anses

Valeurs toxicologiques
de référence

Aluminium et ses composés inorganiques

Avis de l'Anses
Rapport d'expertise collective

Mai 2025

Connaître, évaluer, protéger

Avis de l'Anses
Saisine n° 2023-MPEX-0137
Saisines liées n° 2022-MPEX-0179 et n° 2022-MPEX-0187

Le directeur général

Maisons-Alfort, le 23 mai 2025

AVIS
de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail

relatif à l'élaboration de valeurs toxicologiques de référence (VTR) par voies orale et respiratoire, de VTR interne et de valeur d'imprégnation populationnelle (VIP) pour l'aluminium et ses composés inorganiques

L'Anses met en œuvre une expertise scientifique indépendante et pluraliste.
L'Anses contribue principalement à assurer la sécurité sanitaire dans les domaines de l'environnement, du travail et de l'alimentation et à évaluer les risques sanitaires qu'ils peuvent comporter.
Elle contribue également à assurer d'une part la protection de la santé et du bien-être des animaux et de la santé des végétaux et d'autre part à l'évaluation des propriétés nutritionnelles des aliments.
Elle fournit aux autorités compétentes toutes les informations sur ces risques ainsi que l'expertise et l'appui scientifique technique nécessaires à l'élaboration des dispositions législatives et réglementaires et à la mise en œuvre des mesures de gestion du risque (article L.1313-1 du code de la santé publique).
Ses avis sont publiés sur son site internet.

Dans le cadre du protocole d'accord entre l'Anses, la Direction générale de la santé (DGS) et la Direction générale de la prévention des risques (DGPR) pour la mise en œuvre du programme de travail d'expertise scientifique en matière de valeurs toxicologiques de référence (VTR), établi en décembre 2022, il a été convenu de réaliser des travaux d'expertise nécessaires à l'élaboration de VTR court et long terme par voie respiratoire pour l'aluminium.

1. CONTEXTE ET OBJET DE LA SAISINE

L'agence régionale de santé (ARS) des Hauts de France a informé la DGS d'une possible exposition à l'aluminium par voie respiratoire dans le cadre de l'exploitation d'une fonderie de lingots d'aluminium, située en milieu urbain dense. Une évaluation des risques sanitaires et/ou une interprétation environnementale devront être réalisées par l'exploitant du site. Afin de pouvoir interpréter les résultats à des fins sanitaires, une VTR par voie respiratoire est demandée par la DGS et la DGPR.

Dans ce contexte, l'aluminium a été inscrit au programme de travail de l'Anses en juillet 2023, afin de proposer des VTR respiratoires à court et long terme. Une VTR long terme par voie

orale, une VTR interne et une valeur d'imprégnation populationnelle (VIP) ont également élaborées.

2. ORGANISATION DE L'EXPERTISE

L'expertise a été réalisée dans le respect de la norme NF X 50-110 « Qualité en expertise – Prescriptions générales de compétence pour une expertise (Mai 2003) ».

L'expertise relève du domaine de compétences du comité d'experts spécialisé (CES) « Valeurs sanitaires de référence » (VSR). Concernant les valeurs biologiques, l'Anses a confié l'expertise au groupe de travail « Indicateurs biologiques d'exposition » (GT IBE). Les travaux ont été présentés au CES VSR tant sur les aspects méthodologiques que scientifiques entre le 20 mai 2022 et le 27 juin 2024 (mandature 2021-2024) ainsi que les 27 septembre, 8 novembre et 13 décembre 2024 (mandature 2024-2028). Ils ont été adoptés par le CES VSR réuni le 8 novembre 2024.

L'Anses analyse les liens d'intérêts déclarés par les experts avant leur nomination et tout au long des travaux, afin d'éviter les risques de conflit d'intérêts au regard des points traités dans le cadre de l'expertise. Le résultat de l'analyse des liens d'intérêts n'a pas mis en évidence de risque de conflit d'intérêts. Cependant, un expert a souhaité se porter en déport. Il ne participe pas à l'examen de la saisine concernée.

Les déclarations d'intérêts des experts sont publiées sur le site internet : https://dpi.sante.gouv.fr/.

- **Description de la méthode d'expertise**
  - Définition et élaboration de VTR externes

L'Anses définit une VTR comme une appellation générique regroupant tous les types d'indices toxicologiques permettant d'établir une relation entre une quantité ou concentration d'un agent chimique et un effet néfaste (effet à seuil) ou entre une quantité ou concentration d'un agent chimique et une probabilité d'effet (effet sans seuil), à l'échelle d'une population. Par définition, elles sont construites pour protéger la population dans son ensemble, y compris les populations sensibles (ex. enfants, personnes âgées, etc.), des effets néfastes induits par l'agent chimique (Anses, à paraître). Les VTR sont spécifiques d'un agent chimique, d'une voie (orale, respiratoire, cutanée), d'une durée d'exposition (court, moyen ou long terme). Il existe donc des VTR :

- court terme pour les expositions d'une journée à deux semaines,
- moyen terme pour les expositions supérieures à deux semaines mais inférieures à un an,
- long terme pour les expositions de plus d'un an.

Elles peuvent être utilisées dans le cadre des évaluations quantitatives de risques sanitaires (EQRS) réalisées à l'échelle populationnelle uniquement dans un contexte d'exposition donné et aider ainsi au choix de mesures de gestion des risques. Elles peuvent être également utilisées pour l'élaboration de valeurs guides ou de teneurs maximales réglementaires dans

les aliments. Enfin, elles peuvent également servir à prioriser des agents chimiques, ces valeurs permettant souvent d'évaluer leur toxicité (Anses, à paraître).

La construction des VTR diffère en fonction des connaissances ou des hypothèses formulées sur les mécanismes d'action des agents chimiques. Actuellement, l'hypothèse par défaut est de considérer une relation monotone entre la dose d'exposition et l'effet observé. En l'état actuel des connaissances et par défaut, on considère généralement que, pour les effets non cancérogènes, la toxicité ne s'exprime qu'au-delà d'un certain seuil de dose et une VTR à seuil de dose est alors proposée (Anses, à paraître). Pour les effets cancérogènes, il est possible d'établir des VTR à seuil ou sans seuil selon le mode d'action de l'agent chimique étudié. En pratique, la proposition de VTR externes comprend différentes étapes indiquées en Figure 1.

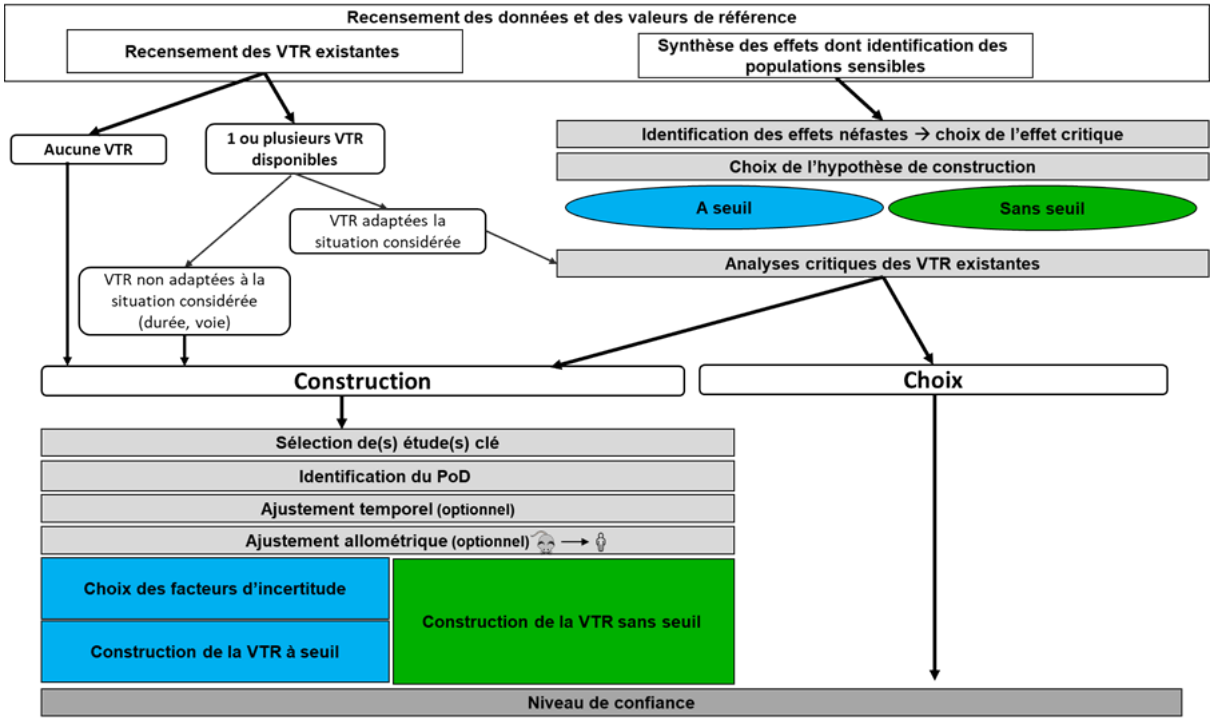


Figure 1 : Schéma des différentes étapes de construction d'une VTR (Anses, à paraître)

- Définition et élaboration de VTR internes et de VIP (valeur d'imprégnation populationnelle)

Au cours des dernières décennies, la surveillance biologique de l'exposition de la population générale à des agents chimiques s'est beaucoup développée. Elle permet de prendre en compte toutes les sources d'exposition, toutes les voies de pénétration dans l'organisme de l'agent d'intérêt, les facteurs individuels et les moyens de protection individuelle éventuellement mis en œuvre.

La surveillance biologique de l'exposition consiste à mesurer, dans une matrice biologique telle que le sang, les excreta, les tissus, les phanères, etc., les agents chimiques de l'environnement ou leurs métabolites, afin d'évaluer la dose interne, l'exposition des individus et/ou les risques pour la santé.

En population générale, les valeurs de référence internes utilisées au sein de l'Anses sont de deux types :

- des valeurs sanitaires en deçà desquelles il n'est pas attendu de risque pour la santé ou VTR internes ;
- des valeurs d'imprégnation populationnelle (VIP) permettant de situer l'exposition de la personne au sein de la population à laquelle elle appartient (population générale dans son ensemble ou fraction de celle-ci de même âge et/ou sexe et/ou de même statut tabagique, etc.).

Plusieurs approches peuvent être utilisées pour dériver ces valeurs, décrites ci-dessous par ordre de priorité en fonction de la disponibilité des données :

- dérivation à partir de données caractérisant la relation entre les variations de concentration du biomarqueur d'exposition (IBE) (agent chimique d'intérêt ou l'un de ses métabolites dans la matrice biologique choisie) et les effets sur la santé (effet avec ou sans seuil de dose) dans les populations exposées ;
- en l'absence de donnée pour identifier une relation avec les effets sur la santé, détermination sur la base d'une VTR externe ou d'un PoD[1], identifié à partir d'une ou plusieurs études clés. Dans ce cas, il est possible d'extrapoler les concentrations de l'IBE correspondant à une VTR/PoD externe à partir de paramètres toxicocinétiques obtenus sur des données humaines ou animales en utilisant (selon les données disponibles) :
    - des mesures d'association entre un indicateur d'exposition externe (VTR ou PoD) et l'IBE (équations de régression),
    - des données toxicocinétiques (modèle PBK[2] ou approche de conservation de la masse).

Les **valeurs d'imprégnation populationnelle (VIP**) renseignent sur la distribution de l'IBE étudié dans la population d'intérêt. Elles identifient des seuils au-delà desquels le niveau d'exposition d'un individu issu de cette population est considéré comme élevé. La situation d'un individu par rapport à la VIP n'a pas, en elle-même, de signification sanitaire. En règle générale, un percentile élevé de la distribution des concentrations de l'IBE dans la population d'intérêt est retenu comme VIP, le plus souvent le 95ème percentile (P95) ou la limite supérieure de son intervalle de confiance à 95 %.

Pour déterminer les VIP, les études réalisées dans des échantillons représentatifs de la population résidant sur le territoire français (étude nationale nutrition santé (ENNS), Esteban, etc.) sont privilégiées. Si des données issues d'études françaises en population générale ne sont pas disponibles, les études conduites dans des échantillons représentatifs de populations européennes sont retenues en seconde intention (ex : HBM4EU en Europe, GeRES en Allemagne), puis les études réalisées en Amérique du Nord (campagnes NHANES des Centers for Disease Control and Prevention (CDC) ou celles de Santé Canada).

[1] PoD : « *point of departure* » pour point de départ, parfois, alternativement désigné par le terme de dose ou concentration critique

[2] Description mathématique simulant la relation entre le niveau d'exposition externe et la concentration d'un agent chimique dans les matrices biologiques au fil du temps. Les modèles cinétiques prennent en compte l'absorption, la distribution, le métabolisme et l'élimination de l'agent administré et de ses métabolites (OMS, 2010).

- Recherche bibliographique

Afin d'élaborer ces valeurs de référence en population générale, une synthèse des données toxicologiques a été réalisée sur la base des rapports réalisés par des organismes reconnus au niveau international (ATSDR, 2008 ; EFSA, 2008 ; ACGIH, 2008 ; JECFA, 2012 ; DFG, 2012 et 2019 ; SCCS, 2014, 2020, 2022 et 2023) et complétée par une recherche bibliographique sur les effets toxiques de l'aluminium et ses composés inorganiques réalisée par l'Anses couvrant la période de 2007 à juillet 2023.

3. ANALYSE ET CONCLUSIONS DU CES VSR ET DU GT IBE

3.1. Synthèse des données toxicologiques

3.1.1. Toxicocinétique

La biodisponibilité de l'aluminium dépend de sa spéciation. Le principal mécanisme d'absorption est probablement la diffusion passive par les voies paracellulaires (ATSDR 2008). Les résultats des études d'absorption *in vivo* et de dissolution *in vitro* montrent que l'aluminium métallique, l'oxyde d'aluminium (Al_2O_3) et l'hydroxyde d'aluminium ($Al(OH)_3$) sont moins biodisponibles par voies orale et respiratoire que les formes d'aluminium solubles dans l'eau comme l'alun ($Al_2(SO_4)_3$). Dans des conditions physiologiques normales, l'exposition aux formes insolubles d'aluminium ne contribue pas de manière significative à la charge corporelle totale d'aluminium (Willhite *et al*. 2021).

Chez l'Homme, l'absorption par inhalation est à la fois dépendante du composé d'aluminium (en particulier sa solubilité) et de la granulométrie de l'aérosol. La fraction absorbée par inhalation est estimée à 1,5-3% de la concentration en aluminium inhalable dans l'air. L'aluminium est faiblement absorbé par ingestion avec une fraction absorbée allant de 0,1 à 0,3% de la dose lorsqu'il provient des aliments et de 0,3% de la dose lorsqu'il provient de l'eau de boisson (Yokel et McNamara 2001). Le Scientific Committee on Consumer Safety (SCCS) a estimé une fraction absorbée, après exposition cutanée, en moyenne de $5{,}2.10^{-4}$ % de la dose d'exposition cutanée (SCCS, 2020).

Une fois absorbé, l'aluminium est distribué dans l'ensemble du corps, particulièrement dans les os qui représentent 50% de la charge corporelle. L'accumulation dans les poumons est principalement due à l'inhalation de formes insolubles qui ne sont pas absorbées. Le ratio érythrocyte/plasma de l'aluminium varie d'une publication à l'autre, avec des valeurs comprises entre 0,1 et 0,9 (Riihimäki and Aitio 2012). Quatre-vingt-quinze pour cent (95%) de l'aluminium plasmatique sont liés aux protéines. L'aluminium est également distribué dans la peau, le tractus gastro-intestinal inférieur et les glandes parathyroïdes. De faibles concentrations d'aluminium ont été mesurées dans la plupart des organes des tissus mous. L'aluminium est également capable de traverser la barrière placentaire (ATSDR 2008).

L'aluminium est principalement éliminé dans l'urine (95%) par filtration glomérulaire, tandis que l'aluminium alimentaire non absorbé est excrété dans les fèces. Une voie d'élimination mineure (~ 2%) est l'excrétion biliaire (Krewski et al. 2007 ; EFSA 2008). L'aluminium a également été détecté dans le lait maternel dans un intervalle de 9,2 à 49 $\mu g.L^{-1}$ (ATSDR 2008), dans la salive, dans la sueur et dans le liquide séminal (Krewski et al. 2007). Les études de toxicocinétique conduites chez l'Homme indiquent une élimination triphasique avec des demi-vies de 1,4 ; 40 et 1727 jours après injection par intra-veineuse. Ces études montrent une

grande variabilité des demi-vies apparentes, quelles que soient les voies d'exposition. Cette large gamme de demi-vies pourrait refléter les différences dans la durée et moment de l'échantillonnage ou même une élimination bi- ou triphasique selon les voies d'exposition. Pour l'heure, plusieurs auteurs ont néanmoins observé une relation linéaire entre les niveaux d'aluminium urinaire après le travail et les niveaux d'aluminium dans l'air au niveau des voies respiratoires des soudeurs au cours du dernier poste ou des postes précédents cumulés (Sjögren *et al.* 1988 ; Letzel, Schaller et Angerer 1996, cités dans ATSDR 2008).

Différents modèles cinétiques pour l'aluminium, avec différents niveaux de complexité, ont été publiés (Nolte *et al*. 2001, Poddalgoda *et al*. 2021, Hethey *et al*. 2021). Les experts considèrent ces modèles comme peu adaptés pour extrapoler des doses externes à partir de concentrations urinaires.

L'ensemble des processus de toxicocinétique de l'aluminium est illustré dans la Figure 2.

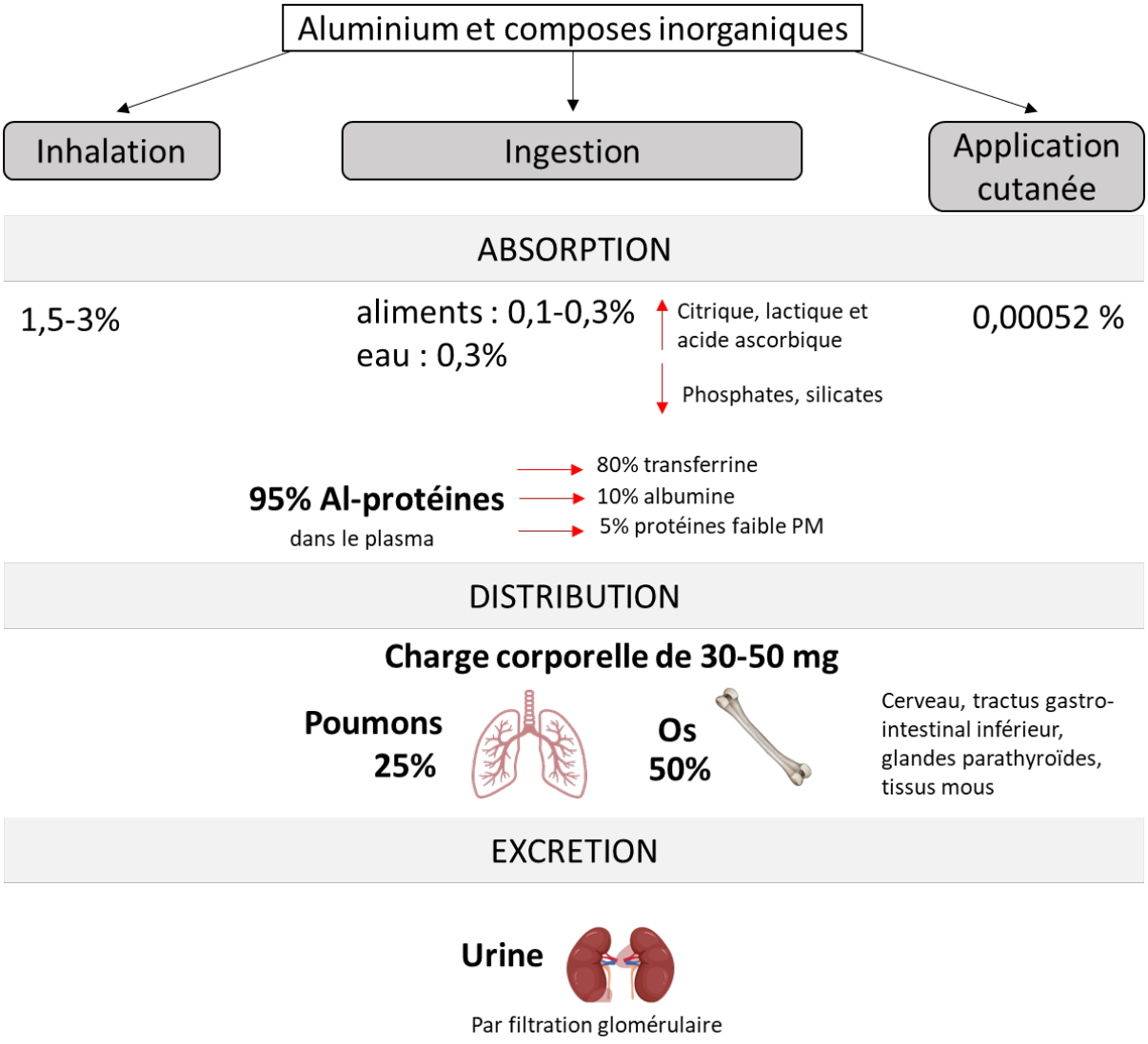


Figure 2 : Schéma de la toxicocinétique de l'aluminium et ses composés inorganiques chez l'Homme

3.1.2. Choix de l'indicateur biologique d'exposition (IBE)

La recherche dans la littérature scientifique n'a pas permis d'identifier de biomarqueurs d'effets précoces pertinents pour la surveillance de l'exposition à l'aluminium. Par conséquent, ces biomarqueurs ne sont pas développés davantage.

L'aluminium peut théoriquement être mesuré dans tous les liquides, tissus ou excréments biologiques (par exemple : le sang, le sérum, l'urine, le liquide céphalorachidien, le sperme, le lait, la salive, les os, les cheveux et les ongles) (ATSDR 2008).

Le sang et l'urine sont les matrices les plus couramment utilisées pour la biosurveillance de routine de l'exposition à l'aluminium. Pour chacun de ces IBE, des avantages et inconvénients ont été relevés.

Les concentrations d'aluminium dans le sang total, les érythrocytes, le sérum et le plasma sont généralement considérées comme approximativement égales. Ces quatre matrices sanguines pourraient théoriquement être prises en compte pour l'évaluation de l'exposition interne (Poddalgoda et al. 2021). Cependant :

- les études sur la distribution de l'aluminium entre le sérum (ou le plasma) et les érythrocytes ont donné des résultats contradictoires, et les études sur l'association des niveaux d'aluminium dans le sang total ou les érythrocytes avec les effets sur la santé ou l'exposition externe à l'aluminium sont rares. Par conséquent, ces deux matrices ne peuvent pas être considérées actuellement pour la biosurveillance de l'exposition à l'aluminium ;
- les niveaux de sérum et de plasma sont théoriquement équivalents, mais les anticoagulants, tels que l'héparine ou le citrate, peuvent contenir de l'aluminium. Pour cette raison, le sérum doit être préféré au plasma.

La détermination de l'aluminium sérique manque de sensibilité pour mettre en évidence de petites variations de l'exposition externe et/ou pour la biosurveillance de la charge corporelle, en particulier dans les situations de faible exposition. Cependant, l'aluminium sérique reste le meilleur biomarqueur de la charge corporelle en aluminium chez les personnes souffrant d'insuffisance rénale, car leur dose interne d'aluminium peut être élevée et le niveau d'aluminium urinaire n'est pas un indicateur d'exposition validé pour ces personnes.

L'aluminium urinaire a été retenu comme IBE car il présente plusieurs avantages :

- il existe des preuves suffisantes d'une association positive entre le niveau d'aluminium urinaire et le risque d'effets sur la santé, avec des NOAEL[3] et LOAEL[4] identifiés chez l'Homme ;
- l'aluminium urinaire est un IBE plus sensible par rapport à l'aluminium sérique lorsque les changements d'exposition externe sont minimes (< 5 $mg.m^{-3}$) ;
- chez les personnes présentant une fonction rénale normale, les variabilités inter- et intra-individuelles sont limitées lorsque les niveaux d'aluminium sont ajustés sur la concentration de créatinine urinaire, la densité spécifique ou l'osmolalité ;
- l'échantillonnage urinaire est non invasif et des méthodes analytiques sont disponibles pour l'analyse.

Le principal inconvénient lié au prélèvement d'aluminium urinaire est le risque élevé de contamination externe lors des échantillonnages et au cours de la préparation et de l'analyse des échantillons.

Ainsi, le CES VSR retient l'aluminium urinaire comme l'IBE pertinent pour la surveillance biologique de l'exposition à l'aluminium, sur la base d'une analyse des

[3] *No observed adverse effect level* (ou dose sans effet néfaste observé)
[4] *Lowest observed adverse effect level* (ou dose minimale entraînant un effet néfaste observé)

avantages et des inconvénients des différents IBE identifiés. En cas d'atteinte de la fonction rénale, l'aluminium urinaire ne peut pas être utilisé comme IBE car cette condition pathologique affecte l'interprétation des résultats de la surveillance biologique.

3.1.3. Toxicité aigue

Chez l'Homme, aucune étude pertinente mettant en évidence des effets de l'aluminium suite à une exposition aiguë par voie orale ou respiratoire n'a été identifiée.

Plusieurs cas d'encéphalopathie liée à l'aluminium ont été rapportés chez des patients ayant subi une otoneurochirurgie avec reconstruction osseuse à l'aide d'un ciment contenant de l'aluminium (Hantson *et al*. 1995 ; Lévêque *et al*. 1996 ; Reusche *et al*. 2001). Des cas d'encéphalopathie aiguë présentant des taux plasmatiques élevés d'aluminium sont également rapportés, après une irrigation vésicale post-chirurgicale à l'alun. Cependant, dans la plupart de ces cas, l'aluminium n'était probablement pas la seule ou la principale cause des symptômes neurologiques, car des troubles hydroélectrolytiques sévères étaient manifestement ou probablement associés (Phelps *et al*. 1999).

Chez l'animal de laboratoire, des DL_{50} (doses létales pour 50% des animaux) sont rapportées pour plusieurs composés d'aluminium chez le rat allant de 162 mg Al.kg pc^{-1} (bromure d'aluminium) à plus de 730 mg Al.kg pc^{-1} (sulfate d'aluminium). Une exposition par inhalation pendant 4 h chez le rat à 1000 $mg.m^{-3}$ n'a pas entraîné d'effet létal mais des microgranulomes multifocaux dans les poumons et des ganglions lymphatiques hilaires ont été détectés (Thomson *et al*. 1986).

3.1.4. Irritation et sensibilisation

Le chlorure d'aluminium anhydre dispose d'une classification et d'un étiquetage harmonisé au niveau européen qui le classe comme corrosif pour la peau de catégorie 1B.

Selon le SCCS, il n'existe pas de données suffisantes chez l'Homme suggérant que les composés d'aluminium utilisés dans les anti-perspirants provoquent des allergies et, compte tenu de leur utilisation répandue, cet effet, s'il existe, semble rare. Les données animales n'indiquent pas d'effet de sensibilisation cutanée des composés d'aluminium utilisés dans ces produits (SCCS 2023).

3.1.5. Toxicités subchronique et chronique

- Données chez l'Homme

De nombreuses études ont documenté des effets respiratoires liés à l'exposition professionnelle à l'aluminium : respiration sifflante, dyspnée, altérations de la fonction pulmonaire, asthme et fibrose pulmonaire. Cependant, le lien entre ces troubles et l'exposition à l'aluminium reste incertain, voire improbable dans de nombreuses études, en raison de facteurs de confusion, notamment la co-exposition à d'autres substances toxiques, en particulier des agents irritants (fluorures, ozone, etc.), des particules ultrafines et de la silice cristalline. Des données contradictoires sont rapportées concernant les effets pulmonaires de la poudre d'aluminium finement broyée : certaines publications font état de cas de fibrose pulmonaire chez des travailleurs exposés, alors que d'autres études ne montrent aucune preuve de fibrose après une exposition prolongée à des particules fines d'aluminium. Cette différence pourrait s'expliquer par le type de lubrifiant utilisé pour empêcher l'oxydation

superficielle des particules d'aluminium pendant le broyage (huiles minérales au lieu d'acide stéarique[5]). Des cas sporadiques de pneumoconiose associés à l'exposition professionnelle à l'aluminium sont également signalés (Korogiannos, Babatsikou et Tzimas 1998 ; Kraus et al. 2000 ; Hull et Abraham 2002). Leur faible nombre et les co-expositions à d'autres agents chimiques limitent leur interprétation.

Vingt-cinq études épidémiologiques (21 transversales et 4 longitudinales) ont évalué l'association ente la dose interne d'aluminium (au moins les niveaux d'aluminium dans le sang total, le plasma, le sérum ou l'urine) et les troubles cognitifs chez des travailleurs de différentes industries de l'aluminium. Les principaux troubles cognitifs rapportés dans plusieurs études épidémiologiques sont une baisse de performances dans des tests psychomoteurs et/ou de l'attention. Les études épidémiologiques ne contenaient soit, pas de données, soit des données insuffisantes concernant la concentration d'aluminium dans l'air (pas de mesure individuelle ou de mesures de concentration en poussières dans l'air). En revanche, les concentrations d'aluminium dans le sang (sérum ou plasma) ou les urines y étaient rapportées et des différences de concentration de l'IBE entre les travailleurs exposés et les non exposés ont pu être observées en lien avec des troubles cognitifs, ce qui a permis d'identifier des NOAEL et/ou des LOAEL. Seules les études pour lesquelles un NOAEL et/ou un LOAEL ont été identifiés sont décrites ci-dessous.

