 100 mg Al/kg bw/d</td>
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<tr>
<td>Sprague-Dawley rats (10–14 per group)</td>
<td>Drinking water, during gestation and lactation</td>
<td>Increase in number of days to sexual maturation.</td>
<td>LOEL = 53 (Dₐ) (females) LOEL = 103 (Dₐ) (males)</td>
<td>Colomina et al. (2005)</td>
</tr>
<tr>
<td>Al nitrate with citrate</td>
<td>Two maternal dose levels: Dₐ: 50 or 100 mg Al/kg bw/d</td>
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<tr>
<td>Sprague-Dawley rats (10–14 per group)</td>
<td>Drinking water, during gestation and lactation</td>
<td>Improved performance in learning tests (passive avoidance, water maze).</td>
<td>LOEL = 103 (Dₐ)</td>
<td></td>
</tr>
<tr>
<td>Al nitrate with citrate</td>
<td>Two maternal dose levels: Dₐ: 50 or 100 mg Al/kg bw/d</td>
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<tr>
<td>Wistar rats (≈ seven pups per group)</td>
<td>Drinking water, during lactation</td>
<td>Deficits in synaptic plasticity in dentate gyrus of hippocampus.</td>
<td>LOEL = 85 (Dₐ)</td>
<td>Chen et al. (2002)</td>
</tr>
<tr>
<td>Al chloride</td>
<td>One maternal dose level: Dₐ: 85 mg Al/kg bw/d</td>
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</tbody>
</table>
Table C2 Subset of experimental animal studies for consideration in the exposure-response analysis: developmental neurotoxicity or reproductive effects (prenatal exposure and/or exposure during lactation)

<table>
<thead>
<tr>
<th>Species, strain and number</th>
<th>Exposure</th>
<th>Critical effects in pups (or dams where indicated)</th>
<th>LOEL or NOEL</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al species (number of dose levels in addition to control)</td>
<td>Al chloride</td>
<td>Drinking water, in three groups: gestation, lactation, and lactation and lifetime.</td>
<td>Reduced body weight; Deficits in synaptic plasticity in dentate gyrus of hippocampus. (greatest effect in rats exposed from parturition throughout life, while prenatal exposure was associated with the least effect)</td>
<td>LOEL = 85 (Dₐ)</td>
</tr>
<tr>
<td>Wistar rats (4–10 per group)</td>
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<td>One maternal dose level: Dₐ: 85 mg Al/kg bw/d (same dose for pups following lactation)</td>
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<tr>
<td></td>
<td>Wistar rats (number not specified)</td>
<td>Drinking water, during gestation</td>
<td>Decrease in pup body weight; Decreased number of cells in cerebellum; Disaggregation of microtubules and neuronal death in cerebellar neuron cultures.</td>
<td>LOEL = 663 (Dₐ)</td>
</tr>
<tr>
<td></td>
<td>Al sulphate</td>
<td>One maternal dose level: Dₐ: 63 mg Al/kg bw/d</td>
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<tr>
<td></td>
<td>Long Evans rats (number not specified)</td>
<td>Drinking water, during gestation or prior to mating and then during gestation and lactation</td>
<td>Delayed expression of phosphorylated high molecular weight neurofilament protein in tracts in diencephalon; Maternal toxicity.</td>
<td>LOEL = 450 (Dₐ)</td>
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<tr>
<td></td>
<td>Al lactate</td>
<td>One maternal dose level: Dₐ: 450 mg Al/kg bw/d</td>
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<td></td>
<td>THA rats (8–20 pups per group)</td>
<td>Gavage, dams exposed one time (GD½)</td>
<td>Maternal toxicity; Decreased pup weight; Delay in pinna detachment and eye opening in females; Delayed development of auditory startle in males.</td>
<td>LOEL = 183 (Dₐ)</td>
</tr>
<tr>
<td></td>
<td>Al chloride</td>
<td>2 maternal dose levels: Dₐ: 183 or 366 mg Al/kg bw/d</td>
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<tr>
<td></td>
<td>Sprague-Dawley rats (15–19 dams per group)</td>
<td>Gavage, during gestation</td>
<td>Fetal body weight reduced; Skeletal variations increased in Al hydroxide + citrate group.</td>