Une étude transversale chinoise a comparé 103 travailleurs exposés à l'aluminium et 64 témoins en utilisant la batterie de tests neurocomportementaux recommandée par l'organisation mondiale de la santé (OMS) (Guo *et al*. 1999). Les travailleurs exposés étaient des employés d'une grande usine de production d'aluminium, travaillant dans les départements d'électrolyse, de fusion ou de soudure depuis au moins cinq ans. Les témoins, travaillant dans d'autres départements, n'étaient pas exposés à l'aluminium et étaient appariés selon l'âge, la durée d'emploi, le niveau d'éducation, la consommation d'alcool et le statut tabagique. Les niveaux d'aluminium urinaire étaient mesurés en fin de poste (jour de la semaine de travail, non précisé) avec des niveaux moyens de 41,8 $\mu g.g^{-1}$ de créatinine chez les travailleurs exposés et de 17,7 $\mu g.g^{-1}$ de créatinine chez les témoins. Les résultats des tests neurocomportementaux montraient des altérations des performances cognitives incohérentes selon les groupes d'âge.

Une étude longitudinale menée dans une usine de production de poudre d'aluminium, en Allemagne, avec, lors du premier examen, 32 travailleurs exposés à la poussière d'aluminium comparés à un groupe témoin de 30 personnes non exposées (Letzel *et al*. 2000). Cinq ans plus tard, lors du deuxième examen, seuls 21 travailleurs exposés et 15 témoins ont accepté de poursuivre l'étude. Les niveaux internes d'aluminium étaient significativement plus élevés dans le groupe exposé lors des deux évaluations (moment d'échantillonnage et méthode d'analyse non spécifiés). En particulier, lors du premier examen, les niveaux médians d'aluminium dans l'urine étaient de 87,6 $\mu g.g^{-1}$ de créatinine chez les travailleurs exposés contre 9,0 $\mu g.g^{-1}$ de créatinine dans le groupe témoin, avec une médiane d'aluminium dans le plasma de 8,7 $\mu g.L^{-1}$ dans le groupe exposé contre 4,3 $\mu g.L^{-1}$ dans le groupe témoin. Lors du second examen, les taux médians d'aluminium urinaire étaient de 19,8 $\mu g.g^{-1}$ de créatinine chez les travailleurs exposés contre 4,5 $\mu g.g^{-1}$ de créatinine dans le groupe témoin, avec un taux médian d'aluminium plasmatique de 6,7 $\mu g.L^{-1}$ dans le groupe exposé contre 4,3 $\mu g.L^{-1}$

[5] L'acide stéarique est aujourd'hui le lubrifiant le plus couramment utilisé. Il réagit avec l'aluminium en formant un film protecteur superficiel de stéarate d'aluminium. Aucun effet fibrogène n'est signalé lors de l'utilisation de ce procédé. En revanche, l'utilisation antérieure et désormais abandonnée de l'huile minérale comme lubrifiant pour le broyage de l'aluminium a été associée à une fibrose pulmonaire.

chez les témoins. La différence entre les deux examens s'explique par l'amélioration de l'hygiène professionnelle. Aucune relation dose-réponse entre les concentrations plasmatiques ou urinaires d'aluminium, ou la durée d'exposition à l'aluminium et les paramètres psychométriques n'a été observée.

Dans une étude transversale, He *et al.* ont étudié les paramètres neurocomportementaux, la fonction du système nerveux autonome et les sous-ensembles de lymphocytes chez 33 travailleurs d'une usine d'aluminium chinoise et 34 témoins d'une meunerie (He *et al.* 2003). Les concentrations urinaires moyennes d'aluminium mesurées dans les urines du matin (sans précision de l'horaire par rapport à la prise de poste et du jour de la semaine de travail) étaient respectivement de 40,1 et 26,8 $\mu g.g^{-1}$ de créatinine chez les travailleurs exposés et les témoins. Une batterie de tests neurocomportementaux comprenant un questionnaire standardisé sur l'état de l'humeur et des tests psychométriques a été réalisée. Le temps de réaction était significativement plus lent chez les travailleurs exposés par rapport aux témoins. Les scores aux tests des symboles numériques et de poursuite étaient significativement plus faibles chez les travailleurs exposés.

Une étude longitudinale a été menée sur 4 ans auprès de soudeurs d'aluminium de l'industrie automobile en Allemagne (Buchta *et al.* 2003 ; Kiesswetter *et al*. 2009). Trois examens ont été effectués en 1999, 2001 et 2003. Quatre-vingt-dix-huit (98) soudeurs d'aluminium en 1999, 97 en 2001 et 92 en 2003, ont été comparés aux 50 mêmes témoins. Les sujets devaient avoir au moins 2 ans d'expérience lors du premier examen. Les personnes ayant des maladies neurologiques non liées à l'exposition, des maladies cérébrovasculaires, du diabète, des blessures à la tête, ou une connaissance insuffisante de la langue allemande étaient exclues. Les concentrations d'aluminium dans le plasma et l'urine étaient mesurées en début et fin de poste. Les évaluations neurocomportementales incluaient des tests standardisés tels que les matrices progressives standard (SPM), un test d'intelligence verbale (WST) et le système européen d'évaluation neurocomportementale (EURO-NES), ainsi que des tests de temps de réaction, de conception de blocs et de performance psychomotrice. Les concentrations urinaires médianes d'aluminium en fin de poste étaient respectivement de 37,87 ; 33,57 et 15,4 $\mu g.g^{-1}$ de créatinine en 1999, 2001 et 2003. La concentration médiane d'aluminium dans l'urine a également été mesurée avant le travail après plusieurs jours de travail et était de 38,4 ; 35,0 et 12,6 $\mu g.g^{-1}$ de créatinine en 1999, 2001 et 2003. Les concentrations plasmatiques médianes étaient respectivement de 8,3 ; 4,1 et 4,3 $\mu g.L^{-1}$ en 1999, 2001 et 2003. Aucune différence de symptômes neurologiques et de performances aux tests psychométriques n'a été rapportée entre les deux groupes, à l'exception d'un temps de décision légèrement plus lent et de mouvements moteurs plus rapides chez les soudeurs.

Une autre étude longitudinale a été réalisée sur 4 ans (1999, 2001, 2003) sur 44 soudeurs d'aluminium et 37 témoins non exposés, issus de la même industrie de construction de trains et de camions en Allemagne (Buchta *et al.* 2005 ; Kiesswetter *et al*. 2007). Les concentrations d'aluminium dans le plasma et l'urine en début et fin de poste ont été mesurées, après plusieurs postes. Les évaluations neurocomportementales incluaient des entretiens standardisés, des examens physiques, un test d'intelligence verbale (WST), un test de rappel de chiffres, un test de conception de blocs, une batterie de tests informatisés de performance motrice, un test de temps de réaction simple et le test des matrices progressives standard (SPM). Les concentrations urinaires et plasmatiques d'aluminium en fin de poste étaient respectivement de 97 $\mu g.g^{-1}$ de créatinine et 11,6 $\mu g.L^{-1}$ en 1999, 143,9 $\mu g.g^{-1}$ de créatinine et 14,3 $\mu g.L^{-1}$ en 2001, et 64,5 $\mu g.g^{-1}$ de créatinine et 13,2 $\mu g.L^{-1}$ en 2003. Les concentrations médianes d'aluminium dans l'urine ont également été mesurées avant le poste et étaient de

92,1 ; 90,1 et 58,8 µg.g^{-1} de créatinine en 1999, 2001 et 2003. Une diminution des performances a été observée chez les soudeurs par comparaison aux témoins, significative uniquement pour les résultats des tests de conception de blocs. Des diminutions non significatives des performances étaient observées dans le groupe des soudeurs pour le QI verbal, le test SPM, le test de traçage de pistes, le test de traçage de lignes et les tâches de commutation de l'attention par rapport aux témoins.

- Données chez l'animal

Plusieurs études ont été menées sur des animaux de laboratoire (souris, rats, gerbilles, cobayes et chiens) pour étudier les effets d'une exposition subchronique ou chronique par voies orale ou respiratoire à divers composés aluminiques.

Certaines de ces études chez la souris par voie orale ont montré des effets neurotoxiques, tels qu'une altération de l'apprentissage et de la mémoire, une diminution de la force de préhension des membres antérieurs et postérieurs, une diminution de la réaction de sursaut, une diminution de l'activité locomotrice et du nombre total d'activités, un test de géotaxie négatif réduit et des lésions et diminution de la densité des cellules de l'hippocampe (Golub *et al*. 1989 : NOAEL = 62 mg Al.kg pc^{-1}.j^{-1} et LOAEL = 130 mg Al.kg pc^{-1}.j^{-1} ; Cao *et al*. 2016 : NOAEL = 10 mg Al.kg pc^{-1}.j^{-1} et LOAEL = 30 mg Al.kg pc^{-1}.j^{-1} ; Yan *et al.* 2017 : NOAEL = 36 mg Al.kg pc^{-1}.j^{-1} et LOAEL = 73 mg Al.kg pc^{-1}.j^{-1}).

Des effets pulmonaires ont été observés chez le rat à la suite d'une exposition respiratoire, tels qu'une augmentation des macrophages alvéolaires et des lésions granulomateuses. Une augmentation du poids relatif des poumons a également été observée (Stone *et al.* 1979 : NOAEL = 0,65 mg.m^3 et LOAEL = 6,5 mg.m^3).

Des effets hématologiques ont été rapportés chez le rat dans certaines études après une administration par voie orale, telles qu'une perturbation de l'homéostasie du fer, une diminution des taux d'hémoglobine, d'hématocrite et d'haptoglobine, une augmentation du compte des réticulocytes. Ces effets ne sont pas systématiquement observés (Gómez *et al*. 1986 : NOAEL = 47 mg Al.kg pc^{-1}.j^{-1} et LOAEL = 95 mg Al.kg pc^{-1}.j^{-1} ; Vittori *et al*. 1999 : LOAEL = 230 mg Al.kg pc^{-1}.j^{-1}).

Toujours chez le rat, des résultats divergents ont été observés dans les études pour les effets sur les os. Une diminution de la densité minérale osseuse ou des changements dans le contenu minéral des os, ainsi qu'une perturbation de la structure histologique du fémur ont été rapportés (Konishi *et al*. 1996 : NOEL = 90 mg Al.kg pc^{-1}.j^{-1} ; Sun *et al.* 2015 : LOAEL = 13 mg Al.kg pc^{-1}.j^{-1}).

D'autres effets ont également pu être rapportés comme une réduction du poids corporel, une augmentation du poids de la rate, une augmentation de la pression artérielle systolique et des lésions histopathologiques du foie.

3.1.6. Effets sur la reproduction et le développement

Chez l'Homme, aucune étude des effets sur la reproduction et le développement n'a été identifiée.

Plusieurs études ont porté sur les effets sur la reproduction et le développement suite à une exposition orale à des composés aluminiques chez des animaux de laboratoire (souris, rats, gerbilles, lapins, cobayes et chiens).

Les effets sur la reproduction observés étaient une augmentation de l'incidence des résorptions, une modification de la durée de gestation chez les souris (un jour à deux jours avant terme après comparaison aux contrôles) (Donald *et al.* 1989), une diminution de la qualité spermatique chez les rats (Gosh *et al*. 2021), des modifications morphologiques des glandes para-urétrales et des gonades chez les gerbilles (Da Silva Lima *et al*. 2020 et 2022) et une diminution des concentrations sériques d'œstrogènes, de progestérone, d'hormone folliculo-stimulante (FSH) et d'hormone lutéinisante (LH) chez les rats (Wang *et al*. 2012 ; Fu *et al.* 2014). D'autres études n'ont montré aucun effet de l'exposition à l'aluminium sur l'histologie des tissus de reproduction et la fertilité des souris et rats, mâles et femelles (Golub *et al.* 1992 ; Steinhagen *et al*. 1978 ; Domingo *et al*. 1987).

Différentes études ont observé des effets sur le développement après exposition à l'aluminium par voie orale tels qu'un nombre réduit de portées, la réduction du poids des petits, une mortalité postnatale plus élevée, des changements dans les schémas de développement de la prostate après la naissance, une ossification retardée, un retard de l'ouverture vaginale, la présence de fentes palatines et une augmentation des malformations congénitales et des anomalies mineures. Des effets sur le neurodéveloppement ont également été mis en évidence dans plusieurs études telles que :

- dans une étude menée par Poirier *et al.* (2011) conformément aux bonnes pratiques de laboratoires (BPL) et selon la ligne directrice 426 de l'OCDE[6] exposant des rats au citrate d'aluminium *via* l'eau de boisson à partir du 6ème jour de conception (GD6) jusqu'au 364ème jour postnatal (PND), des précipités blancs ont été observés dans les voies urinaires, entraînant une hydronéphrose, une dilatation de l'uretère et la formation de calculs. Cet effet a été plus particulièrement observé dans le groupe ayant reçu la dose élevée (300 mg Al.kg $pc^{-1}.j^{-1}$), en particulier chez les petits mâles. Dans le groupe ayant reçu 100 mg Al.kg $pc^{-1}.j^{-1}$, des lésions des voies urinaires, une diminution du poids corporel, une réaction exagérée au pincement de la queue, un écartement plus étroit des pattes chez les femelles et une diminution de la force de préhension des membres postérieurs et antérieurs chez les petits ont été observés ;
- deux études multigénérationnelles conformes aux BPL ont été conduites par Hirata-Koizumi *et al*. (2011a et b) montrant des effets à la suite de l'administration de sulfate d'aluminium *via* l'eau de boisson tels qu'une diminution du poids corporel avant le sevrage, une diminution du poids du foie, de la rate et du thymus et un retard de l'ouverture vaginale.

Inversement, d'autres études n'ont observé aucun effet sur le poids de naissance, la mortalité péri- et post-natale des petits, aucun signe d'embryotoxicité, y compris aucune anomalie morphologique et aucun retard dans l'ouverture du vagin.

3.1.7. Génotoxicité

Les sels d'aluminium étant capables d'induire un stress oxydatif, ils pourraient éventuellement induire une mutagénicité *in vivo via* ce mécanisme d'action. Les études *in vitro* et *in vivo* indiquent que les composés d'aluminium peuvent induire des effets génotoxiques, principalement à des niveaux d'exposition élevés. Toutefois, des tests supplémentaires, comme le test des micronoyaux sur les érythrocytes de mammifères et le test Comet sur les

[6] Organisation de coopération et de développement économiques

cellules de mammifères avec l'oxyde d'aluminium, sont nécessaires pour clarifier davantage le potentiel génotoxique des sels d'aluminium.

3.1.8. Cancérogénicité

Selon le centre international de recherche sur le cancer (CIRC), il existe des preuves suffisantes chez l'Homme de la cancérogénicité de la production d'aluminium par le procédé Söderberg[7]. En effet, cette activité est associée à des incidences élevées de cancers de la vessie et du poumon. Les risques de cancer associés à la production d'aluminium résultent principalement de l'exposition aux hydrocarbures aromatiques polycycliques (HAP) plutôt que de l'exposition à l'aluminium ou à ses composés (CIRC 2012).

Sur la base de la quantification d'aluminium dans les tissus du cancer du sein, un lien potentiel entre les anti-perspirants et le cancer du sein a été supposé (SCCS 2023). Cependant, malgré ses potentiels effets génotoxiques, les données existantes provenant d'études animales et épidémiologiques sont actuellement insuffisantes pour établir définitivement une relation de cause à effet entre l'exposition à l'aluminium et le risque de cancer du sein.

3.1.9. Populations sensibles

Les personnes souffrant d'insuffisance rénale constituent la principale population à risque de sur-imprégnation à l'aluminium, et sont donc plus sensibles à sa toxicité (Krewski *et al*. 2007 ; ATSDR 2008).

3.2. Propositions de VTR

Bien qu'ayant été missionné pour dériver des VTR par voie respiratoire, le CES VSR a également élaboré :

- une VTR long terme par voie orale,
- une VTR interne.

En effet, l'exposition de la population générale à l'aluminium a majoritairement lieu par la voie orale et des données récentes permettent de proposer une VTR pour cette voie. De plus, le CES VSR juge plus pertinent de recourir à une surveillance biologique et donc à une VTR interne pour tenir compte de l'ensemble des voies d'exposition à l'aluminium.

3.2.1. VTR long terme par voie orale

3.2.1.1. Choix de l'effet critique

L'exposition à l'aluminium par voie orale peut entraîner de nombreux effets systémiques sur la santé tel que des effets neurotoxiques, neurodéveloppementaux, osseux ou hématologiques. Les effets neurotoxiques apparaissent à la fois chez l'Homme et les animaux de laboratoire aux plus faibles doses testées, par voie orale chez les animaux de laboratoire, ainsi que par voie respiratoire chez des travailleurs.

Ainsi, le CES VSR retient comme effet critique les effets neurotoxiques.

[7] Production de l'aluminium par électrolyse.

3.2.1.2. Choix de l'hypothèse de construction

Pour la plupart des effets non cancérogènes, il est considéré, par défaut et en l'état actuel des connaissances, que la toxicité ne s'exprime qu'au-delà d'un seuil de dose. Ainsi, **le CES VSR considère que les effets neurotoxiques résultent d'un mécanisme à seuil de dose**.

3.2.1.3. Analyse des VTR long terme par voie orale existantes

Quatre VTR long terme par voie orale (US EPA 2006 ; ATSDR 2008 ; Efsa 2008 ; Jecfa 2012) ont été identifiées (Annexe 1).

La VTR provisoire de l'US EPA considère comme effet critique une diminution de la force de préhension des membres antérieurs chez des souris exposées *via* l'alimentation de la conception au sevrage (Golub *et al.* 1995). Il est à noter que la quantité d'aluminium non ajouté intentionnellement à l'alimentation n'est pas connue et entraîne un biais d'interprétation des résultats. Aucun NOAEL n'a pas pu être identifié. L'US EPA a appliqué au LOAEL un facteur d'incertitude (FI) global de 100 dont un FI_A de 10 par défaut pour la variabilité inter-espèces, un FI_L de 3 pour l'utilisation d'un LOAEL et un FI_H de 3 pour la variabilité inter-individuelle contre un facteur 10 par défaut sans apporter de justification. Cette VTR n'a pas été retenue par le CES au regard des incertitudes et biais décrits ci-dessus.

En 2023, l'US EPA a proposé une dose de référence provisoire par voie orale (pRfD) pour les sels de phosphate d'aluminium. Cette évaluation est motivée par l'impact de l'aluminium sur les sels de phosphate inorganiques. En l'absence de données spécifiques sur la toxicité des sels de phosphate d'aluminium chez l'Homme ou l'animal, une approche par analogie a été adoptée en utilisant l'étude de Golub *et al.* (1995). Cependant, dans cette évaluation, la dose la plus faible testée, soit 26 mg.kg $pc^{-1}.j^{-1}$, a été considérée comme un NOAEL. En appliquant un FI par défaut de 100, une pRfD de 0,3 mg.kg $pc^{-1}.j^{-1}$ a été dérivée. Aucun FI supplémentaire n'a été appliqué, notamment en ce qui concerne la durée de l'étude, puisque « une étude de développement a été sélectionnée comme étude principale, et la gravité des effets toxiques observés ne semble pas augmenter avec la durée d'exposition » (US EPA 2023). Il convient de noter que les sels de phosphate d'aluminium sont des composés insolubles de l'aluminium.

L'ATSDR a élaboré une VTR long terme par voie orale également pour des effets neuromusculaires (diminution de la force de préhension des membres antérieurs et postérieurs) à partir du LOAEL issu d'une étude chez les souris exposées de la conception à 2 ans *via* l'alimentation (Golub *et al*. 2000). Comme pour l'étude de Golub *et al.* de 1995, se pose le problème de la quantité d'aluminium présente initialement dans l'alimentation. Ici, un FI global de 300 est appliqué avec un facteur correctif supplémentaire de 0,3 pour tenir compte de la plus grande biodisponibilité de la forme d'aluminium utilisée (aluminium lactate) par rapport aux autres formes d'aluminium considérées par l'ATSDR comme étant présentes dans l'alimentation humaine. Cette VTR n'a pas été retenue par le CES au regard du biais d'interprétation (pas de prise en compte des apports alimentaires) de l'étude clé décrite ci-dessus.

L'Efsa a proposé une VTR long terme par voie orale pour les mêmes effets neuromusculaires identifiés dans deux études chez le rat avec des expositions par l'alimentation allant de la conception au sevrage (Golub *et al.* 1995) ou à PND35 (Golub & Germann 2001). L'Efsa a moyenné les VTR estimées à partir du LOAEL issu de l'étude de Golub *et al.* et du NOAEL issu de celle de Golub et Germann après application de FI de 300 et 100 respectivement. Le CES VSR n'a pas retenu cette VTR considérant que l'approche consistant à moyenner des

VTR n'est pas pertinente et est très éloignée de la méthodologie recommandée par l'Anses (Anses, à paraître).

La VTR provisoire proposée par le JECFA est basée sur des effets rénaux et neuromusculaires observés dans une étude de neurotoxicité pour le développement, jugée de bonne qualité (ToxRtool 1) (Poirier *et al*. 2011, voir section 3.1.6). Un NOAEL de 30 mg Al.kg $pc^{-1}.j^{-1}$ a été identifié (Poirier et al. 2011). Un FI de 100 a été appliqué au calcul de la VTR provisoire.

Du fait de l'existence de nouvelles études mettant en évidence des effets neurotoxiques de type performance cognitive à des doses plus faibles (Cao *et al.* 2016), le CES VSR ne retient pas les VTR long terme par voie orale existantes. Ainsi, le CES VSR décide de proposer une nouvelle VTR long terme par voie orale.

3.2.1.4. Choix de l'étude clé et du point de départ

Aucune étude épidémiologique en population générale ne renseigne des effets neurotoxiques de l'aluminium après exposition par voie orale.

Des études récentes ont rapporté des effets neurotoxiques de type cognitif suite à une exposition par voie orale chez l'animal et caractérisé la relation dose-réponse : Cao *et al.* (2016) et Yan *et al*. (2017).

Cao *et al*. ont exposé des rats mâles (n = 30/groupe) à du chlorure d'aluminium pendant 3 mois par gavage à des doses de 0, 10, 30 et 90 mg Al.kg $pc^{-1}.j^{-1}$. Une diminution significative des capacités d'apprentissage et de mémorisation a été observée (piscine de Morris) à 30 mg Al.kg $pc^{-1}.j^{-1}$ (LOAEL) permettant d'identifier un NOAEL de 10 mg Al.kg $pc^{-1}.j^{-1}$.

Dans l'étude de Yan *et al.*, des rats ont été exposés à du chlorure d'aluminium de l'allaitement (3 semaines) à 14 semaines *via* l'eau de boisson à des doses de 0, 36, 73 et 108 mg Al.kg $pc^{-1}.j^{-1}$ (n = 15/sexe/dose). Une diminution significative des capacités d'apprentissage et de mémorisation a été observée (piscine de Morris) à 36 mg Al.kg $pc^{-1}.j^{-1}$ (LOAEL) (Yan *et al.* 2017).

L'étude de Cao *et al.* étant jugée de bonne qualité (Klimisch 1) et permettant d'identifier le plus faible NOAEL pour une altération des performances cognitives, le CES VSR la retient comme étude clé et identifie comme PoD le NOAEL de 10 mg.kg $pc^{-1}.j^{-1}$.

3.2.1.5. Ajustement allométrique

Pour réduire l'incertitude sur la variabilité inter-espèces, un ajustement allométrique a été réalisé. Une dose équivalente humaine (HED = Human Equivalent Dose) a été calculée à l'aide de l'équation suivante[8] :

$$\text{Dose équivalente Homme} = \text{Dose animal} \times \left(\frac{\text{Poids animal}}{\text{Poids homme}} \right)^{1/4}$$

Le poids moyen des rats mâles (Sprague Dawley) de 450 g (issu d'un abaque) a été utilisé pour le calcul et celui de 70 kg pour l'Homme et, comme dose animal, le NOAEL identifié de 10 mg.kg $pc^{-1}.j^{-1}$.

Soit **$NOAEL_{HED}$ = 2,83 mg.kg $pc^{-1}.j^{-1}$**

[8] Cette équation est issue des recommandations de l'US EPA (US EPA, 2006).

3.2.1.6. Choix des facteurs d'incertitude

Le calcul de la VTR long terme par voie orale à partir du $NOAEL_{HED}$ a été effectué à l'aide des facteurs d'incertitude (FI) suivants (Anses, à paraître) :

- variabilité inter-espèces (FI_A) : 2,5, pour tenir compte de la variabilité toxicodynamique et d'incertitudes toxicocinétiques résiduelles, un ajustement dosimétrique ayant été réalisé,
- variabilité interindividuelle (FI_H) : 10 par défaut,
- transposition subchronique à chronique (FI_S) : $\sqrt{10}$, pour tenir compte de la transposition d'une étude subchronique à une VTR long terme.
- utilisation d'un point de départ ($FI_{L/B}$) : 1, le PoD étant un NOAEL,
- insuffisance des données (FI_D) : 1, l'aluminium est un agent chimique dont les effets sont très documentés.

Un facteur d'incertitude global de 79 est donc utilisé pour la construction de la VTR.

3.2.1.7. Proposition de VTR long terme par voie orale et niveau de confiance

Une VTR long terme à seuil par voie orale a été calculée en faisant le rapport entre le PoD ajusté et le FI global.

$$VTR = NOAEL_{HED} / FI = 0{,}036 \text{ mg.kg pc}^{-1}.\text{j}^{-1}, \text{ arrondie à } 40 \text{ µg.kg pc}^{-1}.\text{j}^{-1}$$

Le niveau de confiance global pour cette VTR est estimé à 3,5/5, soit un **niveau de confiance moyen-fort**.

3.2.2. VTR court terme par voie respiratoire

Aucune étude chez l'Homme n'a été identifiée concernant les effets de l'aluminium suite à une exposition de courte durée par voie respiratoire ou par ingestion. Les études animales sur les effets de l'aluminium par inhalation révèlent des effets potentiels sur le système respiratoire : augmentation des macrophages alvéolaires, lésions granulomateuses dans les poumons et augmentation du poids des poumons (Mazzoli-Rocha *et al*. 2010, Thomson *et al.* 1986, Drew *et al*. 1974). Cependant, les effets pulmonaires observés chez les animaux dans ces études pourraient également être liés à une surcharge en poussières plutôt qu'à des effets spécifiques liés à l'aluminium.

En l'absence de données par voie respiratoire, il n'a pas été possible de dériver une VTR à court terme par voie respiratoire.

3.2.3. VTR long terme par voie respiratoire

3.2.3.1. Choix de l'effet critique

Des effets pulmonaires ont été observés chez les travailleurs après des expositions à des composés de l'aluminium. Cependant, ces effets ne sont pas directement et seulement imputables à l'aluminium, en raison des co-expositions à d'autres agents. Chez des rats exposés au chlorhydrate d'aluminium de manière subchronique par inhalation, seuls des effets pulmonaires (augmentation du poids des poumons, augmentation des macrophages alvéolaires, lésions granulomateuses) ont été observés (Steinhagen et Cavender, 1978 ; Stone et al. 1979). Ces effets pourraient être imputables à la fois à l'aluminium, à l'ion chlorure

et à un effet non spécifique de l'exposition à des poussières. Il n'est pas donc pas possible de distinguer la part attribuable à l'aluminium.

L'exposition à l'aluminium par voie orale ou respiratoire peut entraîner de nombreux effets systémiques sur la santé tels que des effets neurotoxiques, neurodéveloppementaux, osseux ou hématologiques. Les effets neurotoxiques apparaissent à la fois chez l'Homme et les animaux de laboratoire aux plus faibles doses testées, par voie orale chez les animaux de laboratoire, ainsi que par voie respiratoire chez des travailleurs.

Ainsi, **le CES VSR retient comme effet critique les effets neurotoxiques.**

3.2.3.2. Choix de l'hypothèse de construction

Pour la plupart des effets non cancérogènes, il est considéré, par défaut et en l'état actuel des connaissances, que la toxicité ne s'exprime qu'au-delà d'un seuil de dose. Ainsi, **le CES VSR considère que les effets neurotoxiques résultent d'un mécanisme à seuil de dose**.

3.2.3.3. Analyse des VTR long terme par voie respiratoire existantes

En 2006, l'US EPA a proposé une VTR long terme provisoire par voie respiratoire (pRfC) sur la base d'une diminution des scores de performances cognitive et psychomotrice observée chez des travailleurs exposés en milieu professionnel pendant 12 ans (Hosovski *et al.* 1999, US EPA 2006) (Annexe 2). Cependant, la valeur d'exposition présentée par les auteurs, comprise entre 4,6 et 11,5 $mg.m^{-3}$, n'indique pas clairement s'il s'agit d'une concentration en aluminium ou en poussière d'autant plus que le nombre et la taille des particules de poussières sont mentionnés sans précisions sur la fraction d'aluminium dans l'air. De plus, les concentrations très élevées en aluminium sanguin chez les individus exposés, ainsi que les témoins, suggèrent une forte contamination des prélèvements et donc un risque de biais majeur dans l'analyse des résultats de cette étude. La pRfC est estimée avec un FI de 300, tenant compte de la variabilité inter-individuelle (FI_H = 10), de l'utilisation d'un LOAEL (FI_L = 10) et de la confiance modérée dans la base de données (absence de donnée confirmant les niveaux d'effet (NOAEL et LOAEL supplémentaires), absence de données disponibles pour les effets neurodéveloppementaux par inhalation et nécessité d'avoir une étude de reproduction bien conçue sur deux générations) (FI_D = 3).

Au regard des limites décrites ci-dessus, le CES VSR ne retient pas la VTR respiratoire provisoire de l'US EPA, ni l'étude clé identifiée. Ainsi, le CES VSR décide de proposer une nouvelle VTR long terme par voie respiratoire.

3.2.3.4. Choix de l'étude clé et du point de départ

Aucune étude épidémiologique en population générale ne renseigne des effets neurotoxiques de l'aluminium après exposition par voie respiratoire ou par voie orale. Les données provenant d'études épidémiologiques chez les travailleurs ne sont pas adéquates pour caractériser leur exposition par inhalation à l'aluminium. Les études disponibles présentent généralement des niveaux d'aluminium moyennés pour plusieurs catégories de travailleurs ou encore une concentration en poussière dans l'air non pertinente pour cette expertise. Aucune étude animale étudiant la neurotoxicité de l'aluminium par voie respiratoire n'a été identifiée.

Ainsi, en l'absence d'étude pertinente chez l'Homme et d'étude (sub)chronique chez l'animal mettant en évidence l'effet critique, une extrapolation voie-à-voie est proposée pour construire une VTR respiratoire à partir du PoD de la VTR par voie orale décrite ci-

dessus. Une telle extrapolation voie à voie est possible lorsque l'effet critique est un effet systémique.

Les modèles cinétiques disponibles (Poddalgoda *et al.* 2021 ; Hethey *et al*. 2021) n'incluent pas la voie respiratoire et ne peuvent donc pas être utilisés pour réaliser l'extrapolation voie à voie. Ainsi, celle-ci a été réalisée à partir de l'étude clé identifiée pour la construction de la VTR par voie orale (Cao *et al.* 2016), où l'aluminium est administré par gavage sous forme de chlorure d'aluminium qui est l'une des plus biodisponibles. En l'absence de donnée d'absorption spécifique à ce composé, les valeurs maximales des taux d'absorption des différents composés inorganiques de l'aluminium par voie orale et voie respiratoire ont été retenues, soit respectivement 0,3 et 3%.

$$NOAEC_{HEC} = \frac{NOAEL_{HED} \times Absorption_{orale} \times PC}{Volume\ respiratoire \times Absorption_{resp.}}$$

Avec $NOAEL_{HED}$ = 2,83 mg.kg $pc^{-1}.j^{-1}$, le poids corporel (PC) = 70 kg et le volume respiratoire = 20 m^3/j.

Soit $NOAEC_{HEC}$ = 0,99 $mg.m^{-3}$

Le CES VSR retient une $NOAEC_{HEC}$ de 0,99 $mg.m^{-3}$ comme PoD après extrapolation de la voie orale à la voie respiratoire.

3.2.3.5. Choix des facteurs d'incertitude

Le calcul de la VTR long terme par voie respiratoire à partir de la $NOAEC_{HEC}$ a été effectué à l'aide des FI suivants (Anses, à paraître) :

- variabilité inter-espèces (FI_A) : 2,5, pour tenir compte de la variabilité toxicodynamique et d'incertitudes toxicocinétiques résiduelles, un ajustement dosimétrique ayant été réalisé,
- variabilité interindividuelle (FI_H) : 10 par défaut,
- transposition subchronique à chronique (FI_S) : √10, pour tenir compte de la transposition d'une étude subchronique à une exposition chronique,
- utilisation d'un point de départ ($FI_{L/B}$) : 1, le PoD étant un NOAEL,
- insuffisance des données (FI_D) : 1, l'aluminium est un agent chimique dont les effets sont très documentés.

Un facteur d'incertitude global de 79 est donc utilisé pour la construction de la VTR.

3.2.3.6. Proposition de VTR long terme par voie respiratoire et niveau de confiance

Une VTR long terme à seuil par voie respiratoire a été calculée en faisant le rapport entre le PoD ajusté et le FI global.

VTR = $NOAEC_{HED}$ / FI = 0,0125 $mg.m^{-3}$ soit 12,5 $\mu g.m^{-3}$, arrondie à 12 $\mu g.m^{-3}$

Le niveau de confiance global pour cette VTR est estimé à 2,7/5, soit un **niveau de confiance moyen**.

Bien qu'ayant proposé une VTR long terme par voie respiratoire afin de répondre à la demande, le CES VSR juge qu'il n'est pas pertinent d'en recommander l'usage, celle-ci ne prenant en compte que la voie respiratoire, voie jamais isolée et rarement prédominante. Même lorsqu'il existe des sources d'émission aérienne de composés de l'aluminium dans l'environnement sous forme de fumées ou de poussières, celles-ci se déposent finalement sur les sols, les surfaces et les végétaux et s'y accumulent. Les principaux modes de contamination des individus sont finalement le port à la bouche des mains ou d'objets contaminés par les poussières et la consommation de végétaux produits localement. La voie orale étant largement majoritaire, l'évaluation des expositions à l'aluminium par voie respiratoire est inadaptée ; le respect de la VTR respiratoire ne peut garantir l'absence de surexposition de tout ou partie de la population concernée.

Ainsi, le CES n'en recommande pas l'usage et souligne qu'il est nécessaire d'utiliser une VTR interne et l'a donc dérivée.

3.2.4. Proposition d'une VTR interne

Afin de qualifier et de quantifier le risque pour la santé humaine à partir des études de biosurveillance de la population française, une VTR interne est nécessaire pour l'aluminium et ses composés inorganiques.

3.2.4.1. Choix du biomarqueur d'exposition

L'aluminium urinaire est retenu par les experts comme IBE pertinent pour la surveillance biologique de l'exposition à l'aluminium, sur la base d'une analyse des avantages et inconvénients des différents IBE identifiés (voir section 3.1.2).

3.2.4.2. Choix de l'effet critique

Le principal effet systémique survenant aux plus faibles concentrations urinaires, rapporté dans les études épidémiologiques sur les travailleurs exposés à l'aluminium, est une baisse des performances cognitives objectivée sous la forme d'une diminution des performances neurocomportementales par rapport aux personnes non exposées (Hosovski *et al.* 1990 ; Bast-Pettersen *et al*. 1994 ; Hänninen *et al.* 1994 ; Guo *et al.* 1999 ; Riihimäki *et al.* 2000 ; Bast-Pettersen *et al.*, 2000 ; He *et al.* 2003 ; Buchta *et al.* 2005 ; Kiesswetter *et al*. 2007). Par ailleurs, plusieurs études en population générale explorent l'association entre l'exposition à l'aluminium et les performances cognitives (tests neurocomportementaux). Cependant, seuls les niveaux d'aluminium mesurés dans l'eau de boisson y sont rapportés sans mesures correspondantes de l'aluminium dans les matrices biologiques.

Le choix de l'effet critique est également conforté par les études expérimentales. En effet, plusieurs études expérimentales par voie orale chez l'animal ont montré des effets neurotoxiques tels qu'une altération des capacités de l'apprentissage et de la mémoire, une diminution de la force de préhension des membres antérieurs et postérieurs, une diminution de la réaction de sursaut, une diminution de l'activité locomotrice et du nombre total d'activités, un test de géotaxie négatif réduit et des lésions et diminution de la densité des cellules de l'hippocampe.

Ainsi, le CES VSR retient les effets neurotoxiques (diminution des performances cognitives objectivée par des tests neurocomportementaux) comme effet critique pour l'élaboration d'une VTR interne pour l'aluminium urinaire.

3.2.4.3. Choix de l'hypothèse de construction

Pour la plupart des effets non cancérogènes, il est généralement admis, par défaut et dans l'état actuel des connaissances, que la toxicité ne se manifeste qu'au-delà d'un seuil de dose. **Ainsi, le CES VSR considère que la diminution des performances cognitives résulte d'un mécanisme à seuil de dose.**

3.2.4.4. Choix de l'étude clé et du point de départ

Aucune étude épidémiologique n'a été identifiée dans la recherche bibliographique pour la population générale. Deux études longitudinales, jugées de bonne qualité, portant sur des cohortes distinctes de travailleurs établissant une association entre les concentrations d'aluminium urinaire et les effets cognitifs permettent de déterminer des NOAEL et LOAEL :

- NOAEL de 38 $\mu g.g^{-1}$ créatinine (fin de poste après plusieurs jours de travail) issu d'une étude sur des soudeurs d'aluminium dans la construction automobile (98 travailleurs et 50 témoins) (Buchta *et al*. 2003 et confirmée par l'étude de Kiesswetter *et al*. de 2009) ;
- LOAEL de 97 $\mu g.g^{-1}$ créatinine (fin de poste après plusieurs jours de travail) issu d'une étude sur les travailleurs de la construction de trains et camions (44 travailleurs et 37 témoins) (Buchta *et al*. 2005 et confirmée par l'étude de Kiesswetter *et al*. de 2007).

Aucune altération des performances cognitives n'a été observée dans une étude longitudinale chez des travailleurs présentant des concentrations plasmatiques d'aluminium comparables à celles observées par Buchta *et al*. (2003) mais des concentrations urinaires plus élevées (87,6 $\mu g.g^{-1}$ créatinine) (Letzel *et al*. 2000).

Des LOAEL plus bas ont été observés dans deux études mais n'ont pas été retenus car les résultats relatifs aux effets cognitifs étaient équivoques :

- LOAEL de 41,8 $\mu g.g^{-1}$ créatinine (fin de poste, jour de la semaine non précisé) montrant des altérations des performances cognitives équivoques selon les groupes d'âge (Guo *et al*. 1999) ;
- LOAEL de 40,1 $\mu g.g^{-1}$ créatinine (urines du matin, horaires par rapport à la prise de poste et jour de la semaine non précisés) avec un temps de réaction significativement meilleur chez les travailleurs exposés malgré des scores plus faibles aux tests de symboles numériques et de visée (He *et al.* 2003).

En conclusion, en l'absence d'étude épidémiologique dans la population générale, le CES VSR retient l'étude longitudinale de Buchta *et al.* de 2003 confirmée par celle de Kiesswetter *et al*. de 2009 comme étude clé et le NOAEL de 38 $\mu g.g^{-1}$ créatinine (fin de poste après plusieurs postes) comme PoD.

3.2.4.5. Application des facteurs d'incertitude et proposition de VTR interne

Au regard des données disponibles, la VTR interne a été calculée en utilisant les FI décrits ci-dessous :

- variabilité inter-espèces (FI_A) : 1, car la VTR interne est basée sur des données humaines ;

- variabilité inter-individuelle (FI_H) : 2, en considérant que la population de travailleurs présents dans l'étude clé est représentative de l'ensemble des travailleurs en terme de variabilité inter-individuelle et en considérant le ratio entre l'incertitude inter-individuelle de 10 pour la population générale et de 5 par défaut pour les travailleurs ;
- transposition subchronique à chronique (FI_S) : 1, car les individus étaient exposés de manière chronique (4 ans de suivi et 3 examens) ;
- utilisation d'un PoD ($FI_{L/B}$) : 1, le point de départ retenu est un NOAEL ;
- insuffisance de données (FI_D) : 1, l'aluminium est un agent chimique dont les effets sont très documentés.

Le facteur d'incertitude global pour dériver la VTR interne est de 2.

Une VTR interne de 19 µg.g^{-1} créatinine, arrondie à 20 µg.g^{-1} créatinine, fondée sur la neurotoxicité, est proposée pour l'aluminium urinaire.

3.2.4.6. Accompagnement de la VTR interne

- **Méthodes analytiques pour la détermination de l'aluminium**

Les principales méthodes analytiques pour la mesure de l'aluminium dans le sang et les urines sont décrites dans le Tableau 1 sans pour autant en recommander une. L'objectif est ici d'informer des paramètres métrologiques spécifiques et de présenter les avantages et les limites de chaque méthode.

Tableau 1 : Aperçu des avantages, des limites et des limites de détection / limites de quantification des principales techniques analytiques utilisées pour la mesure de l'aluminium

Méthode analytique	Avantages	Limites	LD	LQ
ETAAS / GFAAS	- Simplicité de préparation des échantillons - Faible volume des échantillons - Peu d'interférences - Sensibilité	- Mesure d'un seul composé à la fois - Gamme analytique limitée	1-2 µg.L^{-1} (0,04-0,07 µmol.L^{-1})	2 µg.L^{-1}
ICP-AES	- Simplicité de préparation des échantillons - Faible volume des échantillons - Analyse multi-éléments - Forte spécificité - Large gamme analytique	- Possible interférences - Faible sensibilité	1-4 µg.L^{-1} (LD élevée)	1 µg.L^{-1}
ICP-MS	- Simplicité de préparation des échantillons - Faible volume des échantillons - Analyse multi-éléments - Très grande sensibilité - Large gamme analytique		0,1–1 µg.L^{-1} (0,004–0,04 µmol.L^{-1})	0,2-10 µg.L^{-1}

LD : limite de détection ; LQ : limite de quantification ; ETAAS/GFAAS : *Electrothermal Atomic Absorption Spectrometry/ Graphite furnace atomic absorption spectrometry* (Spectrométrie d'absorption atomique électrothermique/ spectrométrie d'absorption atomique en four graphite); ICP-AES : *Inductively Coupled Plasma Atomic Emission Spectrometry* (spectroscopie d'émission atomique à plasma à couplage inductif) ; ICP-MS : *Inductively Coupled Plasma Mass Spectrometry* (Spectrométrie de masse à plasma à couplage inductif)

- **Facteurs pouvant influencer l'interprétation des mesures d'aluminium urinaire**

Certaines pratiques peuvent influencer l'interprétation des mesures d'aluminium en augmentant les niveaux d'aluminium et en rendant les résultats de la biosurveillance difficilement interprétables (Tableau 2).

Tableau 2 : Facteurs pouvant influencer l'interprétation des mesures d'aluminium total dans l'urine et le plasma

Traitement médical	La consommation de certains médicaments contenant des sels d'Al comme principe actif ou comme adjuvant pourrait augmenter les niveaux d'Al et devrait être évitée avant le prélèvement (ex. : certains antiacides, aspirines tamponnées, antidiarrhéiques, *etc.*).
Apport alimentaire	Le contact des aliments avec des emballages en Al, des ustensiles de cuisine et des films en Al dans des conditions acides peut entraîner l'émission d'Al et la contamination des aliments (Krewski *et al.* 2007). En outre, les jus de fruits (contenant de l'acide citrique qui augmente l'absorption de l'Al) peuvent augmenter les niveaux d'Al urinaire et devraient être évités dans les 2 jours précédant l'échantillonnage (Biotox[9]).
Tabagisme	Même si des concentrations élevées d'Al dans le tabac sont rapportées, allant de 0,6 à 3,7 mg $Al.g^{-1}$ de produit (Exley *et al.* 2006), le tabagisme n'a pas influencé les concentrations d'Al dans l'urine de sujets non exposés professionnellement (Chiba et Masironi 1992 ; Nisse *et al.* 2017). Il pourrait donc ne pas avoir d'impact sur l'interprétation des résultats de la surveillance biologique.
Facteurs physiologiques ou pathologiques	L'Al étant principalement éliminé dans l'urine, les patients dont la fonction rénale est réduite peuvent présenter des niveaux plus élevés d'Al dans le sang en raison de l'absence de clairance normale (ce qui implique des niveaux urinaires réduits). La mesure de l'Al peut être utilisée pour surveiller les patients porteurs de prothèses métalliques (San Martín, Bauçà et Martinez-Morillo 2022). Par ailleurs, l'augmentation des niveaux d'Al peut également être attribuée à l'usure des implants prothétiques à base d'Al.
Co-exposition à une ou plusieurs substances (travailleurs)	N/A
Voie(s) d'exposition, description de la tâche	N/A
Activité physique, effort, etc.	N/A
Fréquence et dure d'exposition	N/A

N/A : non applicable ; Al : aluminium

- **Choix du moment de prélèvement**

D'un point de vue pratique, les études permettant de caractériser l'association entre la concentration d'aluminium dans l'urine et les effets sur la santé, et d'identifier un NOAEL et un LOAEL, ont été conduites en milieu de travail et ont utilisé des échantillons urinaires en fin de poste. Certaines de ces études ont rapporté les résultats des prélèvements en fin de poste et début de poste après plusieurs jours de travail. Elles n'ont montré aucune différence dans les concentrations d'aluminium urinaire à ces deux moments d'échantillonnage. Les concentrations d'aluminium dans les urines de prélèvements de début ou de fin de poste sont déterminées par la charge corporelle et l'exposition actuelle. La cinétique d'élimination de l'aluminium indique que sa concentration dans des prélèvements urinaires réalisés après

[9] https://www.inrs.fr/publications/bdd/biotox.html, consulté en avril 2024

quelques jours d'arrêt de l'exposition professionnelle (par exemple, avant le premier poste de de la semaine de travail) serait moins influencée par l'exposition actuelle, donc probablement un meilleur indicateur de la charge corporelle. Cependant, les données disponibles ne permettent pas de caractériser l'association de la concentration d'aluminium urinaire avant le premier poste de la semaine de travail et des effets sanitaires.
Dans la population générale, le moment de prélèvement apparaît indifférent puisque cette population est généralement exposée à l'aluminium de manière chronique et de façon peu variable (hors des expositions aiguës). Cependant, pour une bonne reproductibilité et pour éviter la contamination par ce composé omniprésent, les échantillons doivent être prélevés le matin au réveil ou après la douche.

Aucune recommandation sur le moment de prélèvement des urines n'est faite pour la population générale.

- **Prélèvement, collecte et stockage des échantillons biologiques**

Des précautions strictes doivent être prises lors du prélèvement, de la conservation et de la préparation des échantillons et de l'analyse. Comme pour d'autres agents chimiques omniprésents, le risque de contamination externe apparaît comme un problème dans la détermination de l'aluminium.

Ci-dessous quelques recommandations concernant le prélèvement et la conservation d'échantillons d'urine en vue de la mesure de l'aluminium. Toutefois, les matériels de prélèvement doivent être ceux recommandés par le laboratoire en charge de l'analyse, qui doit avoir préalablement vérifié qu'ils ne contiennent pas d'aluminium (OMS 1996 ; Labat 2010 ; San Martín, Bauçà, et Martinez-Morillo 2022). De plus, en règle générale, le matériel d'échantillonnage devrait idéalement être fourni par des laboratoires qui ont préalablement vérifié qu'il convenait à l'analyse.

Les recommandations suivantes sont proposées pour minimiser la contamination et garantir des résultats précis :

1. en premier lieu, utiliser des flaconnages et des consommables étiquetés « sans traces de métaux » et d'éviter les flacons en verre ;
2. si ce n'est pas le cas, le matériel doit être nettoyé avec de l'acide nitrique ultrapur à 10 % (jusqu'à un maximum de 20 %) et trempé pendant une nuit, puis rincé abondamment à l'eau ultrapure ;
3. dans tous les cas, tous les consommables doivent être testés pour identifier les éventuelles contaminations en aluminium (test à blanc avec des concentrations de réactifs et d'acides identiques à celles utilisées pour les échantillons). Ce test doit également être effectué après l'étape de nettoyage.

3.2.5. Valeur d'imprégnation populationnelle (VIP)

En général, lors de la sélection d'une VIP, le 95ème percentile de la distribution dans la population générale d'une étude de référence est utilisé. Dans le cas de l'aluminium, les niveaux urinaires issus de l'étude « ESTEBAN »[10], qui servirait normalement d'étude de référence pour la population française, ne peuvent être interprétés en raison d'une probable contamination externe des échantillons d'urine par l'aluminium. En revanche, l'étude

[10] Étude de santé sur l'environnement, la biosurveillance, l'activité physique et la nutrition

« IMEPOGE » (2008-2010)[11] de Nisse *et al*. (2017), avec un grand nombre de participants adultes (n = 1920 âgés de 20 à 59 ans), représentative de la population adulte vivant dans le Nord de la France (Hauts-de-France), est retenue comme étude de référence, menant à une valeur de référence pour l'exposition à l'aluminium urinaire de 11,5 µg.L^{-1} (ou 13,3 µg.g^{-1} créatinine), correspondant au 95ème percentile de la distribution des niveaux d'aluminium urinaire dans cette population.

Il convient de noter que la population échantillonnée dans cette étude est probablement représentative non seulement de la région Hauts-de-France, mais aussi de l'ensemble de la population française. En effet, comme indiqué dans l'étude, les niveaux médians d'aluminium collectés à partir des mousses végétales du Nord-Pas-de-Calais étaient même inférieurs à ceux au niveau national, suggérant que la population n'est pas surexposée à l'aluminium dans cette région et que les résultats sont extrapolables au reste de la France. De plus, le 95ème percentile de la concentration d'aluminium urinaire observé dans l'étude de Nisse *et al.* (2017) est cohérent avec ceux des études menées en France par Goullé *et al.* (2005) (11,2 µg.L^{-1}, n = 100) et en Belgique par Hoet *et al.* (2013) (9,3 µg.L^{-1}, ou 7,5 µg.g^{-1} créatinine, n = 1022).

Une VIP de 13,3 µg.g^{-1} créatinine est proposée pour l'aluminium urinaire pour la population générale sur la base de l'étude « IMEPOGE » (Nisse *et al*. 2017).

3.3. Conclusion et recommandations

Le CES VSR a proposé trois VTR, des VTR long terme par voies orale et respiratoire et une VTR interne, ainsi qu'une valeur d'imprégnation populationnelle (VIP). Il n'a, en revanche, pas été en mesure de proposer une VTR court terme par voie respiratoire du fait d'une absence de donnée (Tableau 3).

Une VTR interne de 20 µg.g^{-1} de créatinine dans les urines du matin, fondée sur des données humaines issues d'expositions professionnelles, a été dérivée. En effet, dans le cas d'une substance ubiquitaire telle que l'aluminium, qui présente de multiples sources et voies d'exposition, l'utilisation d'une VTR interne permet de prendre en compte l'ensemble des sources et des voies d'exposition à l'aluminium et d'interpréter les concentrations d'IBE dans le cadre de la surveillance biologique et de l'évaluation quantitative des risques pour la santé de la population générale.

En plus de la VTR interne recommandée, une VIP de 13,3 µg.g^{-1} de créatinine correspondant au 95ème percentile de l'étude « IMEPOGE » (Nisse *et al*. 2017), étude considérée comme représentative d'une population générale française d'adultes, est proposée pour l'aluminium urinaire.

Le CES VSR a élaboré une **VTR orale long terme de 40 µg.kg pc^{-1}.j^{-1}**, fondée sur les effets cognitifs observés chez le rat après une exposition de 3 mois, présentant un niveau de confiance moyen-fort. Au regard des moyennes géométriques des apports alimentaires d'aluminium qui sont de 40,3 µg.kg pc^{-1}.j^{-1} chez les adultes et 62,2 µg.kg pc^{-1}.j^{-1} chez les enfants ; les P95 correspondants sont de 69,7 et 118,8 µg.kg pc^{-1}.j^{-1} dans l'étude alimentation

[11] L'étude IMPOGE est une étude transversale descriptive ayant mesuré les concentrations de métaux dans le sang et l'urine de la population générale du Nord de la France entre mai 20008 et septembre 2010.

totale n°2 (EAT2), la VTR orale semble être conservatrice. **Le CES VSR considère que la VTR interne est plus pertinente que la VTR orale.**

Sur la base d'une extrapolation de la voie orale à la voie respiratoire, le CES a élaboré une VTR long terme par voie respiratoire de 12 µg.m^{-3} présentant un niveau de confiance moyen. L'élaboration d'une telle VTR long terme par voie respiratoire a été jugée peu pertinente au regard des sources d'exposition de la population générale à l'aluminium. **Bien qu'ayant proposé une VTR long terme par voie respiratoire afin de répondre à la demande, le CES VSR juge qu'il n'est pas pertinent d'en recommander l'usage, celle-ci ne prenant en compte que la voie respiratoire, voie jamais isolée et rarement prédominante. Même lorsqu'il existe des sources d'émission aérienne de composés de l'aluminium dans l'environnement sous forme de fumées ou de poussières, celles-ci se déposent finalement sur les sols, les surfaces et les végétaux et s'y accumulent. Les principaux modes de contamination des individus sont finalement le port à la bouche des mains ou d'objets contaminés par les poussières et la consommation de végétaux produits localement. La voie orale étant largement majoritaire, l'évaluation des expositions à l'aluminium par voie respiratoire est inadaptée ; le respect de la VTR respiratoire ne peut garantir l'absence de surexposition de tout ou partie de la population concernée.**

Ainsi, le CES n'en recommande pas l'usage et souligne qu'il est nécessaire d'utiliser une VTR interne et l'a donc dérivée.

Le CES VSR recommande la réalisation d'études permettant de mieux caractériser les éventuels effets respiratoires de l'aluminium et de ses composés.

Tableau 3 : VTR par voies orale et respiratoire, VTR interne et VIP

VR	**Organisme**	Anses			
	Année	2024			
	Nom	**$VTR_{Long\ terme,\ orale}$***	**$VTR_{Long\ terme,\ respiratoire}$***	**$VTR_{interne}$**	**VIP**
	Valeur	0,036 mg.kg $pc^{-1}.j^{-1}$	0,0125 $mg.m^{-3}$	20 $\mu g.g^{-1}$ créatinine, prélèvement le matin	13,3 $\mu g.g^{-1}$ créatinine
	IBE	NC	NC	Aluminium urinaire	Aluminium urinaire
Effet critique		Effets cognitifs			NC
Étude clé	**Référence**	Cao *et al.* (2016)		Buchta *et al.* (2003) ; Kiesswetter *et al.* (2009)	Etude IMEPOGE, 2008 – 2010 (Nisse *et al*. 2017)
	Population de l'étude ou espèce	Rats		Travailleurs	N = 1992 (1016 femmes, 976 hommes)
	Exposition (durée, voie)	3 mois par voie orale (gavage)		4,7 ans ± 1,6 Inhalation, ingestion, cutanée au travail	NC
Point de départ (PoD)		NOAEL = 10 mg.kg $pc^{-1}.j^{-1}$		NOAEL = 38 $\mu g.g^{-1}$ créatinine	P95 observé
Ajustement allométrique		$NOAEL_{HED}$ = 2,83 mg.kg $pc^{-1}.j^{-1}$		NA	NC
Extrapolation voie à voie		NC	$NOAEC_{HEC}$ = 0,99 $mg.m^{-3}$	NC	NC
Facteurs d'incertitude (FI)		79 (FI_A 2,5 ; FI_H 10 ; FIs $\sqrt{10}$)		2 (FI_A 1 ; FI_H 2 ; FI_L 1 ; FI_S 1 ; FI_D 1)	NC
Niveau de confiance		**Moyen-Fort**	**Moyen**	**NC**	**NC**

NA : non appliqué ; NC : non concerné ; NOAEL/C : No Observed Adverse Effect Level/Concentration (dose/concentration n'entraînant pas d'effet néfaste observé) ; HED/C : Human equivalent dose/concentration (dose/concentration équivalente humaine) ; FI : facteur d'incertitude

* Le CES ne recommande pas l'utilisation de VTR externes pour l'aluminium, en particulier la VTR respiratoire, étant donné que i) l'exposition à l'aluminium de la population générale se fait principalement par voie orale et ii) le respect de la VTR externe respiratoire ne garantit pas l'absence de surexposition dans la population générale.

4. CONCLUSIONS ET RECOMMANDATIONS DE L'AGENCE

L'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (Anses) endosse les conclusions et recommandations du CES « Valeurs sanitaires de référence » relatives à l'élaboration de valeurs toxicologiques de référence (VTR) par voies orale et respiratoire, de VTR interne et de valeur d'imprégnation populationnelle (VIP) pour l'aluminium et ses composés inorganiques.

Bien que les experts n'en recommandent pas l'utilisation, l'Anses note et acte que des VTR par voies orale et respiratoire ont été déterminées de manière valide en appliquant la méthodologie d'expertise usuelle de l'Anses. Pour autant, l'agence est en phase avec les experts sur les limites que présente l'usage d'une telle valeur prise isolément, dans la mesure où l'exposition de la population générale ne se fait pas par une voie unique et que la voie respiratoire est rarement prédominante.

L'Anses recommande de privilégier, pour l'évaluation quantitative du risque sanitaire à l'échelle d'une population exposée, une surveillance biologique des expositions à l'aluminium et à ses composés. En effet, la mesure de l'aluminium urinaire, qui permet de prendre en compte l'ensemble des sources et voies d'exposition, constitue à ce jour l'indicateur le plus pertinent pour évaluer quantitativement les risques sanitaires en lien avec les expositions à l'aluminium et à ses composés inorganiques.

L'agence indique enfin qu'en milieu professionnel, c'est également la valeur interne, appelée valeur limite biologique pour l'aluminium urinaire qu'elle recommande en première intention pour évaluer les expositions professionnelles à l'aluminium et à ses composés inorganiques.

Pr Benoît Vallet

MOTS-CLÉS

Valeur toxicologique de référence, VTR, orale, inhalation, respiratoire, VTR interne, valeur d'imprégnation populationnelle, indicateurs biologiques d'exposition, effets sur la santé, population générale, aluminium

Keywords

Toxicological reference value, TRV, oral, inhalation, respiratory, internal TRV, populational internal exposure level, biomarkers of exposure, health effects, general population, aluminium

CITATION SUGGÉRÉE

Anses. (2025). Avis relatif à l'élaboration de valeurs toxicologiques de référence (VTR) par voies orale et respiratoire, de VTR interne et de valeur d'imprégnation populationnelle (VIP) pour l'aluminium et ses composés inorganiques. (saisine 2023-MPEX-0137). Maisons-Alfort : Anses, 30 p.