<td>LOEL = 133 (Dₐ)</td>
</tr>
<tr>
<td></td>
<td>Al hydroxide with and without citrate</td>
<td>One maternal dose level: Dₐ: 133 mg Al/kg bw/d</td>
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<tr>
<td></td>
<td>Wistar rats (6–9 dams per group)</td>
<td>Diet during gestation</td>
<td>Impaired negative geotaxis; Impaired performance in suspension and locomotor coordination tests.</td>
<td>LOEL = 400 (Dₐ)</td>
</tr>
<tr>
<td></td>
<td>Al lactate</td>
<td>One maternal dose level: Dₐ: 400 mg Al/kg bw/d</td>
<td>No effects in righting or grasping reflex.</td>
<td>NOEL = 400 (Dₐ)</td>
</tr>
<tr>
<td>Species, strain and number</td>
<td>Exposure</td>
<td>Critical effects in pups (or dams where indicated)</td>
<td>LOEL or NOEL (mg Al/kg bw/d)</td>
<td>References</td>
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<tr>
<td>Wistar rats (6–12 dams per group)</td>
<td>Diet during gestation</td>
<td>Impaired grasping reflex and impaired righting reflex.</td>
<td>LOEL = 300 (Da) NOEL = 100 (Da)</td>
<td>Bernuzzi et al. (1989b)</td>
</tr>
<tr>
<td>Al chloride and Al lactate</td>
<td>Three maternal dose levels</td>
<td>Negative geotaxis and locomotor coordination.</td>
<td>LOEL = 400 (Da) NOEL = 300 (Da)</td>
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<tr>
<td></td>
<td>Al chloride: 100, 300 and 400 mg Al/kg bw/d</td>
<td>Impaired grasping reflex.</td>
<td>LOEL = 200 (Da) NOEL = 100 (Da)</td>
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<tr>
<td></td>
<td>Al lactate: 100, 200 and 400 mg Al/kg bw/d</td>
<td>Impaired righting reflex.</td>
<td>NOEL = 400 (Da)</td>
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<tr>
<td></td>
<td></td>
<td>Negative geotaxis.</td>
<td>NOEL = 200 (Da)</td>
<td></td>
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<tr>
<td>Wistar rats (12 to 14 dams per groups)</td>
<td>Diet, during gestation</td>
<td>Reduced body weight of pups; Impaired negative geotaxis.</td>
<td>LOEL = 160 (Da)</td>
<td>Bernuzzi et al. (1986)</td>
</tr>
<tr>
<td>Al chloride</td>
<td>Two maternal dose levels: Da: 160 or 200 mg Al/kg bw/d</td>
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<tr>
<td>Wistar rats (6–8 per group)</td>
<td>Diet during gestation</td>
<td>No differences in number of live fetuses and resorbed/dead fetuses, fetal body weight and length, or in skeletal anomalies.</td>
<td>NOEL = 50 (Da)</td>
<td>McCormack et al. (1979)</td>
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<tr>
<td>Al chloride</td>
<td>Two maternal dose levels: Da: 25 or 50 mg Al/kg bw/d</td>
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<tr>
<td>MICE</td>
<td>Diet during gestation and lactation, continued exposure of pups via diet for 14 days.</td>
<td>Decreased weight gain in pups; Impaired learning of maze with respect to cue utilization (females).</td>
<td>LOEL = 50 (Da) NOEL = 10 (Da)</td>
<td>Golub and Germann (2001b)</td>
</tr>
<tr>
<td>Swiss Webster mice (15–17 pups per dose group per sex)</td>
<td>Three maternal dose levels: Da: 10, 50 and 100 mg Al/kg bw/d</td>
<td>Impaired performance in rotarod test (males).</td>
<td>LOEL = 100 (Da) NOEL = 50 (Da)</td>
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<tr>
<td>Al lactate</td>
<td>Less than optimal diet—trace element reduction in lab chow based on deficiencies measured in U.S. women.</td>
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<tr>
<td>Swiss Webster mice (15–19 pups per dose group)</td>
<td>Diet during gestation and lactation, continued exposure of pups via diet to PND 35</td>
<td>Reduced forelimb and hindlimb grip strength; Decreased thermal sensitivity.</td>
<td>LOEL = 100 (Da)</td>
<td>Golub et al. (2000)</td>
</tr>
<tr>
<td>Al lactate</td>
<td>One maternal dose level: Da: 100 mg Al/kg bw/d</td>
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</tbody>
</table>