ANNEXE 1 : LISTE DES VTR LONG TERME PAR VOIE ORALE DISPONIBLES POUR L'ALUMINIUM

VTR	**Organisme**	US EPA	ATSDR	Efsa	Jecfa
	Année	2006	2008	2008	2012
	Nom	p-RfD	MRL	TWI	PTWI
	Valeur	1 mg.kg $pc^{-1}.j^{-1}$	1 mg.kg $pc^{-1}.j^{-1}$	1 mg.kg $pc^{-1}.j^{-1}$ (correspondant à 0,14 mg.kg $pc^{-1}.j^{-}$)	2 mg.kg $pc^{-1}.sem^{-1}$ (correspondant à 0,29 mg.kg $pc^{-1}.j^{-1}$)
Effet critique		Effets neuromusculaires (diminution de la force de préhension des membres antérieurs)	Effets neuromusculaires (diminution de la force de préhension des membres antérieurs et postérieurs)	Effets neuromusculaires (diminution de la force de préhension et diminution du gain de poids corporel)	Effets rénaux (hydronéphrose, dilatation urétrale, obstruction et/ou présence de calculs) et effets neuromusculaires (diminution de la force de préhension des membres antérieurs et postérieurs)
Etude clé	**Référence**	Golub *et al.* (1995)	Golub *et al*. (2000)	1) Golub *et al.* (1995) 2) Golub & Germann (2001)	Poirier *et al*. (2011)
	Population de l'étude	Souris (SW)	Souris (SW)	1) et 2) Souris (SW)	Rats (SD)
	Exposition (durée, route)	De la conception au sevrage, alimentation	De la conception à 2 ans, alimentation	1) De la conception au sevrage, alimentation 2) De la conception à l'âge de 35 jours, alimentation	Du 6ème jour de gestation à 364 jours, eau de boisson
Point de départ		LOAEL : 100 mg.kg $pc^{-1}.j^{-1}$	LOAEL : 100 mg.kg $pc^{-1}.j^{-1}$	1) LOAEL: 50 mg.kg $pc^{-1}.j^{-1}$ 2) LOAEL: 50 mg.kg $pc^{-1}.j^{-1}$; NOAEL: 10 mg.kg $pc^{-1}.j^{-1}$	LOAEL: 100 mg.kg $pc^{-1}.j^{-1}$ NOAEL: 30 mg.kg $pc^{-1}.j^{-1}$
Ajustements temporel et allométrique		/	/	/	/
Facteurs d'incertitude (FI)		100 (FI_A: 10; FI_H: 3; FI_L: 3)	300 (FI_A: 10; FI_H: 10; FI_L: 3), facteur modificatif de 0,3 pour les différences de biodisponibilité	1) 300 (FI_A: 10; FI_H: 10; FI_L: 3) 2) 100 (FI_A: 10; FI_H: 10)	100 (FI_A: 10; FI_H: 10)
Niveau de confiance		Faible	/	/	/

/ : non réalisé, FI_A : facteur d'incertitude inter-espèces ; FI_H : facteur d'incertitude inter-individuel ; $FI_{L/B}$: facteur d'incertitude lié au type de PoD ; FI_D : facteur d'incertitude lié au manque de donnée ; LOAEL : *Lowest Observed Adverse Effect Level*, MRL : *Minimal Risk Level*, NOAEL : *No Observed Adverse Effect Level*, p-RfD : *provisory Reference Dose*, TWI : *Tolerable Weekly Intake*, PTWI : *provisory Weekly Intake*

ANNEXE 2 : VTR LONG TERME PAR VOIE RESPIRATOIRE DISPONIBLE POUR L'ALUMINIUM

VR	**Organisme**	US EPA
	année	2006
	nom	p-RfC
	Valeur	5 µg.m^{-3}
Effet critique		Altérations psychomotrice et cognitive
Etude clé	**Référence**	Hosovski *et al.* (1990)
	Population de l'étude	Travailleurs
	Exposition (durée, route)	12 ans, milieu professionnel
Point de départ		LOAEC : 4,6 mg.m^{-3}
Ajustement temporel		$LOAEC_{ADJ}$ = 1,64 mg.m^{-3} (10 m^3/20 m^3 et 5 /7 jours)
Ajustement allométrique		NR
Facteurs d'incertitude (FI)		300 (FI_H: 10; FI_L: 10; FI_D: 3)
Niveau de confiance		Moyen-faible

NR : non réalisé, FI_A : facteur d'incertitude inter-espèces ; FI_H : facteur d'incertitude inter-individuel ; FI_L : facteur d'incertitude lié à l'utilisation d'une LOAEC ; FI_D : facteur d'incertitude lié au manque de données, LOAEC : *Lowest Observed Adverse Effect Concentration,* p-RfC : *provisory Reference Concentration*

Toxicological Reference Value (TRV)

Recommendation of respiratory, oral and internal TRV for aluminium (CAS n°7429-90-5) and its inorganic compounds

TRV Permanent Mission
Requests n°2023-MPEX-0137
Related request n°2022-MPEX-0179 and n°2022-MPEX-0187

Collective expert appraisal REPORT

Expert Committee on « health reference values»
Working group on « biomarkers of exposure »

November 2024

AGENCE NATIONALE DE SÉCURITÉ SANITAIRE de l'alimentation, de l'environnement et du travail
14 rue Pierre et Marie Curie 94701 Maisons-Alfort Cedex
Tél : +33 (0)1 49 77 13 50 — www.anses.fr

Suggested citation

Anses. (2024). Toxicological reference value (TRV). Recommendation of respiratory and oral TRV and evaluation of biomarkers of exposure and recommendation for internal TRV for aluminium (7429-90-5) and its inorganic compounds (request 2023-MPEX-0137). Maisons-Alfort : Anses, 170 p.

Mots clés

Valeur toxicologique de référence, VTR, orale, inhalation, respiratoire, VTR interne, valeur d'imprégnation populationnelle, indicateurs biologiques d'exposition, effets sur la santé, population générale, aluminium

Keywords

Toxicological reference value, internal TRV, populational internal exposure level, biomarker of exposure, health effects, general population, aluminium

Presentation of participants

PREAMBLE: Expert members of expert committees, working groups or reviewers are all appointed in a personal capacity, intuitu personae, and do not represent their affiliated organization.

WORKING GROUP ON BIOMARKERS

Chair

Mr. Robert GARNIER - medicine and toxicologist, Paris - Expertise: medical toxicology, occupational medicine, environmental health

Vice-Chair

Ms. Sophie NDAW – Biomonitoring Researcher and Study Manager (INRS) – Expertise: Exposure Assessment - Biomonitoring - Analytical toxicology

Membres

Mr. Jean-Philippe ANTIGNAC – Research Engineer (INRAE) – Expertise: Analytical Chemistry - Biomonitoring - Exposure Biomarkers - Endocrine Disruptors - Emerging Contaminants - Environmental Health

Mr. Brice APPENZELLER –Head of the Human Biomonitoring Research Unit (Luxembourg Institute of Health) – Expertise: Analytical Chemistry - Exposure Science - Toxicology - Exposure Biomarkers - Biological Matrices

Mr. Jos BESSEMS – Senior Researcher (VITO) – Expertise: Toxicology - Toxicokinetics - Toxicokinetic Modeling - Risk Assessment - Biomonitoring

Mr. Raphaël DELEPEE – University Professor (University of Caen Normandy) – Expertise: Analytical Toxicology - Biomarkers of exposure - Analytical Chemistry

Mr. Sami HADDAD – Full Professor at the University of Montreal – Expertise: PBPK Modeling - Toxicokinetics - Chemical Pollutant Exposure - IBE

Mrs. Nolwenn NOISEL – Clinical Assistant Professor, Department of Environmental and Occupational Health - School of Public Health - University of Montreal – Expertise: Biomonitoring - Public Health - Environmental Health - Occupational Health - Toxicology

Mr. Nicolas VENISSE – Hospital Practitioner in Pharmacology and Toxicology (University Hospital of Poitiers) – Expertise: Toxicology - Pharmacokinetics - Toxicokinetics - Endocrine Disruptors - Environmental Health - Bioanalysis

Mrs. Céline VERNET – Researcher in Epidemiology (Gustave Eiffel University/UMRESTTE) – Expertise: Epidemiology - Environment and Health - Endocrine Disruptors - Pesticides

Mrs. Florence ZEMAN – Research Engineer (INERIS) – Expertise: Toxicokinetics - PBPK Modeling - Biological Monitoring - Ecotoxicology – Chemistry

WORKING GROUP ON BIOMARKERS 2024-2028

Chair

Ms. Sophie NDAW – Biomonitoring Researcher and Study Manager (INRS) – Expertise: Exposure Assessment - Biomonitoring - Analytical Toxicology

Vice-Chair

Mr. Benoît ATGE – Occupational physician-toxicologist, AHI33 – Expertise: Toxicology, Medicine, Occupational medicine, Biomonitoring, Cytotoxics, Exposure assessment, Surface contamination

Members

Mr. Jean-Philippe ANTIGNAC – Research Engineer (INRAE) – Expertise: Analytical Chemistry - Biomonitoring - Exposure Biomarkers - Endocrine Disruptors - Emerging Contaminants - Environmental Health

Mr. Samuel CHOCHOY – Industrial toxicologist (TOXILIST) – Expertise: Biomonitoring, Occupational exposure, Chemical risk prevention

Mr. Raphaël DELEPEE – University Professor (University of Caen Normandy) – Expertise: Analytical Toxicology - Exposure Biomarkers - Analytical Chemistry

M. Robert GARNIER - Medicine and toxicologist, Paris - Expertise: medical toxicology, occupational medicine, environmental health

Mr. Sami HADDAD – Full Professor at the University of Montreal – Expertise: PBPK Modelling - Toxicokinetics - Chemical Pollutant Exposure - IBE

Ms. Elodie LOEUILLET – Occupational physician-toxicologist (Orange) – Occupational medicine, Clinical toxicology, Biomonitoring

Ms. Nolwenn NOISEL – Clinical Assistant Professor, Department of Environmental and Occupational Health - School of Public Health - University of Montreal – Expertise: Biomonitoring - Public Health - Environmental Health - Occupational Health - Toxicology

Ms. Marie PECHEUX – Epidemiologist (Santé Publique France) – Expertise: Biomonitoring, Epidemiology, Chemistry

Mr. Nicolas VENISSE – Hospital Practitioner in Pharmacology and Toxicology (University Hospital of Poitiers) – Expertise: Toxicology - Pharmacokinetics - Toxicokinetics - Endocrine Disruptors - Environmental Health - Bioanalysis

Ms. Florence ZEMAN – Research Engineer (INERIS) – Expertise: Toxicokinetics - PBPK Modelling - Biological Monitoring - Ecotoxicology – Chemistry

REVIEWERS

Mr. Luc BELZUNCES – Research Director and Director of the Environmental Toxicology Laboratory at INRAE – Expertise: toxicology, neurotoxicity, ecotoxicology, analytical chemistry, risk assessment

Ms. Nadia NIKOLOVA-PAVAGEAU – Medical advisor at the French National Research and Safety Institute for Prevention of Occupational accident and disease (INRS) – Expertise: occupational medicine, medical toxicology, biomarkers of exposure

Mr. Henri SCHROEDER – Lecturer at the Faculty of Science and Technology of the University of Lorraine, Department of Neuroscience and Animal Biology and INSERM unit U1256 Nutrition, Genetics and Exposure to Environmental Risks - Pharmacist neurobiologist - Expertise: neurotoxicity, environmental pollutants, animal behaviour, cerebral development, perinatal exposure

EXPERT COMMITTEE (CES) 2020-2024

- The “Health Reference Values” Committee (2020-2024)

Chair

Mr. Fabrice MICHIELS – Occupational physician-toxicologist, Intercompany association for occupational health, Corrèze and Dordogne (SPST 19-24) – Expertise: occupational medicine, occupational and environmental toxicology

Vice-Chair

Mr. Jérôme THIREAU – Standard Grade Researcher, French National Centre for Scientific Research (CNRS) – Doctor of science (PhD) - Expertise: animal physiology, electrophysiology, cell biology, cardiotoxicity

Members

Mr. Benoît ATGE – Occupational physician-toxicologist, AHI33 – Expertise: Toxicology, Medicine, Occupational medicine, Biomonitoring, Cytotoxics, Exposure assessment, Surface contamination

Mr. Luc BELZUNCES – Research Director and Director of the Environmental Toxicology Laboratory at INRAE – Expertise: toxicology, neurotoxicity, ecotoxicology, analytical chemistry, risk assessment

Mrs. Michèle BISSON – Study director, French National Institute for Industrial Environment and Risks (INERIS) – Expertise: Pharmacist-toxicologist, reference toxicological values, general toxicology, risk assessment

Mrs. Anne CHEVALIER – Retired epidemiologist, French Institute for Public Health Surveillance (InVS) - Expertise: epidemiology

Mrs. Fatiha EL-GHISSASSI – Scientist, IARC Monographs Section (IMO) International Agency for Research on Cancer – Expertise: biochemistry, carcinogenicity, genotoxicity

Mr. Claude EMOND – Assistant clinical professor, University of Montréal, Canada - Department of environmental and occupational health – Expertise: toxicology, physiologically based pharmacokinetic (PBPK) modelling, toxicokinetics, nanotoxicology, endocrine disruptors

Mr. Robert GARNIER – medical toxicologist, Paris - Expertise: medical toxicology, occupational medicine, environmental health

Mr. Kevin HOGEVEEN – Toxicologist, Anses – Fougères, Toxicology of contaminants – Expertise: toxicology, genotoxicity, hepatotoxicity, *in vitro* toxicology

Mrs. Yuriko IWATSUBO – Epidemiologist physician, French Public Health Agency (SPF) – Expertise: occupational risks epidemiology

Mr. Jérôme LANGRAND – Hospital doctor (PU-PH), Head of department of Paris Poison control center, AP-HP Fernand-Widal hospital, Paris Poison control center – Expertise: Toxicology, Medicine, Occupational toxicology, Environmental and occupational Pathologies, Toxins

Mrs. Gladys MIREY – Research Director in toxicology, Head of the Genotoxicity & Signaling team, INRAE UMR TOXALIM – Expertise: Cellular Toxicology, Genotoxicity, Mechanisms of action, Contaminants, Study models/alternative methods, Effects of mixtures

Mr. Luc MULTIGNER – Research Director, INSERM U1085 – Research Institute for Environmental and occupational Health (IRSET) – Expertise: epidemiology, endocrine disruptors, pathologies of reproductive functions and organs

Ms. Nadia NIKOLOVA-PAVAGEAU – Medical advisor at the French National Research and Safety Institute for Prevention of Occupational accident and disease (INRS) – Expertise: occupational medecine, medical toxicology, biomarkers of exposure

Ms. Magali OLIVA-LABADIE – Hospital doctor (PU-PH), Head of department, Bordeaux CHU, Pellegrin hospital, Nouvelle Aquitaine Poison control center – Expertise: Toxicology, Medicine, Environmental toxicology, Toxins

Mr. Benoît OURY – Retired from the French National Research and Safety Institute for Prevention of Occupational accident and disease (INRS) – Expertise: atmospheric metrology, workplace atmosphere, occupational exposure assessment

Mr. Henri SCHROEDER – Lecturer at the Faculty of Science and Technology of the University of Lorraine, Department of Neuroscience and Animal Biology and INSERM unit U1256 Nutrition, Genetics and Exposure to Environmental Risks - Pharmacist neurobiologist - Expertise: neurotoxicity, environmental pollutants, animal behaviour, cerebral development, perinatal exposure

Mr. Olivier SORG – Head of research group, University of Geneva, Switzerland - Expertise: biochemistry, experimental toxicology, dermatotoxicology

Mr. Antoine VILLA – Hospital doctor (PU-PH), Occupational physician, La Timone hospital, Marseille – Expertise: occupational pathologies, toxicology, medicine, expology, biomonitoring, asbestos, cytotoxics

Ms. Maeva WENDREMAIRE – Lecturer, University of Bourgogne – Expertise: toxicology, reprotoxicity, pharmacology, analytical toxicology

EXPERT COMMITTEE (CES) 2024-2028

The work carried out as part of this report was adopted by:

- The “Health Reference Values” Committee, 08/11/2024

Chair

Mr. Jérôme THIREAU – Standard Grade Researcher, French National Centre for Scientific Research (CNRS) – Doctor of science (PhD) - Expertise: animal physiology, electrophysiology, cell biology, cardiotoxicity.

Vice-Chair

Ms. Maylis TELLE-LAMBERTON – Epidemiologist, statistician at ORS Ile de France – Expertise: epidemiology, occupational risk, statistics

Members

Mr. Marc BARIL – Assistant Professor University of Montreal – Expertise: chemist, toxicologist, industrial hygiene

Ms. Michèle BISSON – Study director, French National Institute for Industrial Environment and Risks (INERIS) – Expertise: pharmacist-toxicologist, reference toxicological values, general toxicology, risk assessment.

Mr. Nicolas CHEVALIER – Hospital doctor (PU-PH) Nice University Hospital – Expertise: medicine, endocrinology; thyroid; metabolism; epidemiology; diabetes

Mr. Mihai Ciprian CIRTIU – Specialist scientific advisor, INSPQ and associate professor University of Laval and University of Québec at Trois-Rivières– Expertise: toxicology, biometrology, chemistry, method development and validation, nanomaterials

Ms. Fatiha EL-GHISSASSI – Retired from International Agency for Research on Cancer – Expertise: biochemistry, carcinogenicity, genotoxicity.

Mr Claude EMOND – Assistant clinical professor, University of Montreal, Canada - Department of environmental and occupational health – Expertise: toxicology, physiologically based pharmacokinetic (PBPK) modelling, toxicokinetics, nanotoxicology, endocrine disruptors.

Mr. Robert GARNIER – medicine and toxicologist, Paris - Expertise: medical toxicology, occupational medicine, environmental health.

Mr. Kevin HOGEVEEN – Toxicologist, Anses – Fougères, Toxicology of contaminants – Expertise: toxicology, genotoxicity, hepatotoxicity, *in vitro* toxicology.

Ms. Yuriko IWATSUBO – Retired from French Public Health Agency (SPF) – Expertise: occupational risks, epidemiology.

Mr. Jérôme LANGRAND – Hospital doctor (PU-PH), Head of department of Paris Poison control center, AP-HP Fernand-Widal hospital, Paris Poison control center – Expertise: toxicology, medicine, occupational toxicology, environmental and occupational pathologies, toxins.

Mr. Fabrice MICHIELS – Occupational physician-toxicologist, Intercompany association for occupational health, Corrèze and Dordogne (SPST 19-24) – Expertise: occupational medicine, occupational and environmental toxicology.

Mrs. Gladys MIREY – Research Director in toxicology, Head of the Genotoxicity & Signaling team, INRAE UMR TOXALIM – Expertise: cellular toxicology, genotoxicity, mechanisms of action, contaminants, study models/alternative methods, effects of mixtures.

Mrs. Christelle MONTEIL – Professor of Toxicology, University of – Expertise: health impact, experimental toxicology, cardiorespiratory toxicology

Mr Johnny MORETTO – Lecturer in Physiology, University of Franche-Comté – Expertise: pharmacokinetic, physiology, pharmacology, biochemistry

Mr. Luc MULTIGNER – Research Director, INSERM U1085 – Research Institute for Environmental and occupational Health (IRSET) – Expertise: epidemiology, endocrine disruptors, pathologies of reproductive functions and organs.

Ms. Nadia NIKOLOVA-PAVAGEAU – Medical advisor at the French National Research and Safety Institute for Prevention of Occupational accident and disease (INRS) – Expertise: occupational medicine, medical toxicology, biomarkers of exposure.

Ms. Magali OLIVA-LABADIE – Hospital doctor (PU-PH), Head of department, Bordeaux CHU, Pellegrin hospital, Nouvelle Aquitaine Poison control center – Expertise: toxicology, medicine, environmental toxicology, toxins.

Mr. Stéphane PERSONNE – Pharmacovigilance assessor, ANSM – Expertise: general toxicology, experimental toxicology, toxicokinetic, PBPK

Mr. Renaud PERSOONS – Hospital doctor, Grenoble and Teacher University of Grenoble Alpes – Expertise: biological monitoring, toxicology, analysis of toxics, metrology

Mr. Julien ROUSSEL – Teacher researcher, University of Montpellier – pharmacology, physiopathology, neurobiology, electrophysiology, metabolism

Mr. Rachid SOULIMANI – University Professor and head of Neurotox site, University of Lorraine – Expertise: neurotoxicology, exposome, multi-exposure, health risk

Mr. Antoine VILLA – Hospital doctor (PU-PH), Occupational physician, La Timone hospital, Marseille – Expertise: occupational pathologies, toxicology, medicine, expology, biomonitoring, asbestos, cytotoxics.

Ms. Maeva WENDREMAIRE – Lecturer, University of Bourgogne – Expertise: toxicology, reprotoxicity, pharmacology, analytical toxicology.

ANSES PARTICIPATION

Scientific Coordination

Mr. Keyvin DARNEY

Ms Maria TANNOUS

Scientific Contribution

Ms. Dominique BRUNET

Mr. Keyvin DARNEY

Ms. Aurélie MATHIEU-HUART

Ms. Fatoumata SISSOKO

Ms Maria TANNOUS

Administration

Ms. Agnès BRION

Table of contents

Acronyms and abbreviations

Al	:	Aluminium
AAS	:	Atomic Absorption Spectrophotometry
ANSES	:	Agence nationale de sécurité sanitaire alimentation environnement travail (French agency for food, environmental and occupational health and safety)
ACH	:	Aluminium Chloride Hexahydrate
AchE	:	Acetylcholinesterase
ACGIH	:	American Conference of Governmental Industrial Hygienists
ACP	:	Acid phosphatase
Afssaps	:	Previous name of the French National Agency for the Safety of Medicines and Health Products (ANSM)
ALP	:	Alkaline phosphatase
AOR	:	Adjusted Odds Ratio
ATIME	:	Average Reaction Time
ATSDR	:	Agency for Toxic Substances and Disease Registry
ATP	:	Adenosine triphosphate
ATW	:	Aluminium-treated drinking water
AVLT	:	Auditory Verbal Learning Test
BDI	:	Beck depression inventory
BME	:	Biomarker of exposure
BMI	:	Body mass index
BMP-2	:	Bone morphogenetic protein 2
BDNF	:	Brain Derived Neurotrophic Factor
bw	:	Body weight
cAMP	:	Cyclic adenosine monophosphate
CDC	:	Centers for Disease Control and Prevention (Etats Unis)
CDT	:	Clock Drawing Test
CES	:	Expert Committee (Comité d'experts spécialisé)
CFU-E	:	Colony-forming units-erythroid
CLP	:	Classification, Labelling and Packaging
CNS	:	Central Nervous System
Col II	:	Type II collagen
Cu	:	Copper
CX3CL1	:	Fractalkine (= a chemiokine)
DFG	:	Deutsche Forschungsgemeinschaft (German research foundation)
DGPR	:	Direction générale de la Prévention des risques
DGS	:	Direction générale de la Santé
DMN	:	Default mode network
DSBT	:	Digit Span Test backward
DSFT	:	Digit Span Test forward
DST	:	Digit Span Test
ETAAS	:	Electrothermal Atomic Absorption Spectrometry
ECHA	:	European chemicals agency
EEG	:	Electroencephalography
EFSA	:	European Food Safety Authority
ERP	:	Event-related potentials
EURO-NES	:	European neurobehavioral evaluation system
F1	:	First generation bred from a pair of parents
Fe	:	Iron
FOME	:	Fuld Object Memory Evaluation
FSH	:	Follicle-stimulating hormone

GerES	:	German Environmental Survey
Gd	:	Gestational day
GFAAS	:	Graphite furnace atomic absorption spectrometry
GFA-P	:	Glial fibrillary acidic protein
GHS	:	Globally Harmonized System
GSH-PX	:	Glutathione peroxidase
HBM4EU	:	Human biomonitoring for Europe
HCSP	:	Haut Conseil de la Santé Publique
HRV	:	Health reference value
HSL	:	Health and Safety Laboratory (Buxton, Derbyshire, UK)
IARC	:	International Agency for Research on Cancer
CI	:	Confidence Interval
ICP-AES	:	Inductively Coupled Plasma Atomic Emission Spectrometry
ICP-MS	:	Inductively coupled plasma mass spectrometry
INERIS	:	Institut national de l'environnement industriel et des risques
INRS	:	Institut national de recherche et de sécurité
INSPQ	:	Institut national de santé publique du Québec
ip	:	Intraperitoneal injection
IQR	:	interquartile range
IRSST	:	Institut de recherche Robert-Sauvé en santé et en sécurité du travail
IV	:	Intravenous
Ld	:	Lactation day
LD50	:	Median lethal dose
LDH	:	Lactate dehydrogenase
LDH-x	:	Lactate dehydrogenase isoenzyme
LH	:	Luteinizing hormone
LLNA	:	Local lymph node assay
LMW	:	Low molecular weight proteins
LOAEL	:	Lowest observed adverse effect level
LOD	:	Level of detection
LOQ	:	Limit of quantification
MCH II	:	Major histocompatibility complex class II
MCI	:	Mild cognitive impairment
MCT	:	Monocarboxylate transporter
MMF	:	Macrophagic myofasciitis
MMSE	:	Mini-mental state examination
MMSE-AE	:	Mini-mental state examination adjusted for age and education
MoCA	:	Montreal cognitive assessment basic (screening tool for cognitive impairment)
N/A	:	Not applicable
NCTB	:	Neurobehavioral core test battery
NHANES	:	National Health and Nutrition Examination Survey
NPC	:	Nonparametric test combination
NIOSH	:	National Institute for Occupational Safety and Health
NMU	:	N-nitroso-N-methylurea
NOAEL	:	No observed adverse effect level
NS	:	Not specified
NTP	:	National toxicology program
OEHHA	:	Office of Environmental Health Hazard Assessment (California - USA)
OR	:	Odds ratio
OSHA	:	Occupational Safety and Health Administration
PAHs	:	Polycyclic aromatic hydrocarbons
P-Al	:	Aluminium levels in plasma
PARC	:	Partnership for the Assessment of Risks from Chemicals
PBK	:	Physiological-based toxicokinetic
PND	:	Post natal day
PNR	:	Post-rotatory nystagmus

POMS	:	Profile of mood states questionnaire
PPM	:	Parts per million
PSQI	:	Pittsburg sleep quality index
PSS14	:	Perceived stress scale
QSM	:	Quantitative susceptibility mapping
REACh	:	Regulation (EC) No 1907/206 of 18/12/06 concerning the registration, evaluation, and authorisation of chemicals
RT	:	Reaction time
S-Al	:	Aluminium level in serum
SCCS	:	Scientific committee on consumer safety
SDH	:	Succinate dehydrogenase
SEM	:	Standard error of the m
SOD	:	Superoxide dismutase
SPF	:	Santé Publique France (French Public Health Agency)
SPM	:	Standard progressive matrices test
SRT	:	Simple reaction time
SST	:	Static steadiness test
TGF-b1	:	Transforming growth factor b1
TLV	:	Threshold limit value
TNO	:	Netherlands organisation for applied scientific research
TWA	:	Time weighted average
U-Al	:	Aluminium levels in urine
UF	:	Uncertainty factor
UF_A	:	Uncertainty factor for interspecies variability
UF_D	:	Uncertainty factor for insufficient data
UF_H	:	Uncertainty factor for intra-species or inter-individual variability
$UF_{L/B}$	:	Uncertainty factor due to the point of departure
UF_s	:	Uncertainty factor due to the duration of the key study transposition
US EPA	:	United States Environmental Protection Agency
VFT	:	Verbal fluency test
WG	:	Working group
WAIS	:	Wechsler adult intelligence scale
WMS	:	Wechsler memory scale
Zn	:	Zinc

List of tables

List of figures

1 Background, purpose and procedure for carrying out the expert appraisal

1.1 Presentation of the issue

The Regional Health Agency (agence régionale de santé, ARS) of Hauts-de-France informed the Directorate General for Health (DGS) of possible exposure to aluminium via the respiratory route in connection with the operation of an aluminium ingot smelter, located in a dense urban environment. A health risk assessment and/or environmental interpretation will have to be carried out by the site operator. In order to be able to interpret the results for health purposes, respiratory toxicological reference value (TRV) is required.

In this context, aluminium was included in the ANSES work program in July 2023, in order to propose short- and long-term respiratory TRVs. An internal TRV and an oral TRV have also been developed.

1.2 Purpose of the request

In the scope of the protocol of agreement between Anses, the Direction générale de la Prévention des risques (DGPR) and the DGS for the implementation of the scientific expertise work programme on TRVs established in December 2022, Anses has been requested to derive short and long-term respiratory TRV for aluminium and its inorganic compounds.

In addition, under the European Partnership for the Assessment of Risks from Chemicals (PARC), human biomonitoring guidance values (HBM-GVs) are derived for the general population and workers. These values are proposed for priority substances of interest, such as aluminium and its inorganic compounds. HBM-GVs are currently being proposed within PARC.

1.3 Organisation of the expert appraisal

Anses entrusted examination of this request to the Expert Committee on Health Reference Values (HRV Committee).

The Working Group on Biomarkers of Exposure (BME) was also mandated for the assessment of data on biological monitoring in order to assess the suitability of recommending one or more biomarkers and the elaboration of an internal TRV for the selected biomarker(s).

The methodological and scientific aspects of the expert appraisal work were regularly submitted to the HRV Committee.

The report produced takes into account the comments and additional information provided by the members of the HRV Committee.

This expert appraisal was therefore conducted by a group of experts with complementary skills. It was carried out in accordance with the French Standard NF X 50-110 “Quality in Expertise Activities”.

This collective expert appraisal work and its conclusions and recommendations were adopted by the HRV Committee on 7 November 2024.

1.4 Prevention of risks of conflicts of interest

ANSES analyses interests declared by the experts before they are appointed and throughout their work in order to prevent potential conflicts of interest in relation to the points addressed in expert appraisals.

The experts' declarations of interests are published on the website https://dpi.sante.gouv.fr/.

2 Method

Two types of toxicological reference values (TRVs) exist: external TRVs and internal TRVs.

- **External TRVs**

Anses defines an external TRV as a generic term encompassing all types of toxicological indices allowing to establish a relationship between a quantity or concentration of a chemical agent and an adverse effect (threshold effect) or between a quantity or concentration of a chemical agent and a probability of effect (non-threshold effect), on a population scale. By definition, they are constructed to protect the population as a whole, including sensitive populations (e.g., children, elderly people, etc.), from adverse effects induced by the chemical agent.

TRVs are specific to a chemical agent or a family of chemical agent, a route of exposure (oral, respiratory, dermal), and a duration of exposure (short, medium, or long term). Therefore, there are TRVs:

- "short-term" for exposures from one day to two weeks,
- "medium-term" for exposures greater than two weeks but less than one year,
- "long-term" for exposures of more than one year.

They can be used as part of quantitative health risk assessments carried out at population level only, in a given exposure context, and thus help in the choice of risk management measures. They can also be used to either draw up guide values, regulatory maximum levels in foodstuffs or to prioritize chemical agents, as these values often enable their toxicity to be assessed (Anses, to be released).

Depending on the corpus of data and knowledge available on the biological action mechanism(s) of the chemical agent of interest, two main types of long-term TRVs can be developed:

- TRVs "with a dose threshold" corresponding to an estimate of the maximum quantity or concentration of the chemical agent to which an individual or a population can theoretically be exposed without risk of adverse health effects over a specified duration and based on all available information at the time of its development. They are derived in the case of chemical agents causing, beyond a certain dose, effects whose severity increases with the absorbed dose;
- TRVs "without a dose threshold" derived in the case of chemical agents for which adverse effects can occur regardless of the received dose, the probability of adverse effects increasing with the dose. These mainly concern carcinogenic effects resulting from a direct genotoxic mechanism. TRVs "without a dose threshold" correspond either to the additional probability per unit dose of exposure to the chemical agent, to develop the critical effect for an individual or a population exposed during their entire life, or to concentrations/doses corresponding to a determined risk level (usually 10^{-4}, 10^{-5}, and 10^{-6}).

To derive TRVs, Anses relies on its TRV derivation guide (Anses, to be released). The development of TRVs follows a structured and demanding approach that involves collective evaluations by groups of specialists. The construction of TRVs differs according to the knowledge or assumptions formulated on the action mechanisms of the substances. At

present, the default assumption is to consider a monotonic relationship between exposure, or dose, and effect, or response. In the current knowledge and by default, it is generally considered that, for non-carcinogenic effects, toxicity is only expressed beyond a dose threshold (Anses, to be released).

In practice, the construction of an external TRV involves the following steps (Figure 1):

- identify the target organ(s) and the critical effect based on the toxicological profile;
- identify the construction hypothesis, with or without a dose threshold, depending on the substance's mode of action;
- carry out a critical analysis of each of the TRVs identified in order to identify whether one of them can be retained (choice). This analysis was carried out taking into account various analysis criteria described in the Anses methodological guide (Anses, to be released), such as transparency and argumentation, the various construction choices (choice of critical effect, key study and PoD, use of temporal and allometric adjustments, choice of uncertainty factors for dose-threshold effects or method of extrapolation to low doses for non-threshold TRVs) and the year in which the TRV was developed or revised. If no TRV was deemed relevant, the WG then set about constructing the TRV;
- choose one (or more) high-quality study/studies most relevant among epidemiological or toxicological studies to establish a dose-response relationship;
- define a starting point (PoD) in humans or animals based on this/these study/studies;
- make temporal and allometric adjustments if necessary;
- make a route-to-route extrapolation if necessary and possible (for example oral route to inhalation route or internal to inhalation route);
- for a threshold TRV, apply uncertainty factors (UFs) to this PoD to derive a TRV applicable to the entire population;
- for a TRV without a threshold, determine a slope and/or concentrations/doses associated with several risk levels;
- establish a level of confidence.

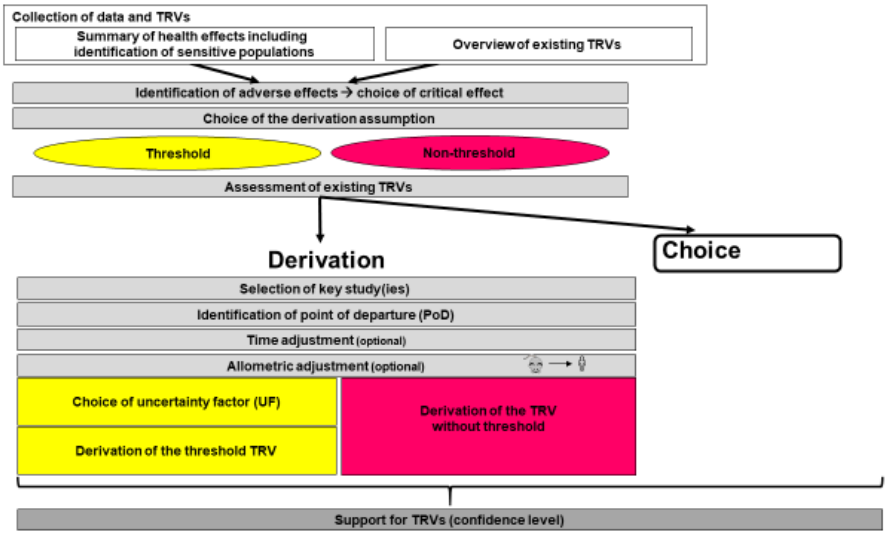


Figure 1. Steps for proposing a TRV (Anses to be published)

The HRV Committee assigns an overall confidence level to each external TRV, whether developed or selected. Five confidence levels are possible: high, medium-high, medium, medium-low or low. The overall confidence level of external TRVs is estimated using a tool established by Anses based on various criteria, as mentioned in the Anses methodological guide (Anses, to be released). This tool must be used blind by at least three assessors who were involved in the construction or selection of the TRV, or who have knowledge of the subject. The overall confidence level is set collegially on the basis of the confidence levels assigned by these 3 assessors and the associated arguments. Up to date, Anses does not assign confidence level for internal TRVs.

- **Internal TRVs and populational internal exposure levels**

The internal TRVs used for the health interpretation of biological monitoring of exposure to chemical agents at population level are called internal toxicological reference values.

Internal TRVs are used to interpret Biomarker of exposure (BME) concentrations as part of biological monitoring of exposure to chemical agents in the general population. They can be used as part of quantitative health risk assessments carried out at population level in a given exposure context, and thus help in the choice of risk management measures. Finally, they can also be used to prioritize substances, as these values are often used to assess their toxicity.

A BME to a chemical agent is a parameter (the parent substance, one of its metabolites, or the product bound to targets or non-critical sites), measured in a biological matrix and whose variation is associated with exposure to the agent and/or health effects. It is neither a biological indicator of early effect, nor an indicator of susceptibility/sensitivity.

To derive TRVs, Anses relies on its TRV derivation guide (Anses, to be released). Several approaches can be used to derive internal TRVs. They are described below (Figure 2) in order of priority according to data availability:

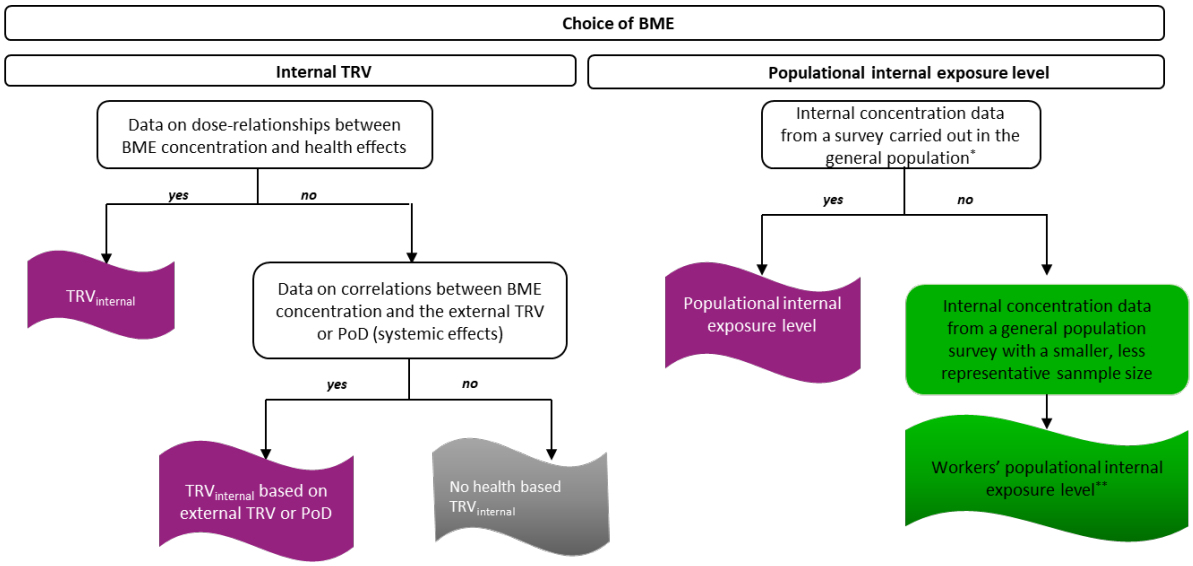
- derivation from data characterising the relationship between variations in concentration of the BME and health effects (threshold or non-threshold) in exposed populations;
- in the absence of data to identify a relationship with health effects, determination on the basis of an external TRV or a PoD, identified from one or more key studies. In this case, the BME concentration corresponding to an external TRV/PoD can be extrapolated from toxicokinetic parameters obtained from human or animal data using (depending on available data):
    - measurements of the association between an external exposure indicator (TRV or PoD) and the BME (regression equations),
    - toxicokinetic data (PBK[1] model or mass conservation approach).

Populational internal exposure levels (previously called biological reference values or BRVs) are proposed by the HRV committee for interpreting BME concentrations. The populational internal exposure levels make it possible to situate the concentrations of a BME measured in workers in relation to those observed for the same parameter in a general population of adults of working age. Populational internal exposure levels are based on the results of impregnation studies conducted in a sample representative of the general population or its sub-population

[1] Mathematical descriptions simulating the relationship between the level of external exposure and the concentration of a chemical agent in biological matrices over time. Kinetic models take into account the absorption, distribution, metabolism and elimination of the agent administered and its metabolites (WHO 2010).

of interest (Esteban, NHANES, Health Canada, etc.) or, failing that, in the case of workers' populational internal exposure levels, in a population with a smaller number of workers and/or not representative of the general population as a whole, without any specific source of exposure to the agent of interest. Workers' populational internal exposure levels should be used exclusively to monitor occupational exposure. As a general rule, a high percentile of the distribution of BME concentrations in the population of interest is selected as the populational internal exposure level, most often the 95th percentile (P95) or the upper limit of its 95% confidence interval, etc.). Populational internal exposure levels cannot be interpreted in terms of health risk.

Specific populational internal exposure levels can be assigned to certain sub-groups of the population, depending on the type of chemical agent, the effect and the factors influencing the results. It is thus possible to recommend values according to sex, age, smoking habits, etc.



* In the working population, the Populational internal exposure levels proposed by ANSES for interprating BME concentrations enable measured concenatrations of a BME in workers to be compared with those observed for the same parameter in the general population of working-age adults.
** Workers' populational internal exposure level are reserved exclusively for monitoring occupational exposure.

BME: biomarker of exposure ; PoD : point of departure ; TRV : toxicological reference value

Figure 2. Steps to derive an internal TRV and populational internal exposure level.

Before elaborating TRVs, a collection of data useful for characterizing the chemical agent is carried out (identification, physicochemical properties, classifications), as well as general information on uses, sources, and exposures.

A toxicological profile is also systematically prepared to define the effects from observations in humans and animals, related to different types of exposure to a chemical agent, characterized by their duration and route of exposure (oral, respiratory, dermal), as well as the mechanisms of action and sensitive populations. Any beneficial effects of chemical agents are not described in toxicological profiles.

According to the DGS' request, the synthesis of toxicity data by respiratory route for aluminium and its inorganic compounds was written based on synthesis reports provided by ATSDR (ATSDR 2008), EFSA (EFSA 2008), ACGIH (ACGIH 2008), JECFA (JECFA 2012), DFG (DFG 2013 and 2019) and SCCS (SCCS 2014, 2019, 2020, 2022 and 2023), supplemented by a literature review. This literature search was conducted using the PubMed and Scopus

databases between 2007 and July 2023 based on the following keywords: “aluminium”, “aluminium compound*”, “toxicity”, “toxicokinetic”, “health effect*”.

An inventory was made of existing internal, oral and inhalation TRVs published up to 2024 by the main health safety organizations recognized at supranational (WHO), European (EFSA) or national/regional level (US EPA, ATSDR, OEHHA, Health Canada, RIVM, etc.). Only TRVs published by a health agency and accompanied by a robust scientific argument written in English or French have been included in this inventory. Draft positions have also been described. Where several TRVs have been produced over time by a given organization, only the most recently published TRV has been taken into account.

3 Background information

3.1 Substance identification

Aluminium (Al) is a silver-coloured, low-density, malleable and ductile metal (INRS 2021). Ubiquitous, it is the metallic element which is the most widespread in the earth's crust with 8% Al (INERIS 2015), mainly as a silicate. There are many compounds of aluminium. A non-exhaustive list below presents the compounds mostly described in the literature (Table 1Table 1).

Table 1. General information on the mostly described aluminium compounds (INERIS 2005; 2015)

Name	CAS Number	EC Number	Physical state	Molecular weight [2] (g/mol)
Aluminium (Al)	7429-90-5	231-072-3	Solid	26.98
Aluminium carbonate ($Al_2(CO_3)_3$)	14455-29-9	238-440-2	White powder	233.99
Aluminium chloride ($AlCl_3$)	7446-70-0	231-208-1	Solid	133.34
Aluminium chloride, basic ($Al_2(OH)_nCl_{6-n}$)	1327-41-9	215-477-2	Aqueous solution	
Aluminium chlorohydrate / Aluminium chloride hydroxide ($Al_2Cl(OH)_5$)	[12042-91-0]	[234-933-1]	Crystallised solid when n=5	174.45
Aluminium citrate ($C_6H_5AlO_7$)	31142-56-0	250-484-4	White crystallised solid	216.08
Aluminium fluoride (AlF_3)	7784-18-1	232-051-1	Solid	83.98
Aluminium hydroxide (AlH_3O_3)	21645-51-2	244-492-7	Crystallised solid or amorphous powder	78.00
Aluminium lactate ($C_9H_{15}AlO_9$)	18917-91-4	242-670-9	White powder	294.19
Aluminium nitrate (AlN_3O_9)	13473-90-0	236-751-8	Crystallised solid	213.00
Aluminium oxide (Al_2O_3)	1344-28-1	215-691-6	Crystalline	101.96
Aluminium oxide hydroxide, Boehmite (AlOOH)	1318-23-6	215-284-3	Crystalline solid	59.99
Aluminium orthophosphate /	7784-30-7	232-056-9	Powder	121.95

[2] PubChem: https://pubchem.ncbi.nlm.nih.gov/

aluminium phosphate (AlO_4P)				
Aluminium silicate (Al_2SiO_5)	12141-46-7	235-253-8	Crystalline solid	162.05
Aluminium sodium dioxide (AlO_2Na)	1302-42-7	215-100-1	Solid	81.97
Aluminium sulphate ($Al_2O_{12}S_3$)	10043-01-3	233-135-0	Solid and Aqueous solution	342.2

3.2 Physico-chemical properties

Some aluminium salts, for example, aluminium sulphate, aluminium chloride (hydrated) and aluminium nitrate, are readily soluble in water, whereas other aluminium species such as elemental Al, aluminium oxide, aluminium phosphate, and aluminium silicate are very sparely soluble (Riihimäki and Aitio 2012). Actually, aluminium citrate is the most soluble and bioavailable aluminium salt (Poirier et al. 2011). The table below (Table 2) presents the solubility of the different aluminium salts in water and in other solvents.

Table 2. Solubility of Al salts in water and other solvents

Name of Al compound	Solubility in water	Solubility in other solvents
Aluminium (Al)	Insoluble in water at 20°C	Soluble in HCl, H_2SO_4, hot water, and alkalies
Aluminium carbonate ($Al_2(CO_3)_3$)	Insoluble	Dissolves in hot HCl or H_2SO_4
Aluminium chloride ($AlCl_3$)	450-458 $g.L^{-1}$ at 20 °C	Soluble in benzene, carbon tetrachloride, chloroform
Aluminium chlorohydrate ($Al_2Cl(OH)_5$)	Dissolves in water forming slightly turbid colloidal solutions (up to 550 $g.L^{-1}$)	No data
Aluminium citrate ($C_6H_5AlO_7$)	Most soluble	No data
Aluminium fluoride (AlF_3)	5.59 $g.L^{-1}$ at 25 °C	Sparingly soluble in acids and alkalies; insoluble in alcohol and acetone
Aluminium hydroxide ($Al(OH)_3$)	Insoluble in water at 20°C	Soluble in alkaline or acid solutions
Aluminium lactate ($C_9H_{15}AlO_9$)	Freely soluble in water: 206 $g.L^{-1}$ at 25 °C	No data
Aluminium nitrate (AlN_3O_9)	Very soluble in water: 637 $g.L^{-1}$ at 25 °C	Very soluble in alcohol; very slightly soluble in acetone; almost insoluble in ethyl acetate, pyridine

Aluminium oxide (Al_2O_3)	Cold water, 0.000098 $g.L^{-1}$; insoluble in hot water	Very slightly soluble in acids, alkalies
Aluminium oxide hydroxide (AlO(OH))	No data	No data
Aluminium phosphate (AlO_4P)	Practically insoluble in water	Practically insoluble in acetic acid; very slightly soluble in concentrated HCl and HNO_3 acids
Aluminium silicate (Al_2SiO_5)	Insoluble in water	Insoluble in organic solvents
Aluminium sodium dioxide (AlO_2Na)	No data	No data
Aluminium sulphate ($Al_2O_{12}S_3$)	Soluble in water: 360 - 364 $g.L^{-1}$ at 20 °C	Insoluble in ethanol

Data from: Krewski et al. 2007; ATSDR 2008; Poirier et al. 2011; INRS 2021

As mentioned in the above table, elemental aluminium is insoluble in water. At acidic pH, below 4, the dominant speciation of aluminium corresponds to its only oxidation state Al^{3+}, generally in the form of the hydrated complex $Al(H_2O)_6^{3+}$. At a pH between 5 and 6, the species $Al_2(OH)_2^{4+}$ and $Al(OH)_5^{2-}$ dominate. The insoluble form $Al(OH)_3$ is predominant in the pH range between 5.2 and 8.8. Above a pH of 9, the soluble species $Al(OH)_4^-$ is dominant. It is the only species present at pH above 10. Because of the behaviour of its hydroxycomplexes, aluminium is considered amphoteric (INERIS 2005).

3.3 Classification

Elemental aluminium and some of its compounds are subject to harmonised classification under regulation (EC) n°1272/2008 (i.e. CLP regulation). Among the aluminium compounds included in the scope of research (Table 1), an harmonised classification is provided only for aluminium powder (pyrophoric and stabilized) and for anhydrous aluminium chloride (Table 3).

Table 3. Harmonised classification according to Annex VI of the EU Regulation (EC) n°1272/2008[3]

Name	Classification		Labelling	
	Hazard Class & Category code(s)	Hazard statement code(s)	Pictogram, Signal Word code(s)	Hazard statement code(s)
Aluminium powder (Pyrophoric)	Flam. Sol. 1 Water-react. 2	H250 [1] H261 [2]	 Flame GHS02 Dgr	H250 [1] H261 [2]
Aluminium powder (stabilised)	Flam. Sol. 1 Water-react. 2	H228 [3] H261 [2]	 Flame GHS02 Dgr	H261 [2] H228 [3]
Aluminium chloride, anhydrous	Skin Corr. 1B	H314 [4]	 Corrosion GHS05 Dgr	H314 [4]

[1] H250: catches fire spontaneously if exposed to air; [2] H261: in contact with water releases flammable gas; [3] H228: flammable solid; [4] H314: causes severe skin burns and eye damage

According to the International agency for research on cancer (IARC), there is sufficient evidence in humans for the carcinogenicity of aluminium production using the Söderberg process. This activity is associated with elevated incidences of cancers of bladder and lung. The cancer hazards associated with aluminium production mainly result from exposure to polycyclic aromatic hydrocarbons (PAHs) rather than from exposure to aluminium or its related compounds (INRS 2021). Samples of air emitted from aluminium smelters are mutagenic in bacteria; however, mutagenicity studies based on urine from exposed workers, as well as DNA-adducts studies of blood samples from these workers, gave equivocal results. There is sufficient evidence in experimental animals for the carcinogenicity of airborne particulate polynuclear organic matter from aluminium-production plants. Globally, based on both experimental and human studies, there is weak-to-moderate evidence for a genotoxic mechanism underlying the effects of occupational exposures during aluminium production. IARC concluded that occupational exposures during aluminium production are carcinogenic to humans (Group 1) (IARC 2012).

3.4 Sources and major uses

Aluminium production

In 2022, world aluminium production was 69 000 000 tons, the main producers being China (40 000 000 tons), India (4 000 000 tons), Russia (3 700 000 tons), Canada (3 000 000 tons) and the United Arab Emirates (2 700 000 tons) (USGC 2023[4]). Aluminium domestic annual

[3] https://echa.europa.eu/information-on-chemicals/cl-inventory-database (accessed 21 April 2023)
[4] https://pubs.usgs.gov/periodicals/mcs2023/mcs2023-aluminum.pdf (accessed on May 2023)

production and consumption in France are around 600 000 to 700 000 tons and 1 200 000 to 1 300 000 tons, respectively[5].

First fusion aluminium metal is mainly obtained from bauxite or bauxitic laterite. Bauxite is mainly constituted of hydrated alumina, iron oxide (10-20%) and silica (about 5%). Alumina is extracted from bauxite, then transformed into primary aluminium which is refined to the desired degree of purity.

Since the end of the 19th century, the main industrial manufacturing process of aluminium has been electrolysis of alumina dissolved in a molten cryolite (Na_3AlF_6)-based hot bath (also known as the Hall-Héroult process). Alumina in its cryolite bath is introduced into a rectangular steel cell, whose carbon-coated inner walls form the cathode. A direct electric current between 100,000 and 320,000 amperes flows between the anode (either pre-baked or continuously self-baking Söderberg anode) and the cathode in a bath composed of cryolite and alumina. The electric current allows the alumina to react in contact with the carbon anode and to be transformed into aluminium and carbon dioxide which will concentrate at the top of the cell. The aluminium obtained by this method is 99.5% pure. The electrolytic cells are called pots, and the work area is called the potroom. To obtain purer aluminium, it is refined. There are two refining techniques: molten salt electrolysis and fractional crystallisation. These two methods lead to aluminium that is at least 99.99% pure. Casting is the final step in the process where molten aluminium is poured into ingots in the foundry (Health Council of the Netherlands 2010; IARC 2012; INERIS 2015).

The nature and level of contaminants and other agents in the potroom may be influenced by the type of pot (prebake or Söderberg) and design (vertical- or horizontal-stud Söderberg), hooding and hood exhaust rate, building ventilation, size of operation and, electrical current used (cell amperage) (IARC 1984). Actually, pre-baked anodes are produced by moulding petroleum coke and coal-tar pitch binder, which are baked at 1000-1200°C. Söderberg anodes are formed continuously from a paste of petroleum coke and coal-tar pitch. Consequently, both anodes constitute a source of exposure to carcinogenic PAHs. PAHs are formed from partial anode pyrolysis during electrolysis. In a study conducted by Konstantinov and Kuz'minykh (1971), the concentrations of benzo(a)pyrene in the prebake potrooms were found to be lower than in the Söderberg potrooms and, when pre-burned electrodes (presumably prebake) were used, benzo(a)pyrene concentrations were below the level of detection (IARC 1984).

Potential exposures to chemicals other than PAHs and aluminium reported in these occupational settings include fluorides and sulphur dioxide (skin and respiratory irritants), carbon monoxide, carbon dioxide, various trace metals (chromium, nickel, vanadium), asbestos, and also extreme heat and magnetic fields. Exposure to PAH, fluorides and sulphur dioxide have progressively decreased over time (the late 1950s and the late 1980s), as demonstrated by atmospheric measurements and biomonitoring studies. This decrease can be explained by the progressive implementation of improved control technology; the increasing use of both collective and personal protective devices, and the increasing predominance of prebake pot-rooms (IARC 2012).

Coupled atmospheric and biomonitoring studies also demonstrate that inhalation is not the only and generally not the main route of exposure to PAH, aluminium and fluorides in the potroom, and that dermal exposure and ingestion should be taken into account.

Aluminium can be recycled multiple times without losing its original properties (lightness, conductivity, formability, durability, impermeability and multiple recyclability). Actually,

[5] https://www.latribune.fr/entreprises-finance/industrie/industrie-lourde/souverainete-industrielle-et-energetique-le-cas-exemplaire-de-l-aluminium-francais-928225.html#:~:text=La%20production%20nationale%20actuelle%20tourne,importer%20100%25%20de%20ses%20besoins (accessed on May 2023).

aluminium recycled from old and new scraps is equivalent to about 50% of both aluminium production and consumption. It is estimated that 75% of the aluminium produced since 1880 is still in use today. In Europe, recycling rates are over 90% in the automotive and building sectors, and 75% for aluminium cans. The aluminium recycling process requires only 5% of the energy needed to produce the primary metal[6,7].

Aluminium recycling involves 5 steps[8]:

1. Collecting scrap: there are 2 categories of aluminium scrap:
   - new scrap – material that arises during the manufacture and fabrication of aluminium products, up to the point where they are sold to the final consumer;
   - old scrap – material that has been used by the consumer and subsequently discarded (e.g.: used beverage cans, window frames, electrical cabling and car cylinder heads);
2. Sorting scrap – grouping all coated aluminium together and grouping all uncoated aluminium together. Paper, plastic and other non-aluminium recycling needs to be removed;
3. Crushing – by compacting the aluminium scrap, it reduces freight, storage and handling costs;
4. Remelting – uncoated scrap is loaded directly into a large furnace, where it is heated at high temperatures and turned into molten form;
5. Casting – molten aluminium is cast at a temperature of just over 700°C to form ingots.

Employees who process aluminium scrap might be exposed to high levels of aluminium dust during pre-processing steps that involve crushing and/or shredding and drying[9]. Thus, aluminium recycling does not involve the use of the Söderberg electrolytic refining process and therefore do not induce co-exposure to carcinogenic PAHs.

Aluminium uses

Aluminium metal and its compounds have many industrial applications (INRS 2021).
In the USA, in 2022, transportation applications (automobile, railway wagons and aircraft parts, signalling panels), accounted for 35% of domestic consumption; in descending order of consumption, the remainder was used in packaging (containers and foils), 23%; building, 16%; electrical, 10%; machinery, 7%; consumer durables, 6%; and other, 3% (U.S. Geological Survey, Mineral Commodity Summaries, January 2023)[10].
The table below (Table 4) presents the different, non-exhaustive, applications of the Al compounds (INERIS 2005; 2015; Krewski et al. 2007; INRS 2021) and their production in the European Union (ECHA REACH)[11].

[6] https://www.aluminium.fr/cycle-de-vie-et-recyclage/ (accessed on June 1, 2023)
[7] https://european-aluminium.eu/blog/enabling-the-circular-economy-with-aluminium/ (accessed on June 1, 2023)
[8] https://aluminium.org.au/how-aluminium-is-made/recycling-aluminium-chart/ (accessed on 1 June 2023)
[9] https://www.osha.gov/sites/default/files/publications/OSHA3348-metal-scrap-recycling.pdf (accessed on July 2023)
[10] https://pubs.usgs.gov/periodicals/mcs2021/mcs2021-aluminum.pdf (accessed on April 2023)
[11] Tonnage: Manufactured in and / or imported to the European Economic Area from: https://echa.europa.eu/fr/information-on-chemicals (accessed on April 2023)

Table 4. Summary of aluminium uses

Name of Al compound	Tonnage (tons per annum)	Industrial uses	Uses in pharmaceuticals, food additives, cosmetics and other household products
Aluminium	≥ 10 000 000	Metal and alloys: building and vehicles metal parts; pipes; foils;—powder for propellant and pyrotechnics manufacturing). Used in various sectors: aerial electric cables, doors and windows, automobile and aircraft parts, shipbuilding and railways, signaling panels, kitchen utensils paints, explosives and fireworks.	Aluminium foil; colour ingredient; topical drugs, food packaging
Aluminium carbonate	No data		Antacid; phosphate binder
Aluminium chloride	≥ 10 000 to < 100 000	Acid catalyst; as a hydrophobic agent for cotton impregnation, leather tanning, retention agent in paper production; flocculent and clarifying agent in water treatment	Antiperspirant
Aluminium chloride, basic	≥ 100 000 to < 1 000 000		
Aluminium chlorohydrate	≥ 10 000 to < 100 000		Antiperspirant; Astringent; anti-hyperphosphatemic
Aluminium citrate	No data		Antiperspirant
Aluminium fluoride	≥ 100 000 to < 1 000 000	In ceramics; metallurgical flux; inhibitor of fermentation; catalyst; temperature and pH regulator in aluminium production processes; optical coatings and semiconductors	
Aluminium hydroxide	≥ 1 000 000 to < 10 000 000	Adsorbent; emulsifier; dyeing mordant; manufacture of glass; lubricants; detergents; waterproofing fabrics; flame retardant	Antacid; antidiarrheal agents; food colouring agent; topical drugs: diaper rash, antifungal; food packaging

			ingredient; vaccine adjuvant; opacifying agent in cosmetics and personal care products (e.g.: toothpastes)
Aluminium lactate	≥ 1 000 to < 10 000	Fire extinguishing foam	Antiseptic; in dental impression material
Aluminium nitrate	≥ 1 000 to < 10 000	Tanning agent (for leather); corrosion inhibitor; nitrating agent; extraction of uranium	Antiperspirant
Aluminium oxide	≥ 10 000 000	Adsorbent; abrasive; in lubricants; water-proofing agent	
Aluminium oxide hydroxide	≥ 10 000 to < 100 000		
Aluminium phosphate	≥ 1 000	Cement component; ceramic flux	Antacid; vaccine adjuvant; dental cement
Aluminium silicate	No data	In glass; ceramics; semiprecious stones; enamels; paint fillers	Dental cement; food packaging ingredient
Aluminium sodium dioxide	≥ 100 000 to < 1 000 000	Water treatment, solidification of the concrete, in the paper industry to increase the opacity, fibre retention and strength of the paper	
Aluminium sulphate	≥ 100 000	Tanning agent (leather); dyeing mordant; fire / waterproofing agent; decolorizing and clarifying agent; flocculating agent in the water purification	Antiperspirant; topical diaper; anti-fungal agent; food additive (in baking powder)

4 Toxicological profile

Treatment doses given in mg.kg $bw^{-1}.d^{-1}$ as reported by ATSDR (ATSDR 2008) had been reassessed using the molar mass ratio of aluminium and aluminium compounds (see Table 1).

4.1 Toxicokinetics

4.1.1 Absorption

The bioavailability of aluminium is dependent on the nature and speciation of the aluminium substance. The main mechanism of absorption is probably passive diffusion through paracellular pathways (ATSDR 2008). Results from *in vivo* uptake and *in vitro* dissolution studies show that metallic Al, Al_2O_3, and $Al(OH)_3$ are less bioavailable via the oral and inhalation routes compared to water-soluble aluminium forms like alum ($Al_2(SO_4)_3$). Under normal physiological conditions, exposures to insoluble aluminium forms do not contribute significantly to total aluminium body burden (Willhite et al. 2021).

4.1.1.1 Absorption by inhalation

Absorption mechanism

The percentage of aluminium absorbed after inhalation is depending on the inhaled compounds (especially, their solubility) and on the granulometry of the aerosol. Insoluble and/or large particles and those not absorbed, are eliminated from the respiratory tract by macrophage entrapment and mainly via mucociliary clearance (and subsequent expectoration or ingestion). Only particles with an aerodynamic diameter under 5 µm can reach alveoli where the soluble aluminium can be absorbed (ATSDR 2008; Klotz et al. 2019).

Human data

In humans, inhalation of aluminium or aluminium compounds is mostly related to occupational exposure. Many studies conducted in the workplace report exposure to aluminium from different sources (fumes, dust). Exposure of the general population essentially occurs through ingestion, including ingestion of indoor or outdoor dust. Possible sources of consumer respiratory exposure are aerosols from antiperspirants or other sprays (ATSDR 2008; SCCS 2020).

In alveoli, aluminium bioavailability increases with the solubility of the inhaled substances with aluminium salts being the more soluble. Studies in workers suggest a mean absorption rate of 1.5-3% of inhaled aluminium (Yokel and McNamara 2001; ATSDR 2008; SCCS 2020).

In a cross-sectional study, pre- and post-shift aluminium serum and urinary levels were measured in 235 workers from 15 different plants employed in areas with potential exposure to aluminium dust, and 44 unexposed workers. In this study, for exposed workers, median aluminium values were 25 and 100 µg m^{-3} for respirable and total particulates in air, respectively. Significant differences were found between exposed and controls for pre-shift serum aluminium only (4.92 $\mu g.L^{-1}$ vs 3.60 $\mu g.L^{-1}$ for exposed workers and controls respectively) and for both pre-shift and post-shift urinary aluminium (pre-shift: 17.11 $\mu g.L^{-1}$ for

workers vs 7.39 µg.L^{-1} for unexposed controls; post-shift: 20.08 µg.L^{-1} for workers vs 7.67 µg.L^{-1} for unexposed controls) and urine aluminium/creatinine ratios (pre-shift: 12.06 µg.g^{-1} vs 6.39 µg.g^{-1} for workers and controls, respectively; post-shift: 13.74 µg.g^{-1} vs 5.73 µg.g^{-1} for workers and controls, respectively) (Gitelman et al. 1995).

In another study, after an 8 hour exposure to 0.3-10.2 mg.m^{-3} (mean: 2.4 mg.m^{-3}) aluminium in welding fumes, 3 volunteers (not previously exposed) had urinary aluminium concentrations of 15-414 µg.L^{-1} at the end of shift against less than 3 µg.L^{-1} before exposure (Sjögren et al. 1985).

Animal data

ATSDR reported studies showing that aluminium is retained in the lung after exposure to inhalable aluminium oxide (Christie, Mackay, and Fisher 1963; Thomson et al. 1986) and aluminium chlorohydrate (Steinhagen, Cavender, and Cockrell 1978; Stone et al. 1979). There was no significant increase in aluminium levels in tissues other than the lungs or serum (Steinhagen, Cavender, and Cockrell 1978; Stone et al. 1979) (ATSDR 2008).

Results of experimental studies on intranasal aluminium-containing compounds, in either solution or in particulate form, on the absorption through the olfactory pathway in rats, show a low olfactory nerve uptake and subsequent neuronal distribution to the cortex of instilled soluble aluminium compounds. Concerning nanoparticular aluminium, there are very few studies and the results are controversial, with one study showing some transfer (aluminium nanoparticles) (Kwon et al. 2013) when another did not (nanometric aluminium oxide) (Chalansonnet et al. 2018).

4.1.1.2 Absorption by oral route

Absorption mechanism

Aluminium is poorly absorbed after oral intake. This oral absorption depends on several factors, including the concerned aluminium species, its solubility, and the presence of complexing ligands or competing ions (Affourtit, Bakker, and Pronk 2020). Actually, the bioavailability appears to be generally associated with water solubility; however, there is insufficient data to directly extrapolate from solubility in water to bioavailability (ATSDR 2008). Aluminium's gastrointestinal absorption from aluminium compounds highly depends on its ionic availability in the gut content, which is mainly linked to the prevailing pH, the present complexing ligands which the metal may form absorbable aluminium species with and also the ingested aluminium compound's chemical form. Acid digestion in the stomach is thought to degrade most of the ingested aluminium compounds to generate "free" and soluble Al^{3+}, some of which might be complexed with mono-, di- and tricarboxylic acids like citric acid. The increase in pH during the transition from the stomach to the intestines, leads to successive deprotonations and the formation of complexes of aluminium with hydroxide ion and ultimately, the formation of insoluble aluminium hydroxide at neutral pH. Consequently, when the pH is neutralised in the duodenum, the aluminium ion is progressively converted to aluminium hydroxide and the majority of it is then expected to precipitate in the intestine, with subsequent excretion in the faeces, leaving only a minor fraction available for absorption (EFSA 2011). The large hydration of the Al^{3+} ion can allow it to cross the intestinal epithelium paracellularly, which is probably the main mechanism of absorption. A neutralisation by complexation (e.g. by the anion of the ingested salt), can facilitate the diffusion of the metal through the intestinal membrane. This absorption is therefore generally perceived as a biphasic process involving a fast mucosal uptake, followed by slow transport of aluminium into the blood. On the other hand, a transferrin/vitamin D-dependent active transport is also involved where aluminium shares absorption pathways with other mineral cations (e.g. Mg^{2+}, Fe^{2+}); this hypothesis is

incompletely elucidated and complicated by the differences in oxidation states between aluminium and iron ions (Berthon 2002; ATSDR 2008).

Human data

Studies conducted on this topic showed that aluminium present in food and drinking water is poorly absorbed through the gastrointestinal tract.

Based on daily aluminium dietary consumption and urinary daily excretion, the oral global bioavailability of aluminium from the diet has been estimated to be 0.1-0.3 % (Yokel and McNamara 2001; ATSDR 2008; EFSA 2008). Absorption of aluminium from drinking water is estimated to be around 0.3 % (Yokel and McNamara 2001).

Stauber et al., 1999 estimated, on 29 healthy volunteers, the relative bioavailability of aluminium species naturally present in food and in aluminium-treated drinking water (ATW) (aluminium compound not specified) (ATW ;140±9 µg.L^{-1} of Al). Volunteers drank ATW, during two-day periods, while on a controlled diet. Volunteers' average total intake of aluminium from food and tea contributed about 3,000 µg AL.d^{-1}. Aluminium from ATW contributed to 208 µg.d^{-1} Al. Only 0.3–0.4% of the aluminium in ATW was absorbed in the digestive tract, a percentage close to that absorbed from food (Stauber et al. 1999). Several studies indicated that simultaneous consumption of citric acid or citrates increases aluminium intestinal absorption. However, though higher than the absorption of most other aluminium compounds, intestinal absorption of aluminium citrate is still low (0.5-5%). In fact, aluminium absorption is probably indirectly facilitated by citrate through binding the Ca^{2+} ions that line the lateral membranes of the intestinal cells and thus, widening the loose junctions between them (Desroches, Daydé, and Berthon 2000). Other carboxylic acids, such as lactic acid or ascorbic acid also enhance aluminium absorption in the digestive tract (ATSDR 2008). Citric acid and other carboxylic acids have the potential to form neutral and more soluble species, making aluminium more available for active-transport pathways (DeVoto and Yokel 1994). On the conversely, some complexing agents (e.g., phosphates or silicates) form insoluble compounds with aluminium, limiting its uptake (DeVoto and Yokel 1994; EFSA 2008; ATSDR 2008).

For oral exposure, there is limited information on the bioavailability of aluminium from sources other than diet and water:

Aluminium in soils being mainly constituted of insoluble species (silicates, oxides, and hydroxides), its bioavailability is expected to be low; this is confirmed by the available studies showing a low oral bioaccessibility[12] of aluminium from soils (median 1.1%; upper limit of the confidence interval of the 95th percentile: 2 %) (Kierulf et al. 2022).

The bioavailability of aluminium hydroxide from antacids is also very low. It was estimated to be 0.004% in volunteers with normal renal function (increasing to 0.2% with concomitant citric acid absorption) (Weberg and Berstad 1986).

Animal data

Several animal studies used [^{26}Al]-aluminium (compound not specified) to estimate aluminium bioavailability from drinking water. In the study by Jouhanneau et al., (compound not specified), when aluminium levels in urine, bone, liver, and brain were considered, an absorption rate of 0.1% was estimated in rats (Jouhanneau et al. 1997). Absorption of soluble salts (citrate, nitrate, sulphate) in the rat was 0.05%-0.2% compared to 0.02%-0.1% for insoluble

[12] Bioaccessibility is defined as the fraction of a compound which can be solubilised in the digestive tract. Bioavailability is the fraction of the ingested substance which can be absorbed in the digestive tract, then distributed in the body. For inorganic compounds, bioaccessibility can be considered as a proxy of their bioavailability.

compounds (oxide, hydroxide, sodium aluminium silicate) (Priest, Skybakmoen, and Jackson 2021). In the same species, oral absorption was greater for aluminium oxide nanoparticles than for aluminium chloride (a soluble salt); absorption of elemental aluminium nanoparticles was lower but still higher than $AlCl_3$ absorption (Krause et al. 2020). In rats, the bioavailability of aluminium from tea infusion of ^{26}Al citrate injected tea leaves was estimated to be 0.37 % (Yokel and Florence 2008) and it was 0.1%-0.3% for aluminium from basic aluminium sodium phosphate (a food additive) in biscuit or cheese (Yokel and Florence 2006; 2008). As in humans, numerous studies in animals have shown that the addition of citric acid or lactic acid enhances aluminium absorption through the digestive tract (ATSDR 2008). In a study conducted by Cunat et al., where an *ex vivo* rat gut was used to evaluate the potential of aluminium absorption from different chemical aluminium species, aluminium absorption was positively correlated with the theoretic affinity of aluminium and the anion. The absorption of aluminium after ingestion of organic aluminium compounds was more important than after ingestion of inorganic aluminium compounds, with the following order: aluminium citrate > aluminium tartrate, aluminium gluconate, aluminium lactate > aluminium glutamate, aluminium chloride, aluminium sulphate, aluminium nitrate (Cunat et al. 2000).

4.1.1.3 Absorption by dermal route

Human data

Skin application of personal care and cleaning products appears as one of the main sources of external exposure to aluminium for the general population. In most of the aluminium-containing cosmetics, insoluble species are concerned. Antiperspirants are a notable exception, as they contain soluble aluminium salts (e.g., aluminium chlorohydrate) and their pH is generally low, increasing the bioaccessibility of aluminium. However, when applied to skin, aluminium compounds form inert complexes with basic components of sweat and skin, limiting the bioaccessibility of the element (SCCS 2014). No data were identified regarding dermal exposure of workers in aluminium industries.

Human data on aluminium dermal absorption are limited. Older studies indicate a large range of absorbed fraction values ranging from 0.012% to 10% (SCCS 2014). However, these studies were conducted with a low number of volunteers (1 or 2) or *in vitro*, with skin preparations, and their results should be considered with caution.

A study in 12 volunteers using several exposure scenarios was recently published. It concluded that the aluminium fraction absorbed dermally from antiperspirants was 0.002% to 0.06 % (mean: 0.0094%, standard deviation: 0.0131) (de Ligt et al. 2018). SCCS estimated that this study also suffered from several methodological flaws (gaps in the mass-balance of ^{26}Al and lack of information on how the missing amounts could be accounted for). SCCS asked the cosmetic industry a new study, which was finally performed by the Netherlands organisation for applied scientific research (TNO) and is presented in the SCCS 2020 report (SCCS 2020). This last study with 6 female volunteers showed a mean dermal fraction absorbed of 0.00052 % (min-max: 0.00026%-0.00108%) from a topical application of roll-on formulation, containing aluminium chlorohydrate labelled with [^{26}Al]-aluminium (0.75 g antiperspirant per axilla (total of 1.5 g), ~2,500Bq, nominal dose of ^{26}Al of 3730317 pg). The volunteers were biomonitored for 11 days by measuring the presence of ^{26}Al in urine and faeces (de Ligt et al. 2022; SCCS 2020). At the same time, they were biomonitored by taking regular blood samples for up to 7 days. Combined with the aluminium found in the faeces in the same study (0.0014%), this would yield an overall percentage of bioavailable aluminium of 0.00192%. However, De Ligt et al. (2022) argued not to include this additionally recovered test material from faeces. SCCS (2020) agreed to this arguing that no paired faecal samples were collected following intravenous (IV) dosing for relative comparison. Thus, the mean dermal

fraction absorbed value of 0.00052% was regarded by SCCS as an appropriate value to use in risk assessment (SCCS 2020).

Fourteen-day use of aluminium-based antiperspirants did not increase plasma or urine aluminium levels in 21 volunteers (Letzel et al. 2020). In this study, shaving habits did not impact the systemic aluminium load.

Animal data

In mice daily percutaneously exposed to 0.1 or 0.4 µg of aluminium chloride for 130 days (i.e. 0.02 - 0.08 µg $Al.d^{-1}$), Anane et al., reported a significant increase in aluminium levels in urine, serum and brain. This study shows that aluminium was absorbed through the skin of mice. In fact, the concentration of aluminium in serum was 317.5 $\mu g.L^{-1}$ (SEM ±63.7) and 380.0 $\mu g.L^{-1}$ (SEM ±84.6) when mice were exposed to 0.02 and 0.08 µg $Al.d^{-1}$ respectively (versus 125.0-227.5 $\mu g.L^{-1}$ in the control group). It is noteworthy that, in this study, no measures were taken to prevent animal from licking their fur, and thus, ingesting aluminium (Anane et al. 1995).

4.1.2 Distribution

Once in the body, aluminium ion binds to blood proteins and is distributed to all tissues, especially the bones and lung (Ganrot 1986).

Aluminium erythrocyte/plasma partition ratio varies from one publication to another with values between 0.1 and 0.9 (Riihimäki and Aitio 2012). Around 95% of plasma aluminium is protein-associated, with 80% bound to transferrin at the sites left vacant by iron, 10% bound to albumin, and 5% bound to a low molecular weight protein fraction (Priest 2004). It was demonstrated that aluminium, bound to low molecular weight proteins (LMW–Al), present in spiked human serum of eight healthy volunteers, corresponded to Al-citrate, Al-phosphate and ternary Al-citrate–phosphate complexes (Polak et al. 2001).

It should be emphasized that cellular uptake of aluminium by organs and tissues most likely occurs from the aluminium bound to transferrin. Thus, it is likely that the relative high density of transferrin receptors in different organs influences the distribution of aluminium to organs, with higher aluminium levels present in regions of high transferrin receptor density (ATSDR 2008).

Total aluminium body burden is usually 30-50 mg in hlealthy adults. In the general population, serum aluminium level is usually 1-3 $\mu g.L^{-1}$ and exceptionally above 10 $\mu g.L^{-1}$. Half of the total body burden is in the skeleton and about one fourth in the lung (ATSDR 2008).

Aluminium levels in bone tissue of healthy individuals range from 5 to 10 $mg.kg^{-1}$. They are around 20 $mg.kg^{-1}$ wet weight in lungs of adults; lung aluminium concentration can be higher in workers after prolonged exposure to aluminium-containing respirable particles, especially when the aluminium species in particles have a low solubility (Ganrot 1986; ATSDR 2008). According to ATSDR, an increase of aluminium concentration with age in lung tissue is due to an accumulation of insoluble aluminium compounds that have entered the body via the airways (Ganrot 1986; ATSDR 2008). Ganrot (1986), have also reported data showing aluminium concentration increasing with age in lung, liver, kidney, bone and brain tissues.

The aluminium concentration levels typically reported in the human brain ranges from 0.25 to 0.75 $mg.kg^{-1}$, with grey matter containing about twice the concentration found in white matter (ATSDR 2008). Increased brain aluminium level is observed in patients with dialysis encephalopathy. Studies in Alzheimer's disease patients inconsistently showed elevated brain aluminium levels (Krewski et al. 2007). It has been suggested that the aluminium flux through the blood-brain barrier results from transferrin receptor-mediated endocytosis of transferrin-

bound aluminium and of transferrin-independent mechanisms involving aluminium citrate. Actually, a study by Yokel et al., showed that the transport of Al citrate across the blood–brain barrier is carrier-mediated, involving either an uncharacterized monocarboxylate transporter (MCT) isoform expressed in the brain such as MCT7 or MCT8 and/or one of the many members of the organic anion transporting protein family, some of which are known to be expressed at the blood–brain barrier (Yokel et al. 2002).

Aluminium is also present in human skin, lower gastrointestinal tract, parathyroid glands; low aluminium concentrations were measured in most soft tissue organs, other than lungs. Aluminium is also able to cross the placental barrier and to accumulate in foetal tissue (ATSDR 2008).

Distribution following intramuscular injection (case of vaccine):

Aluminium compounds are commonly used as adjuvant in vaccines making the intramuscular route a pathway of exposure to aluminium in the general population. Once injected in tissues, aluminium-containing adjuvants form an extracellular depot; then, they are slowly solubilised (by citrate ions) and can enter blood (Affourtit, Bakker, and Pronk 2020).

A study conducted in 12 preterm infants (mean gestational age: 27.1 weeks, mean weight at birth: 1021 g, mean weight at vaccination: 2254 g) did not show a significant change in serum and urine aluminium levels 24 hours after the routine 2-month vaccination, with vaccines containing a total of 1200 µg of aluminium (Movsas et al. 2013). The administered vaccines were Prevenar 13 (containing aluminium phosphate), PedvaxHIB (containing aluminium hydroxyphosphate sulphate) and Pediarix (containing aluminium hydroxide and aluminium phosphate). This shows that serum aluminium does not significantly increase following vaccination.

However, in animals, after intramuscular administration of ^{26}Al hydroxide or ^{26}Al phosphate vaccine adjuvants in rabbits, increased levels of ^{26}Al were found in the kidney, spleen, liver, heart, lymph nodes, and brain (in decreasing order of aluminium concentration) (Flarend et al. 1997). In this study, aluminium from intramuscular deposits of both solutions appeared in blood as early as 1 hour after injection. The area under the curve showed that during the first 28 days after exposure, three times as much aluminium diffused from the aluminium phosphate deposits than from the aluminium hydroxide deposits; the terminal phase of the blood concentration curve was not reached by that time.

In a study conducted in rats, very low aluminium levels were found in brain after aluminium phosphate or aluminium hydroxide adjuvanted vaccines (adjuvant group means 0.14–0.29 µg.g^{-1} ww; control 0.13 ±0.04 µg.g^{-1} ww), and the authors concluded that the diffusion of aluminium from vaccine deposits to the brain, if there is any, is marginal. In this study, aluminium from both aluminium phosphate and aluminium hydroxide adjuvants and adjuvanted vaccines increased aluminium levels mainly in bone (5-12% of the administered dose). The release from injected muscle was faster for aluminium phosphate than for aluminium hydroxide: 85.5% vs 22.3%, over 80 days. Different rates of absorption were noted, with markedly higher systemic availability from aluminium phosphate than from aluminium hydroxide-adjuvanted vaccines (Weisser et al. 2019).

Other studies conducted in mice have shown that after intramuscular injection, aluminium particles (administered as oxyhydroxide or hydroxide nanodiamants) were slowly translocated to draining lymph nodes, then to blood, spleen, and liver (Khan et al. 2013; Eidi et al. 2015). Crépeaux et al. in a study conducted in mice, showed that the translocation from muscular deposits to lymph nodes and spleen was very slow, the highest number of particles being observed in these tissues at day 270; in this last study, no translocation of aluminium to brain was observed (Crépeaux et al. 2015).

4.1.3 Metabolism

Aluminium does not undergo metabolism but can be transformed from one species to another. In living organisms, aluminium is thought to exist in four different forms: Al-ions (free and weakly or more strongly bound in salts), as low-molecular-weight complexes (with organic acids, amino acids, nucleotides, phosphates, and carbohydrates), as physically bound macromolecular complexes (with proteins, polynucleotides, and glycosaminoglycans), and as covalently bound macromolecular complexes (Ganrot 1986; Priest 2004). The free ion, Al^{+3}, is easily bound to many substances and structures; therefore, its fate is determined by its affinity to each of the ligands and their relative amounts and metabolism. The low-molecular-weight (LMW) complexes are often chelates and may be very stable. The macromolecular complexes are expected to be much less active than the LMW-complexes. Aluminium may also form complexes with macromolecules that are so stable that they are essentially irreversible (Daydé et al. 2003; ATSDR 2008).

4.1.4 Excretion

Aluminium is primarily eliminated in the urine (95%) via glomerular filtration process, while the unabsorbed dietary aluminium is excreted in the feces. A minor, secondary route (~ 2%) is excretion *via* bile (Krewski et al. 2007; EFSA 2008). Aluminium has also been detected in breast milk at a typical range of 0.0092 to 0.049 $mg.L^{-1}$ (ATSDR 2008), in saliva, in sweat and in the seminal fluid (Krewski et al. 2007).

Multiple reported values for serum and urine elimination half-lives of aluminium (from hours to years, according to the duration of the period of observation) in humans and animals suggest that there is more than one compartment of aluminium storage, in particular bones and lungs (EFSA 2008; Klotz et al. 2019). Typically, the longer half-life can only be determined with increased duration of sampling, and retention times for aluminium appear to be longer in humans than in rodents. Actually, in most individuals, the largest aluminium reservoir is the skeleton; elimination from bone is very slow with a half-life of several years (Klotz et al. 2019). Slow aluminium elimination coupled with continuous exposure may explain the increasing body burden with age (Affourtit, Bakker, and Pronk 2020).

4.1.4.1 Excretion following inhalation

Human data

Urinary excretion is the primary route of elimination of absorbed aluminium after inhalation exposure (Klotz et al. 2019). Elevated levels of aluminium in urine have been detected in aluminium welders and aluminium flake workers (ATSDR 2008). Exposure studies showed that aluminium excretion is biphasic. As reported in ATSDR 2008, the excretion half-life for the first phase ranged from 7.5 to 9 days among workers exposed to welding fumes or aluminium dust (Sjögren et al. 1985; 1988; Pierre et al. 1995). The half-lives for the second phase ranged from 6.8 to 24 weeks (Sjögren et al. 1988; Schaller et al. 2007). The wide range of apparent half-lives reflects differences in the duration of sampling. Furthermore, several investigators (Sjögren et al. 1988; Letzel, Schaller, and Angerer 1996) have found a linear relationship between post-shift urinary aluminium levels and levels of aluminium in air around welders during the last or the cumulated preceding shifts (ATSDR 2008).

Animal data

No available studies in ATSDR (2008) and since then after literature search.

4.1.4.2 Excretion after oral intake

Human data

An acute exposure of 4 days to 54.3 mg Al.kg^{-1}, as aluminium carbonate, produced peak concentrations ranging from 4- to 10-fold elevation in base-line urinary levels (<200 µg.d^{-1} (± SEM) on control days vs 380-580 µg.d^{-1} (± SEM) after aluminium intake) (Recker et al. 1977). In addition, a 40-day balance study was conducted by Greger and Baier, where eight adult males were fed two levels of aluminium, as aluminium lactate: 5 mg.d^{-1} for 20 days (control diet) and 125 mg.d^{-1} for 20 days (test diet). Subjects excreted two- to five-fold more aluminium in their urine when fed the test diet (47 to 212 µg aluminium.d^{-1}; mean 1.71 mg.kg bw^{-1}.d^{-1}) rather than the control diet (24 to 58 µg Al.d^{-1}; mean 0.07 mg.kg bw^{-1}.d^{-1}) (Greger and Baier 1983). Patients taking aluminium hydroxide antacids (1-3 g Al.d^{-1}) had a 3-fold increase in urinary aluminium urine and serum levels, e.g.: a subject excreted 0.098 mg of Al in urine.d^{-1} before taking Amphogel 90 (aluminium hydroxide) and then excreted 0.282 mg Al.d^{-1} in urine. Aluminium concentration in plasma were 36 µg.L^{-1} and 46 µg.L^{-1} before and after taking the antacid, respectively (Gorsky et al. 1979).

Animal data

A single oral dose of 11 mg aluminium (administered as aluminium chloride) to healthy Sprague-Dawley rats resulted in a 14-fold increase in urine aluminium levels after 5 days (9.23±2.21 µg.d^{-1}), as compared to baseline levels (0.40±0.54 µg.d^{-1}) (Ittel et al. 1987). Rats administered by gavage a single dose of one of eight aluminium compounds (each one containing 35 mg aluminium) excreted 0.015–2.27% of the initial dose in the urine. In this experiment, 24-hour urine was collected from rats for 2 days before the gavage and 3 days afterwards (Froment et al. 1989). The range of urinary elimination most likely reflects differences in gastrointestinal absorption (ATSDR 2008).

Fecal aluminium results from unabsorbed aluminium and aluminium excreted via bile (ATSDR 2008). In rats receiving a gavage dose of 6.7–27 mg Al.kg bw^{-1} (administered as aluminium lactate in a sodium citrate aqueous solution to enhance aluminium absorption from the gastrointestinal tract), 1.3-2.8% of the total dose was excreted in urine and 0.06 to 0.14% of the total dose was excreted in bile within 3 hours. Within 15 minutes, the levels of aluminium in bile were significantly higher than in controls (Sutherland and Greger 1998).

4.1.4.3 Excretion after dermal exposure

Human data

No available studies in ATSDR (2008) and since then after literature search.

Animal data

No available studies in ATSDR (2008) and since then after literature search.

4.1.4.4 Excretion after intramuscular injection

In the rabbit study by Flarend et al., the cumulative amount of aluminium eliminated in the urine over 28 days was 6% of the aluminium hydroxide adjuvant dose and 22% of the aluminium phosphate adjuvant dose. Aluminium from both adjuvants was still being excreted at a steady rate on day 28 (Flarend et al. 1997). While this indicates that the body can eliminate the aluminium absorbed from the adjuvants, elimination is slow for the aluminium phosphate

adjuvant and even slower for the aluminium hydroxide adjuvant (Affourtit, Bakker, and Pronk 2020).

4.1.4.5 Excretion after intravenous injection

Two studies conducted in healthy human volunteers described aluminium elimination after intravenous injection of [^{26}Al]-aluminium citrate (Priest et al. 1995; Talbot et al. 1995).

In the study of Priest et al. (1995) a single volunteer received 0.7 µg ^{26}Al. After 15 minutes, more than half of ^{26}Al had left blood and the decline continued afterwards, leaving less than 1 % of the injected dose in blood after 2 days. This initial rapid decrease resulted from both distribution and excretion. The proportion of dose that is excreted, estimated up to 13 days after injection, was 83 % in urine and 1.8 % in faeces. The fraction retained in whole body was of 15.2 % at 13 days, and it then slowly declined to around 4 % after 1178 days (3 years) (Priest et al. 1995). A re-analysis of these data in a later publication indicated that they could be adequately interpreted by a three-compartment model with half-lives of 1.4, 40, and 1727 days. This volunteer was re-examined 10 years after the injection, and collected data indicated that the current elimination half-life for this volunteer was very prolonged, in the region of 50 years (Priest 2004).

In the study of Talbot et al., 6 healthy male volunteers received the same injection of [^{26}Al]-aluminium as citrate salt (4 ml containing 84 ng ^{26}Al and 25 mg citrate). Blood concentration decreased by 98 % in one day (mean value of 2% of injection remaining after 1 d); 59 ± 10 % were excreted in the urine within 24 hours; fecal excretion was negligible during the first 5 days (1 %). Whole-body retention was still 27 ± 7 % at 5 days (Talbot et al. 1995).

Globally, these two studies reported convergent results, evidencing a rapid excretion of most absorbed aluminium in the urine and a fraction that persists a very long time in the body.

4.1.5 PBPK model

Various kinetic models for aluminium, with different levels of complexity, have been published. In the three models developed below, insoluble aluminium compounds are not considered.

The open compartmental model is represented in Figure 3. Open compartmental model for aluminium biokinetics (Nolte et al. 2001). The parameters of this model are based on 4 studies in rats with oral administration of ^{26}Al-chloride and 3 human studies with IV administration of ^{26}Al-citrate. The essential features of the model are a central compartment, three compartments for the digestive tract and three peripheral compartments. The central compartment consists of transferrin-bound aluminium and citrate-bound aluminium in plasma and in the interstitial fluid. The peripheral compartments are used for organs like liver and spleen, muscles and bones. Liver and spleen receive aluminium from the transferrin-bound aluminium in the plasma, the muscles from the transferrin-bound aluminium in the interstitial fluid and the extracellular bone tissue from the citrate-bound aluminium of the interstitial fluid. With regards to the gastrointestinal absorption, aluminium uptake is considered to take place in the duodenum and proximal jejunum. Excretion of incorporated aluminium occurs from the soluble ultrafiltrable phase of the citrate-bound aluminium in the plasma via the kidneys. Measured values of ^{26}Al in serum and urine were used to determine absorption, speciation, distribution, retention, and excretion of aluminium in healthy volunteers and in patients with chronic renal failure following administration of a single oral or IV dose of ^{26}Al (Steinhausen et al. 2004).

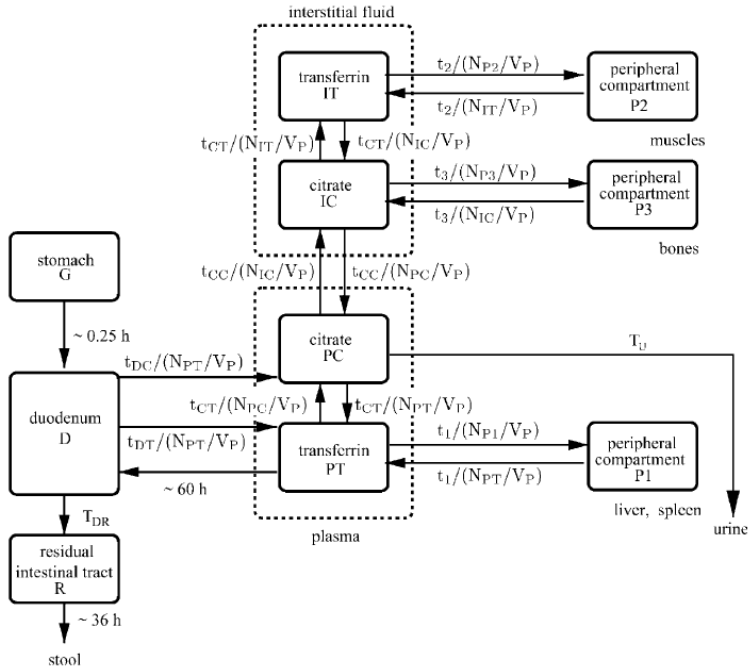


Figure 3. Open compartmental model for aluminium biokinetics (Nolte et al. 2001)

Poddalgoda et al considered a 3-compartment human model (Poddalgoda *et al.* 2021). The model tracks the amount of aluminium in each of three compartments (plasma, rapid and slow tissues) as well as excretion in urine.

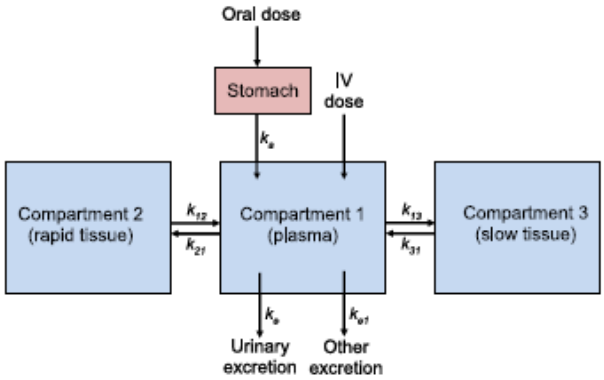


Figure 4. Structure of the three-compartment aluminium pharmacokinetic model (Poddalgoda et al. 2021)

Hethey et al. 2021 described a physiological-based toxicokinetic model of aluminium citrate or chloride salts in rats and humans (Figure 5). This PBK model accounts for aluminium kinetics in plasma, blood, liver, spleen, muscle, bone, brain, kidney, and urine. A 'rest of body' compartment describes the sum of the remaining body spaces (carcass, adipose tissue, lung and sites escaping quantification in before-mentioned tissue homogenates). The organs are in exchange via a central blood compartment that includes the arterio-venous space as well as the vascular space of the tissues. In the figure below, mass transfers are indicated by black arrows. Different aluminium species are considered in the blood compartment: iv-administered citrate, and chloride salts as well as a 'mixed' state, where all aluminium species, including transferrin bound Al, are assumed to be in quasi-steady state. Routes of administration are indicated by red arrows and are intravenous and oral administration. In this model, the amount of aluminium in erythrocytes is assumed to be negligible compared to the amount in plasma. The detailed model structure with three Al states in blood was designed to account for potential

differences in renal elimination depending on the route and aluminium salt (citrate or chloride) administered.

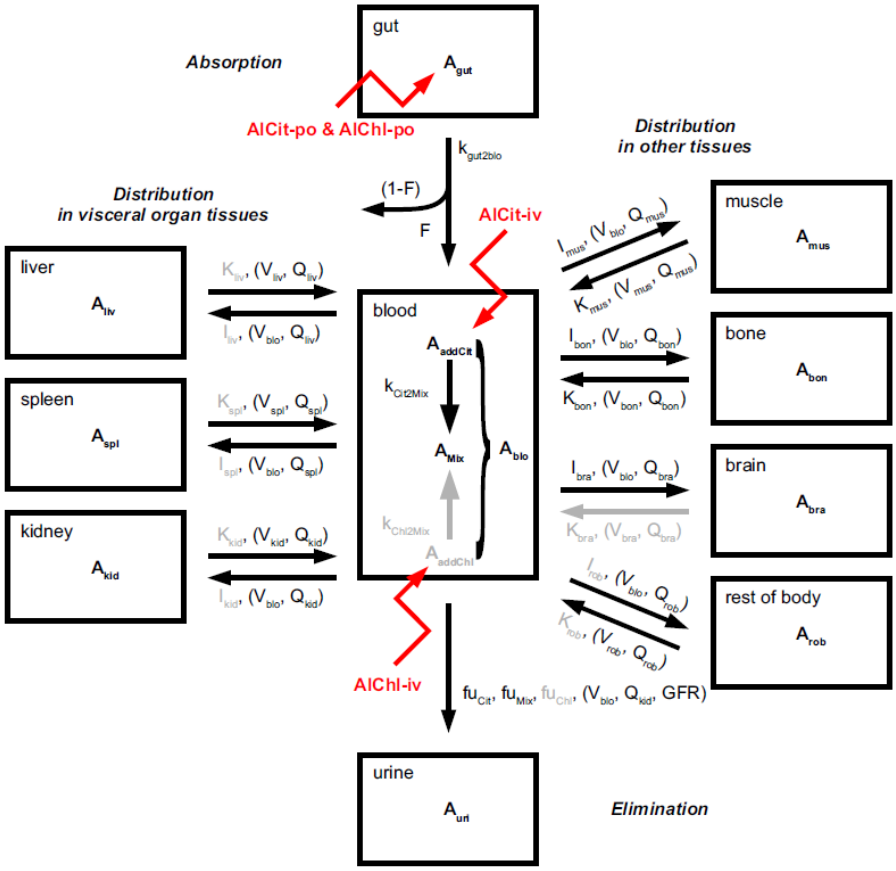


Figure 5. PBK model structure of aluminium (Hethey et al. 2021)

4.1.6 Overview ADE (absorption, distribution, excretion)

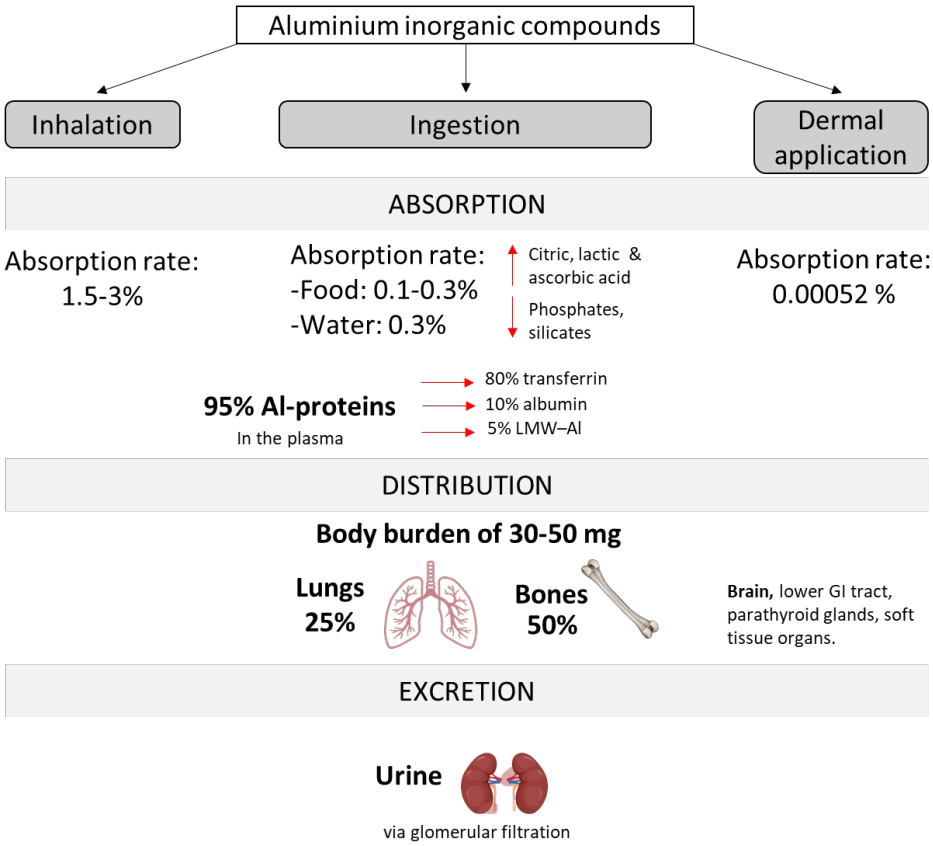


Figure 6. Absorption, distribution and excretion of aluminium inorganic compounds in human

The aluminium load in the human body, from daily absorption through the digestive, pulmonary, and even dermal routes, is distributed mainly to the bones (50%) and the lungs (25%); aluminium is also found in small amounts, in the brain, the lower gastrointestinal tract and soft tissue organs other than the lungs. The transport protein of aluminium (as Al^{+3}) is transferrin and the main route of excretion is the urinary route.

4.2 Biomarkers of exposure

The scientific literature search failed to identify any relevant biomarkers of early effects for the biomonitoring of occupational exposure to aluminium. Therefore, biomarkers of early effects will not be developed further.

4.2.1 Identification of biomarkers of exposure

Aluminium can theoretically be measured in different biological liquids, tissues, or excreta(e.g.: blood, serum, urine, cerebrospinal fluid, semen, milk, saliva, bone, hair or even nails) (ATSDR 2008). However, in practice, blood and urine appear as the most commonly used matrices for the routine biomonitoring of aluminium exposure, both in an occupational or an environmental context.

The deferoxamine challenge test (measurement of aluminium excretion after deferoxamine administration) and bone aluminium concentration are probably good indicators of aluminium

body burden, but they do not appear adapted for routine surveillance. Indeed, the challenge test is invasive and deferoxamine is not always well tolerated (Yokel 1994). Non-invasive *in vivo* bone aluminium measurement is still in the field of research (Aslam et al. 2009).

Already demonstrated to be of valuable use in forensic for several classes of substances in particular inorganic compounds, hair has multiple advantages for human biomonitoring: it is stable, easy to access for sampling, well tolerated and reflects long-term exposure (Peña-Fernández A, González-Muñoz Mj, and Lobo-Bedmar Mc 2014). Similarly, metal concentration in toenails is a non-invasive biomonitoring tool and early warning indicator that is favoured over fingernails because of the lower risk of external contamination (Di Ciaula et al. 2020). Indeed, the measurement of aluminium in hair and nails has gained considerable interest in recent years. The use of ICP-MS provides high sensitivity and reproducibility in these matrices. However, specifically in the context of environmental exposure, the relevance of aluminium in hair or nails as effective biomarkers of exposure remain to be established, particularly with regard to the prediction of health effects. Indeed, while measurement in these matrices offers the advantage of being non-invasive, it remains challenging to differentiate between aluminium incorporated in the hair (internal exposure) and aluminium deposited on the hair (external exposure), even with advances in technology and especially in the case of aluminium, where the substance itself is measured in the hair and nails and not as a metabolite.

Most of the toxicological studies and data available concern aluminium measured in urine and/or blood. These two matrices will be developed further in the following chapters.

4.2.1.1 Aluminium in urine

Many studies in workers or volunteers have demonstrated that urine aluminium levels measured at the end of a shift and after several shifts is a good biological indicator of the mean exposure of the preceding week (Lauwerys and Hoët 2001; Rossbach et al. 2006; Bertram et al. 2015; Riihimäki and Aitio 2012).
In addition, urine aluminium is possibly a good indicator of aluminium body burden, especially when measured at least 2-3 days after discontinuation of exposure (before the shift) (most of the elimination of the amounts recently absorbed occurring within 2 days). There is no human data validating this hypothesis.
Actually, cross sectional and longitudinal epidemiological studies have shown an increase of the risk of neurotoxic cognitive effects, associated with the elevation of urine aluminium concentration in occupationally exposed workers (see section 6.5.1).

4.2.1.2 Aluminium in blood

Concentrations of aluminium in whole blood, erythrocytes, serum and plasma are usually considered approximately equal and all four blood matrices could theoretically be considered for internal exposure assessment (Poddalgoda et al. 2021). However:

- studies on the distribution of aluminium between serum (or plasma) and erythrocytes gave conflicting results (see section 4.2), and studies on the association of whole-blood or erythrocytes aluminium levels with health effects or aluminium external exposure are scarce. Consequently, these two matrices cannot be presently considered for aluminium exposure biomonitoring.
- serum and plasma levels are theoretically equivalent, but anticoagulants, such as heparin or citrate, may contain aluminium. For this reason, serum should be preferred over plasma.

When measured at the end of shift with stable chronic exposure (e.g. welding), serum aluminium levels are well correlated with atmospheric exposure (Biotox INRS assessed in April 2024). A good correlation (r=0.824) was reported between circulating (serum) and excreted (urine) aluminium concentrations (Riihimäki et al. 2000). However, urinary aluminium is considered as a more sensitive indicator of variations of exposure and/or body burden. Indeed, for low-level occupational exposures (lower than 5 $mg.m^{-3}$ of elemental aluminium), serum

aluminium levels are not significantly different from those of the general population, when small variations of exposure are detectable through urinary aluminium monitoring. In addition, after the end of exposure, serum aluminium levels return to normal more rapidly than urinary aluminium concentrations (Riihimäki and Aitio 2012; INRS 2021)
In conclusion, determination of serum aluminium lacks sensitivity for revealing small variations of external exposure and/or for the biomonitoring of the body burden, especially in low exposure situations. However, serum aluminium is still the best biomarker for aluminium body burden in people with renal failure, as their aluminium internal dose can be high and urine aluminium level is not a validated exposure indicator for those people.

Table 5 summarises the advantages and limitations of the most commonly used matrices for the measurement of total aluminium. Other potential matrices are not included in the table as they are rarely used and because of the lack of available literature.

Table 5. Overview of the advantages and limitations of the main matrices used for total aluminium measurement

Analyte	Matrix	Advantages	Limitations
Aluminium	Urine	• Non-invasive • Reflects both aluminium body burden and recent exposure • More sensitive than blood aluminium to changes in external exposure • Association established with risk of neurological effects for urine aluminium levels at the end of a shift after several shifts (see chapter 8)	• Influenced by impaired renal function • Intra- and inter-individual variations in urine concentration (related to water intake and excretion); those variations can be managed through adjustment on urine creatinine level, urine density or urine osmolality • High risk of external contamination of samples, at sampling time and during sample preparation and analysis
Aluminium	Whole blood, Plasma, Serum	• Reflects recent exposure • More reliable than urine aluminium when renal function is not normal	• Invasive • Less sensitive than urine aluminium to changes in external exposure • High risk of external contamination of samples, at sampling time and during sample preparation and analysis
Aluminium	Hair	• Non-invasive, stable, possibility to observed past exposure	• Challenging to differentiate internal and external exposure • Limited data on the association with health effects
Aluminium	Nails	• Non-invasive, easy to access for sampling, well tolerated, possibility to observe past exposure	• Challenging to differentiate internal and external exposure • Limited data on the association with health effects

4.2.2 Choice of the biomarker of exposure

- **Biomarker of exposure**

When selecting an exposure biomarker, several criteria are generally taken into account: the association between concentrations of the potential biomarker and health effects and/or external concentrations or doses, the elimination half-life (important for choosing the sampling time), the specificity of the biomarker, the intra-individual and/or inter-individual variability of the association between exposure and the biomarker (in terms of co-exposures, pathologies or predispositions), the sampling conditions and, the availability of analytical methods (ANSES, to be released) .

As shown in Table 5, urinary aluminium appears to be the biomarker of exposure of choice:

- there is sufficient evidence of a positive association between urinary aluminium level and the risk of health effects, with identified NOAEL and LOAEL in humans (see section 4.7.1);
- urine aluminium is a biomarker of greater sensitivity compared to serum aluminium when external exposure changes are minimal;
- in individuals with normal renal function, inter- and intra-individual variabilities are limited, when aluminium levels are adjusted on urine creatinine concentration, specific gravity or osmolality.

Furthermore, urine sampling is non-invasive and analytical methods are available to conduct the analysis (see above section).

In conclusion, urinary aluminium is selected as the relevant BME for biological monitoring of exposure to aluminium, on the basis of an analysis of the advantages and disadvantages of the various BMEs identified. In the case of impaired renal function, urinary aluminium cannot be used as BME because this pathological condition affects the interpretation of biomonitoring results.

4.3 Acute and subacute toxicity

4.3.1 Human data

No reliable studies have been identified regarding the effects of acute inhalation or ingestion of aluminium or its compounds in humans.

Several cases of aluminium related encephalopathy were reported in patients who underwent otoneurosurgery with bone reconstruction using an aluminium-containing cement (Hantson et al. 1995; Lévêque et al. 1996; Reusche et al. 2001).

Cases of acute encephalopathy with high aluminium plasma levels are also reported, after post-surgical bladder alum irrigation. However, in most of these cases, aluminium was probably not the only or the main cause of the neurological symptoms, as severe hydroelectrolytic disturbances were obviously or probably associated (Phelps et al. 1999).

4.3.2 Animal data

ATSDR reported several acute toxicity studies in animal following **oral exposure** to aluminium or its compounds.

- **Mice**

In mice (Swiss-Webster), LD50s (median lethal doses) were 286, 222 and 164 mg Al.kg bw^{-1} for aluminium nitrate, aluminium chloride and aluminium bromide, respectively (Llobet et al. 1987). In another mice strain (Dobra Voda), LD50 values were higher, with 770 mg Al.kg $bw^{-1}.d^{-1}$ for aluminium chloride and 980 mg Al.kg $bw^{-1}.d^{-1}$ for aluminium sulphate (Ondreicka, Ginter, and Kortus 1966).

- **Rats**

The LD50 in rats were 261 mg Al.kg bw^{-1} for aluminium nitrate, 370 mg Al.kg bw^{-1} for aluminium chloride, 162 mg Al.kg bw^{-1} for aluminium bromide and >730 mg Al.kg bw^{-1} for aluminium sulphate (Llobet et al. 1987).

- **Rabbits**

Five female New Zealand rabbits died from a single 540 mg Al.kg bw^{-1} dose of aluminium lactate administered by gavage (Yokel and McNamara 1985).

Following acute **inhalation,** ATSDR (2008) found no study assessing mortality of aluminium or its compounds in animals. However, some respiratory effects following acute and subacute inhalation of aluminium compounds have been reported.

- **Mice**

Mice (n=11) exposed in a whole-body chamber, for one hour, to a suspension of 8 $mg.m^{-3}$ of aluminium dust had a significant higher fraction of alveolar collapse (69.7±1.2%) and influx of poly-morphonuclear cells in lung parenchyma (27.5±1.1%) than the control group (n=11) exposed to saline (Mazzoli-Rocha et al. 2010).

- **Rats**

In male rats (Fischer-344) whole-body exposed 0, 10, 50 100, 200 or 1000 $mg.m^{-3}$ aluminium flakes (median diameter: 1.58 µm) for (5x) 4 hours, multifocal microgranuloma in the lungs and hilar lymph nodes were detected at the 2 highest concentrations starting 200 mg $Al.m^{-3}$. An increase of lactate dehydrogenase, glucose-6-phosphate dehydrogenase and alkaline phosphatase activities in lavage fluid was observed at 50 mg $Al.m^{-3}$. No respiratory effects were observed at the concentration of 10 mg $Al.m^{-3}$ (NOAEL) (Thomson et al. 1986).

- **Hamsters**

In a series of studies, on hamsters (Golden Syrian), a 13% increase in lung weight was observed after inhalation (whole-body exposed) of aluminium chlorohydrate for 3 days (4 $hr.d^{-1}$) from the dose of 7 mg $Al.m^{-3}$ (LOAEL), and no significant increase of the lung weight was observed at 3 mg $Al.m^{-3}$ (NOAEL). An alveolar wall thickening, and an increased number of macrophages were observed after a 3-day exposure (4 or 6 $hr.d^{-1}$) to 31 or 33 mg $Al.m^{-3}$. In this experiment, a progressive decrease in the severity of the pulmonary effects was observed after the end of exposure (Drew et al. 1974).

- **Rabbits**

Similar effects were observed in New Zealand rabbits. In this species, a thickening of the alveolar wall, an increase in the number of macrophages and a 65% increase in lung weight were observed after inhalation (whole-body exposed) of aluminium chlorohydrate for 5 days ($4hr.d^{-1}$) at a LOAEL of 43 mg $Al.m^{-3}$ (Drew et al. 1974).

4.4 Irritation

As indicated in section 3.3, anhydrous aluminium chloride is classified as skin corrosive (category 1B) under the harmonised CLP classification. In addition, ECHA website[13] reports several CLP notifications and information from REACH registration dossiers concerning the skin and/ or ocular irritation effect of other aluminium compounds including, aluminium citrate, aluminium hydroxide, aluminium lactate, aluminium nitrate, aluminium phosphate, aluminium silicate, aluminium sodium dioxide and aluminium sulphate.

[13] https://echa.europa.eu/information-on-chemicals (accessed on February 2024)

In fact, it is predictable that, in contact with a humid environment, partially hydrolysed aluminium salts may cause irritation to the skin and mucous membranes following the liberation of the corresponding acid.

4.4.1 Human data

SCCS mentioned some studies reporting skin irritation following the application of a high dose of aluminium hexahydrate chloride (ACH) in ethanol (20% ACH) in a formulation for the treatment of axillary / palmar hyperhidrosis (Ellis and Scurr 1979; Goh 1990; Reisfeld and Berliner 2008) and following the use of aluminium-containing crystal deodorant (Gallego, Lewis, and Crutchfield 1999). SCSS also explained that, although associations have been reported between axillary irritation and aluminium chloride in antiperspirants for the treatment of hyperhidrosis, the history of use of this compound in antiperspirants shows that this effect is not very common (SCCS 2023).

Furthermore, the review by Krewski et al. reported cases of contact dermatitis and irritant dermatitis in workers following exposure to aluminium alloys and aluminium dust. It was also concluded that aluminium inhalation could cause irritation. This is based on several old studies in the workplace reporting dry cough, dyspnoea and shortness of breath following the exposure to aluminium powder (Krewski et al. 2007).

4.4.2 Animal data

- **Ocular irritation**

Conjunctivitis and purulent ophthalmitis were observed following the instillation of potassium alum (aluminium potassium sulphate) (Grekhova et al. 1994) and ammonium alum into rabbit's eyes (Krewski et al. 2007).

- **Dermal irritation**

SCCS reported a study (Lansdown 1973) in which epidermal lesions, hyperkeratosis, acanthosis and micro-abscesses were observed in mice, rabbits and pigs after 5 days of dermal application (once.d^{-1}) of aluminium chloride or nitrate (10% [w/v]), but not with aluminium acetate, hydroxide or hydrochloride compounds (SCCS 2023).

4.5 Sensitisation

4.5.1 Human data

ATSDR reported a case described by De Vuyst et al. (1987) where T-helper lymphocyte alveolitis and blastic transformation of peripheral blood lymphocytes in the presence of soluble aluminium compounds *in vitro* were observed in an individual exposed to metallic aluminium and aluminium oxide dust with sarcoid-like epithelioid granulomas (ATSDR 2008).

ATSDR (2008) also reported hypersensitivity to aluminium chloride in patch testing in some children and one adult who had previously received injections of vaccines or allergens in aluminium-based vehicles (Böhler-Sommeregger and Lindemayr 1986; Veien et al. 1986).

SCCS specified that there are no sufficient data in humans suggesting that aluminium compounds used in antiperspirants cause allergies and given their widespread use, this effect, if it exists, seems to be rather rare (SCCS 2023).

4.5.2 Animal data

SCCS reports a study conducted by Basketter et al. (1999) where doses up to 25% of aluminium chloride were tested in a murine local lymph node assay (LLNA), with no indications

of a skin sensitisation potential. A guinea pig maximisation test with aluminium chlorohydrate dosed at 25 %, was also negative (SCCS 2020).

SCCS confirmed that animal data do not indicate a skin sensitisation effect of the aluminium compounds used in antiperspirants (SCCS 2023).

4.6 Subchronic toxicity

No **human** reliable studies were identified on health effects following subchronic exposure to aluminium compounds.

Among the studies identified in **animals**, seven studies involved administering aluminium chloride to rats via drinking water, at dose levels ranging 0-8.3 mg.kg $bw^{-1}.d^{-1}$ (Martinez et al. 2017a, 2017b, 2017c, 2018) or by gavage at dose levels ranging 0, 8.3 or 32 mg.kg $bw^{-1}.d^{-1}$ (Fernandes et al. 2020; Souza-Monteiro et al. 2021; Bittencourt et al. 2022) or 0-100 mg.kg $bw^{-1}.d^{-1}$ (Martinez et al. 2017a, 2017b, 2017c, 2018). These studies investigated effects on bone mineralisation (Souza-Monteiro, 2021), cardiotoxicity (Martinez et al., 2017a), male reproductive toxicity (Martinez et al., 2017b), and neurotoxicity (Martinez et al. 2017c, 2018; Fernandes et al. 2020; Bittencourt et al. 2022). All the studies referred to human dietary levels of exposure to calculate the doses to be used in rodent studies but the human values used for calculation were not clearly justified and did not refer to benchmark values calculated by regulatory agencies. In addition, the doses received by the animals were not confirmed by analysis of aluminium in drinking water nor supported by drinking water consumption measurement. A high level of uncertainty regarding the doses received by the animals led the experts not to consider these studies for the hazard assessment of aluminium chloride.

4.6.1 Neurotoxicity

4.6.1.1 Human data

No human reliable studies were identified on neurotoxic effect following subchronic exposure to aluminium compounds.

4.6.1.2 Animal data

Several animal studies (mice and rats) reported neurotoxicity effects after subchronic exposure to aluminium compounds. These studies are described below and summarised in Table 6.

- Mice

Swiss-Webster female mice (dams) exposed to aluminium lactate from Gestational day (Gd) 1 to Lactation day (Ld) 21 through diet did not show signs of toxicity in the neurobehavioral test battery (fore and hindlimb grip strength, temperature sensitivity, negative geotaxis, air puff startle reflex, auditory startle reflex, foot splay) when they were exposed to 25 (control), 500 or 1000 µg $Al.g^{-1}$ diet (Donald et al. 1989). The NOAEL was 1000 $µg.g^{-1}$ diet equivalent to 330 mg Al.kg $bw^{-1}.d^{-1}$, referring to the highest tested dose.

Female Swiss-Webster mice (8-12 weeks of age) were exposed to aluminium lactate for 6 weeks in the diet at doses of 25 (control), 500 or 1000 µg $Al.g^{-1}$ diet. In the high dose group, there was a significant reduction in total activity counts, and counts of vertical movement and a significantly lower percent of activity in the highest activity level category (Golub et al. 1989). The NOAEL was of 500 $µg.g^{-1}$ diet, or 62 mg Al.kg $bw^{-1}.d^{-1}$ and the LOAEL of 1000 $µg.g^{-1}$ diet, or 130 mg Al.kg $bw^{-1}.d^{-1}$.

Swiss-Webster female mice (dams) exposed to aluminium lactate in the diet at doses of 25 (control) or 1000 µg Al.g^{-1} diet, during gestation or lactation or both, did not show effects of aluminium exposure in the neurobehavioral test battery performed at time of weaning (Golub, Keen, and Gershwin 1992a). The NOAEL was 1000 µg.g^{-1} diet, or 250 mg Al.kg bw^{-1}.d^{-1}, referring to the highest tested dose.

Golub et al. administered aluminium lactate (25 mg (control) or 1000 mg Al.kg^{-1} diet) to female Swiss-Webster (3-4 weeks old) mice through diet for 13 weeks. In the high dose group, decreased forelimb and hindlimb grip strengths and startle response, a decreased in total activity counts, horizontal activity counts and in the percentage of intervals with high activity counts were reported (Golub et al. 1992b). The LOAEL for this study was 1000 mg.kg^{-1} diet, or 195 mg Al.kg bw^{-1}.d^{-1}.

Aluminium chloride was also given to 42-day-old female Swiss Webster mice through the diet for 5-7 weeks at dose of 3 (control) or 1000 mg Al.kg^{-1} diet. A decrease in forelimb and hind limb grip strength was reported at the high dose (Oteiza et al. 1993). The LOAEL for this study was 1000 mg.kg^{-1} diet, that is 195 mg Al.kg bw^{-1}.d^{-1}.

Aluminium ammonium sulphate was administered in drinking water to C57BL/6J female mice at 0 or 0.075 g.L^{-1} from 4 weeks old to 9 weeks old of age (20 per group) or to male and female mice at 0 or 1 g.L^{-1} from Gd 11 until 9 weeks old of age (20 per group). Behavioural effects were observed in mice from the low dose group (increase in total arm entries in the elevated plus maze test, initial decrease followed by increase in immobility in the forced swim test, decreased freezing in the fear conditioning test 1 month after the conditioning session compared with controls). However, considering that only one dose was tested in each experiment and that these effects were not observed in the high-dose Al-treated mice, it appears that the observations were probable false positives, even if the exposure protocols were not identical at the lower and the higher doses. Indeed, these behavioural differences did not reach a statistically significant level after correction for multiple testing. In the high dose experiment, increased social contacts, impaired reference memory performance, decreases in pre-pulse inhibition and in correct responses in the working memory task were observed. The differences in any of the behavioural measures, in this second experiment did not reach the significance level after correction for multiple testing (Shoji et al. 2018).

- Rats

When aluminium lactate was administered through gavage to Wistar rats, from PND 5 to PND 14, at doses of 0, 100, 200 or 300 mg Al.kg bw^{-1}.d^{-1}, no effects were observed regarding the grasping reflex. Results of negative geotaxis test was significantly reduced at 200 and 300 mg Al.kg bw^{-1}.d^{-1} compared to the control group and significant differences were observed in the suspension test (reduced time of suspension) and the locomotor coordination test (increase time to put the 4 feet on the platform) between the control group in the 300 mg Al.kg bw^{-1}.d^{-1} dose group (Bernuzzi, Desor, and Lehr 1989b). The LOAEL was 200 mg Al.kg bw^{-1}.d^{-1} and the NOAEL 100 mg Al.kg bw^{-1}.d^{-1}.

Increased brain aluminium levels with decreased choline acetyltransferase activity and general activity were reported at a LOAEL of 200 mg Al.kg bw^{-1}.d^{-1} in Wistar rats also orally exposed to aluminium lactate through gavage from Post Natal Day (PND) 5 To PND 14 at doses of 0, 100, or 200 mg Al.kg bw^{-1}.d^{-1} (Cherroret et al. 1992). The NOAEL was 100 mg Al.kg bw^{-1}.d^{-1}.

Male rats (16 days old and18 months- strain not specified) were exposed to aluminium nitrate for 100 days in drinking water at doses of 0 or 100 mg Al.kg bw^{-1}.d^{-1} (citric acid was added to water). No significant effects of aluminium exposure on behaviour (motor activity in an open-field apparatus and learning using passive avoidance test) could be detected between groups. The total number of synapses in the left CA1 fields of hippocampal formation was decreased

in the aluminium aged group compared to the aluminium young group (Colomina et al. 2002). The NOAEL was 100 mg Al.kg $bw^{-1}.d^{-1}$, the highest tested dose.

In the study by Mameli et al., Wistar rats (n= 270) at 3, 10- and 24-months age, were exposed through drinking water to aluminium chloride (0.5, 1, 2 $g.L^{-1}$ in drinking solution providing 11.1, 21.5, 43.1 mg Al.kg $bw^{-1}.d^{-1}$) for 90 days. The study also included a control group (Mameli et al. 2006). Rats were tested at 30, 60 and 90 days of exposure. Considering the amount of aluminium present in the diet, they were approximatively exposed to 20, 30 or 52 mg Al.kg $bw^{-1}.d^{-1}$ (EFSA 2008). Results of this study showed significant impairment of post-rotatory nystagmus (PRN) parameters (delayed onset latency of PRN, decrease in jerk frequency and jerk amplitude), regardless of animal age, in rats exposed to 52 mg Al.kg $bw^{-1}.d^{-1}$ (LOAEL). NOAEL was considered to be 30 mg Al.kg $bw^{-1}.d^{-1}$.

Twelve months aged male Wistar rats (12-13 per group) received 0, 2 or 20 ppm of aluminium in their drinking water, as aluminium chloride, which resulted in an exposure of total aluminium of 0.4, 0.5 and 1.7 mg Al.kg $bw^{-1}.d^{-1}$, respectively, considering aluminium from the feed. From 6 months old, rats were trained to perform a rewarded continuous alternation T-maze task. Performance scores on T-maze task were analysed from 16 months old onwards. Among the rats who survived for at least 28 months, (0/10 low-dose group, 2/10 mid-dose group and 7/10 high-dose group), had significant lower scores in old age (> 28 months old) compared to middle age (12-24 months old) rats. Rats with impaired performance had significant higher aluminium serum levels and a larger percentage of aluminium-loaded pyramidal cells in their entorhinal cortex (ie a multi-sensory area, important for memory and navigation), compared to rats with intact T-maze performance. Furthermore, functionally impaired rats had aberrant behaviours including inability to focus attention on their task, perseverative activity, and incontinence while in the T-maze. LOAEL for impaired cognitive function was 0.5 mg Al.kg $bw^{-1}.d^{-1}$ (Walton 2009). JECFA considered this study difficult to interpret because, among other considerations, rats had an unusual feeding regimen (JECFA 2012).

In another study Wistar rats also received aluminium chloride in their drinking water at 0 or 3 $g.L^{-1}$ during 4 months in adulthood (at 3 months old). There was a significant increase of glial fibrillary acidic protein (GFA-P)-immunoreactive astrocytes in brains of aluminium treated rats, that also had a significant reduced locomotor activity compared to controls (Erazi et al. 2010). The LOAEL was 3$g.L^{-1}$ in water, or 55 mg Al.kg $bw^{-1}.d^{-1}$.

In another study, Wistar rats (15 per group) were administered aluminium chloride at 0, 0.18, 0.72 or 3.6 g $AlCl_3.L^{-1}$ in drinking water during 6, 12 and 18 months. A significant increase in aluminium concentration in plasma and brain was observed in a dose dependent and time dependent manner. Exposure to aluminium chloride caused a significant decrease in body weight (highest dose, month 18) and brain weight (mid and highest dose at 18 months); a significant correlation was confirmed between body and brain weight during 12 and 18 months. Aluminium chloride produced, at all doses, lesions of sub-granular and granular layers (significant at month 18) (Hichem et al. 2014). The LOAEL was 0,18 $g.L^{-1}$ aluminium chloride in water, or 2 mg Al.kg $bw^{-1}.d^{-1}$.

In a study by Cao et al., aluminium chloride was administered, through gavage, to Sprague-Dawley rats (30 per group) for 90 days at doses of 0, 50, 150 or 450 mg $AlCl_3$.kg $bw^{-1}.d^{-1}$. Increased mRNA levels of IL-1b, IL-6, TNF-a and MCH II, decreased mRNA levels of CX3CL1 and BDNF, and, decreased density of dendritic spine and impaired learning and memory were reported following aluminium chloride exposure in a dose dependent manner but were significant from the mid dose exposure (Cao et al. 2016). The NOAEL was of 50 mg $AlCl_3$.kg $bw^{-1}.d^{-1}$, that is 10 mg Al.kg $bw^{-1}.d^{-1}$ and the LOAEL was 150 mg $AlCl_3$.kg $bw^{-1}.d^{-1}$, or 30 mg Al.kg $bw^{-1}.d^{-1}$.

Wistar rats (30 per group) were orally exposed to aluminium chloride, from birth until 3 months and a half of age (early exposure via maternal milk for 3 weeks, then after weaning, exposure

via spontaneous drinking of water (post-natal 3 weeks to 14 weeks) at doses of 0.015, 0.030 or 0.045 mol.L^{-1} ie., 2, 4, 6 g.L^{-1}. Following aluminium chloride exposure, aluminium concentration in blood increased in a dose-dependent manner, morphology of the hippocampus and neuronal ultrastructure were aberrant, the escape latency and distance travelled became longer in the Morris water maze test and intracellular Ca^{2+} and cAMP levels in hippocampus cells declined significantly (Yan et al. 2017). The LOAEL was 2 g.L^{-1} aluminium chloride equivalent to 36 mg Al.kg $bw^{-1}.d^{-1}$ for impaired learning and memory performances.

Neurotoxicity of aluminium was also assessed in 3-month-old male Wistar rats (6 per group) administered aluminium chloride over 60 days at doses of 0, 1.5 or 8.3 mg Al.kg $bw^{-1}.d^{-1}$ through drinking water or over 42 days at doses of 0 or 100 mg Al.kg $bw^{-1}.d^{-1}$ by gavage. Impaired results on object recognition memory were reported in all treated groups. Reactive oxygen species (from low dose) and lipid peroxidation (from 8.3 mg.kg bw^{-1}) were increased and, AChE activity and hippocampal antioxidant capacity were decreased in all treated groups (Martinez et al. 2017c). Martinez et al. also conducted another study where Wistar rats (8 per group) were administered 0 or 8.3 mg Al.kg bw^{-1} (dose similar to human dietary levels) through drinking water for 60 days or 0 or 100 mg Al.kg bw^{-1} through gavage for 42 days. In all treated groups, the development of mechanical allodynia, catalepsy, increased inflammation in the sciatic nerve and systemic oxidative stress were reported. Aluminium was also able to be retained in the sciatic nerve (Martinez et al. 2018). The LOAEL was of 1.5 mg Al.kg $bw^{-1}.d^{-1}$ for the first study and of 8.3 mg Al.kg $bw^{-1}.d^{-1}$ for the second one.

Wistar rats (10 per group) received, by gavage, aluminium chloride solutions at doses of 0, 8.3 or 32 mg.kg $bw^{-1}.d^{-1}$ for 60 days. At the high dose group, aluminium level increased significantly in hippocampal parenchyma. Aluminium at both concentrations affected long-term memory and induced oxidative stress in prefrontal and hippocampus but did not affect short-term memory (Fernandes et al. 2020). The LOAEL was 8.3 mg mg.kg $bw^{-1}.d^{-1}$ of aluminium chloride, or 1.7 mg Al.kg $bw^{-1}.d^{-1}$.

In another study, male Wistar rats (12 per group) received through gavage either 0 or 8.3 mg.kg $bw^{-1}.d^{-1}$ of aluminium chloride for 60 days. Aluminium exposed rats had a significantly increased learning deficiency and spatial memory, deregulation of proteins expression, essentially the ones regarding the regulation of the cytoskeleton, cellular metabolism, mitochondrial activity, redox regulation, nervous system regulation, and synaptic signalling and, reduced hippocampal cell body density in CA1, CA3, and hilus (Bittencourt et al. 2022). The LOAEL was of 8.3 mg.kg $bw^{-1}.d^{-1}$ of aluminium chloride, that is1.7 mg Al.kg $bw^{-1}.d^{-1}$.

In another study by Massand et al., male Wistar rats (6 per group) were orally exposed, through gavage, to aluminium chloride at 0, 100 or 300 mg.kg $bw^{-1}.d^{-1}$ for 30 days. Results showed that rats exposed to aluminium chloride had a significant damage in all hippocampus regions compared to the control group. At 300 mg.kg $bw^{-1}.d^{-1}$, marked neuronal damage in CA1 and CA3 were reported, in comparison with the group exposed to the lower aluminium dose (Massand et al. 2022). The LOAEL was 100 mg.kg $bw^{-1}.d^{-1}$ aluminium chloride, or 20 mg Al.kg $bw^{-1}.d^{-1}$.

Table 6. Animal studies on aluminium neurotoxicity

Strain	Duration and route of exposure	Dose	Al compound	Endpoint	NOAEL	LOAEL	Reference
Mice							
Swiss-Webster (n= 16 per group)	Gd1 to Ld 21 In the diet	25 (control), 500 or 1000 µg Al.g^{-1} diet	Aluminium lactate	Neurobehavioral test battery No effect was observed at the highest dose	330 mg Al.kg bw^{-1}.d^{-1}		Donald et al. (1989)
Swiss-Webster (n= 5 per group)	6 weeks In the diet	25 (control), 500 or 1000 µg Al.g^{-1} diet	Aluminium lactate	Reduced total activity counts, counts of vertical movement and a lower percent of activity in the highest activity level category	62 mg Al.kg bw^{-1}.d^{-1}	130 mg Al.kg bw^{-1}.d^{-1}	Golub et al. (1989)
Swiss-Webster (Control: n = 14; Al: n = 9)	Gd1-Gd21 or Ld1-Ld21 or Gd1-Ld21 In the diet	25 (control) or 1000 µg Al.g^{-1} diet	Aluminium lactate	Neurobehavioral test battery No effect observed at the highest dose	250 mg Al.kg bw^{-1}.d^{-1}		Golub et al. (1992a)
Swiss-Webster (n= 12 per group)	13 weeks In the diet	25 (control) or 1000 mg Al.kg^{-1} diet	Aluminium lactate	Decreased forelimb and hindlimb grip strengths and startle response, decreased total activity counts		195 mg Al.kg bw^{-1}.d^{-1}	Golub et al. (1992b)
Swiss Webster (n= 10 per group)	5-7 weeks In the diet	3 (control) or 1000 mg Al.kg^{-1} diet	Aluminium chloride	Decrease in forelimb and hind limb grip strength		195 mg Al.kg bw^{-1}.d^{-1}	Oteiza et al. (1993)
Rats							
Wistar (n= 25-25-29-38 respectively)	PND 5 to PND 14 Gavage	0, 100, 200 or 300 mg Al.kg bw^{-1}.d^{-1}	Aluminium lactate	Reduced negative geotaxis test	100 mg Al.kg bw^{-1}.d^{-1}	200 mg Al.kg bw^{-1}.d^{-1}	Bernuzzi, Desor & Lehr (1989b)

Wistar (n= 4 per group)	PND 5 to PND 14 Gavage	0, 100, or 200 mg Al.kg $bw^{-1}.d^{-1}$	Aluminium lactate	Increased brain aluminium levels with decreased choline acetyltransferase activity and general activity	100 mg Al.kg $bw^{-1}.d^{-1}$	200 mg Al.kg $bw^{-1}.d^{-1}$	Cherroret et al. (1992)
(NS) (n= 16 per group)	100 days In water	0 or 100 mg Al.kg $bw^{-1}.d^{-1}$ (+citric acid added)	Aluminium nitrate	Motor activity in an open-field apparatus and learning using passive avoidance test No effect was observed	100 mg Al.kg $bw^{-1}.d^{-1}$		Colomina et al. (2002)
Wistar (n= 20-30 per group)	90 days In water	11.1, 21.5, 43.1 mg Al.kg $bw^{-1}.d^{-1}$	Aluminium chloride	Impairment of post-rotatory nystagmus parameters	30 mg Al.kg $bw^{-1}.d^{-1}$	52 mg Al.kg $bw^{-1}.d^{-1}$	Mameli et al. (2006)
Wistar (n= 5 per group)	4 months In water	0 or 3 $g.L^{-1}$	Aluminium chloride	Reduced locomotor activity		55 mg Al.kg $bw^{-1}.d^{-1}$	Erazi et al. (2010)
Wistar (n =15 per group)	6, 8 and 12 months In water	0.18, 0.72 or 3.6 g $.L^{-1}$	Aluminium chloride	Lesions of sub-granular and granular layers in hippocampus		2 mg Al.kg $bw^{-1}.d^{-1}$	Hichem et al. (2014)
Sprague Dawley (n= 30 per group)	90 days Gavage	0, 50, 150 or 450 mg.kg $bw^{-1}.d^{-1}$	Aluminium chloride	Impaired learning and memory	10 mg Al.kg $bw^{-1}.d^{-1}$	30 mg Al.kg $bw^{-1}.d^{-1}$	Cao et al. (2016)
Wistar (n=30 per group)	Birth to 14 weeks of age Lactation then in water	2, 4, 6 $g.L^{-1}$	Aluminium chloride	Morphological injury of the hippocampus and neuronal ultrastructure longer escape latency and distance travelled the Morris water maze test		36 mg Al.kg $bw^{-1}.d^{-1}$	Yan et al. (2017)
Wistar (n= 6 per group)	60 days in water	0, 1.5 or 8.3 mg Al.kg $bw^{-1}.d^{-1}$	Aluminium chloride	Impaired results on object recognition memory		1.5 mg Al.kg $bw^{-1}.d^{-1}$	Martinez et al. (2017c)
	42 days Gavage	0 or 100 mg Al.kg $bw^{-1}.d^{-1}$					
Wistar (n= 8 per group)	60 days in water	0 or 8.3 mg Al.kg $bw^{-1}.d^{-1}$	Aluminium chloride	Development of mechanical allodynia, catalepsy		8.3 mg Al.kg $bw^{-1}.d^{-1}$	Martinez et al. (2018)
	42 days Gavage	0 or 100 mg Al.kg $bw^{-1}.d^{-1}$					

Wistar (n=10 per group)	60 days Gavage	0, 8.3 or 32 mg.kg $bw^{-1}.d^{-1}$	Aluminium chloride	Impairment of long-term memory		1.7 mg Al.kg $bw^{-1}.d^{-1}$	Fernandes et al. (2020)
Wistar (n= 12 per group)	60 days Gavage	0 or 8.3 mg.kg $bw^{-1}.d^{-1}$	Aluminium chloride	Increased learning deficiency and spatial memory and, reduced hippocampal cell body density		1.7 mg Al.kg $bw^{-1}.d^{-1}$	Bittencourt et al. (2022)
Wistar (n= 6 per group)	Gavage 30 days	0, 100 or 300 mg.kg $bw^{-1}.d^{-1}$	Aluminium chloride	Damage in hippocampus regions		20 mg Al.kg $bw^{-1}.d^{-1}$	Massand et al. (2022)

4.6.2 Respiratory toxicity

4.6.2.1 **Human data**

No human reliable studies on respiratory toxicity were identified following subchronic exposure to aluminium compounds.

4.6.2.2 **Animal data**

Some animal studies (rats, hamsters and guinea pigs) demonstrating respiratory toxicity following subchronic exposure to aluminium compounds have been identified. These studies are described below and summarised in Table 7.

- Rats

The inhalation of aluminium chlorohydrate by rats (Fischer- 344), 0.25, 2.5 or 25 mg.m^{-3} whole body exposed) over six months (5d/wk and 6hr.d^{-1}) led to an increase in alveolar macrophages and to granulomatous lesions in lung at the medium and high concentrations. The LOAEL of 2.5 mg.m^{-3} Al chlorohydrate, corresponds to a concentration of 0.65 mg Al.m^{-3}; this increase was dose related. Histological alterations or changes in lung weights did not occur at 0.065 mg Al.m^{-3} (Steinhagen, Cavender, and Cockrell 1978).

In another study, Fischer-344 rats were exposed (whole body exposed) to aluminium chlorohydrate for 6 months (5d/wk and 6hr.d^{-1}), at doses of 0.25, 2.5 or 25 mg.m$^{-3.}$ A statistically significant increase in relative lung weight was observed in both sexes at the highest concentration (LOAEL 25 mg.m^{-3}, corresponding to 6.5 mg.m^{-3} Al; NOAEL 2.5 mg.m^{-3}, corresponding to 0.65 mg.m^{-3} Al). In male rats, the same effect was observed from the mid concentration (LOAEL = 0.65 mg Al.m^{-3} and NOAEL=0.065 mg Al.m^{-3} (Stone et al. 1979).

No organ weight or histological changes were observed in the lungs of Sprague-Dawley rats exposed to 70 mg.kg bw^{-1}.d^{-1} Al as aluminium chloride in drinking water for 30, 60, or 90 days (base dietary aluminium was not reported) (Dixon, Sherins, and Lee 1979).

Sprague-Dawley rats exposed to aluminium nitrate through water over one month at doses of 0, 375, 750 or 1500 mg.kg bw^{-1}.d^{-1} had also no organ weight or histological changes of the lungs (Gómez et al. 1986). The NOAEL was of 1500 mg.kg bw^{-1}.d^{-1} of aluminium nitrate, equivalent to 190 mg Al.kg bw^{-1}.d^{-1} (the highest tested dose).

- Hamsters

In Hamsters (Golden Syrian) inhaling (whole body exposed) 10 mg Al.m^{-3} as aluminium chlorohydrate over 5 or 6 weeks (5d/wk and 6hr.d^{-1}), granulomatous nodules and thickening of alveolar walls due to infiltration of macrophages and heterophils were observed (Drew et al. 1974).

- Guinea pigs

The inhalation (whole body exposed) of aluminium chlorohydrate by guinea pigs (Hartley) over six months (5d/wk and 6hr.d^{-1}) led to an increase in alveolar macrophages and to granulomatous lesions in lung at a dose of 0.65 mg Al.m^{-3} (LOAEL), this increase was dose related. Histological alterations or changes in lung weights did not occur at 0.065 mg Al.m^{-3} (Steinhagen, Cavender, and Cockrell 1978).

Guinea pigs were exposed to aluminium chlorohydrate (whole body exposed) for 6 months (5d/wk and 6hr.d^{-1}), at concentrations of 0.25, 2.5 or 25 mg.m^{-3} . A statistically significant increase in relative lung weight was observed in both sexes at the higher concentration (LOAEL 25 mg.m^{-3}, corresponding to 6.5 mg.m^{-3} Al; NOAEL 2.5 mg.m^{-3}, corresponding to 0.65 mg.m^{-3} Al) (Stone et al. 1979).

Table 7. Animal studies on aluminium sub-chronic exposure respiratory toxicity

Strain	Al compound	Duration and exposure route	Concentration	Endpoint	NOAEL	LOAEL	Reference
Rats							
344-Fischer (n= 20 per group)	Aluminium chlorohydrate	6 months (5d/wk and 6hr.d^{-1}) Inhalation	0, 0.25, 2.5 or 25 mg.m^{-3}	Increase in alveolar macrophages, granulomatous lesions in lung	0.065 mg Al.m^{-3}	0.65 mg Al.m^{-3}	Steinhagen et al. (1978)
344-Fischer (n≈ 17 per group)	Aluminium chlorohydrate	6 months (5d/wk and 6hr.d^{-1}) Inhalation	0, 0.25, 2.5 or 25 mg.m^{-3}	Increase in relative lung weight	M: 0.065 mg Al.m^{-3} F: 0.65 mg.m^{-3} Al	M: 0.65 mg Al.m^{-3} F: 6.5 mg.m^{-3} Al	Stone et al. (1979)
Sprague-Dawley (n= 31 per group)	Aluminium chloride	30, 60 or 90 days Water	0, 5, 50 or 500 mg $Al.L^{-1}$	No histological changes in lungs	70 mg.kg $bw^{-1}.d^{-1}$		Dixon et al. (1979)
Sprague-Dawley (n= 10 per group)	Aluminium nitrate	1 month Water	0, 375, 750 or 1500 mg.kg $bw^{-1}.d^{-1}$	Weight and histological changes in lungs No effect observed at the highest dose	190 mg Al.kg $bw^{-1}.d^{-1}$		Gómez et al. (1986)
Hamsters							
Golden Syrian	Aluminium chlorohydrate	5 or 6 weeks (5d/wk and 6hr.d^{-1}) Inhalation	10 mg Al.m^{-3}	Alveolar thickening, increased number of foci of macrophages and heterophils	-	10 mg Al.m^{-3}	Drew et al. (1974)
Guinea pigs							

Hartley (n= 20 per group)	Aluminium chlorohydrate	6 months (5d/wk and 6hr.d^{-1}) Inhalation	0, 0.25, 2.5 or 25 $mg.m^{-3}$	Increase in alveolar macrophages, granulomatous lesions in lung	0.065 mg $Al.m^{-3}$	0.65 mg $Al.m^{-3}$	Steinhagen et al. (1978)
Hartley (n= 15 per group)	Aluminium chlorohydrate	6 months (5d/wk and 6hr.d^{-1}) Inhalation	0, 0.25, 2.5 or 25 $mg.m^{-3}$	Increase in relative lung weight	0.65 mg $Al.m^{-3}$	6.5 mg $Al.m^{-3}$	Stone et al. (1979)

M: male ; F: female.

4.6.3 Haematological effects

4.6.3.1 **Human data**

No adverse haematological effects were noted in a group of seven workers after 6 months of exposure to aluminium fumes or dust (Mussi et al. 1984). Exposure levels ranged from 1 to 6.2 $mg.m^{-3}$ Al, predominantly as aluminium oxide. No other human study was found regarding this effect.

4.6.3.2 Animal data

Some animal studies (mice, rats, guinea pigs and dogs) have been identified regarding haematological effects after subchronic exposure to aluminium compounds. These studies are described below and summarised in Table 8.

- Mice

Female Swiss-Webster mice were exposed to aluminium chloride for 5-7 weeks, in the diet at doses of 3 (control) or 1000 µg $Al.g^{-1}$ diet. No alteration in haematocrit levels was observed (Oteiza et al. 1993). The NOAEL is 1000 mg.kg $bw^{-1}.d^{-1}$ Al chloride, or 195 mg Al.kg $bw^{-1}.d^{-1}$ (the highest tested dose).

- Rats

Rats (Fischer-344) exposed over 6 months (5d/wk, 6hr.d^{-1}), whole body exposed, to aluminium chlorohydrate 0, 0.25, 2.5 or 25 $mg.m^{-3}$ did not present haematological adverse effects (Steinhagen, Cavender, and Cockrell 1978) leading to a NOAEL of 25 $mg.m^{-3}$ Al chlorohydrate corresponding to 6.5 mg $Al.m^{-3}$ (the highest tested dose).

In the study by Stone et al., rats (Fisher-344) were exposed over 6 months (5d/wk, 6hr.d^{-1}) to 0.25, 2.5 or 25 $mg.m^{-3}$ of aluminium chlorohydrate (whole body exposed). At necropsy, peripheral blood was collected for haematological determinations (total red cells count, total white cells count, haematocrit, mean corpuscular volume and total haemoglobin). The authors did not report any haematological effect following this exposure (Stone et al. 1979). The NOAEL is 25 $mg.m^{-3}$ Al chlorohydrate corresponding to 6.5 mg $Al.m^{-3}$ (the highest tested dose).

In the study by Gómez et al., Sprague-Dawley rats were exposed to aluminium nitrate through water over one month at doses of 0, 375, 750 or 1500 mg.kg $bw^{-1}.d^{-1}$. A hyperaemia in the red pulp of the spleen was observed in the 750 and 1500 mg.kg $bw^{-1}.d^{-1}$ groups; it was also observed in the liver at the highest dose (Gómez et al. 1986). The LOAEL was 750 mg.kg $bw^{-1}.d^{-1}$ Al nitrate corresponding to 95 mg Al.kg $bw^{-1}.d^{-1}$ and the NOAEL was of 375 mg.kg $bw^{-1}.d^{-1}$ corresponding to 47 mg Al.kg $bw^{-1}.d^{-1}$.

In a study by Domingo et al., Sprague-Dawley rats were exposed to aluminium nitrate over 100 days at doses of 0, 360, 720 or 3600 mg.kg $bw^{-1}.d^{-1}$ through drinking water. Rats exposed to aluminium did not show a difference in haematocrit or haemoglobin levels compared to controls (Domingo et al. 1987b). The NOAEL for haematological effects is 3600 mg.kg $bw^{-1}.d^{-1}$ of aluminium nitrate equivalent to 468 mg Al.kg $bw^{-1}.d^{-1}$ (highest tested dose).

Rats (Sprague-Dawley) exposed to aluminium citrate over 8 months, through drinking water (80 $mmol.L^{-1}$), presented decreased haemoglobin, haematocrit and haptoglobin levels, increased reticulocyte levels, and inhibition of colony-forming units-erythroid (CFU-E) proliferation compared to controls (Vittori et al. 1999). The corresponding LOAEL is 230 mg Al.kg $bw^{-1}.d^{-1}$. Anisocytosis, anisochromia and poikilocytosis were also observed in aluminium exposed rats. Furthermore, in this study, rats exposed to aluminium were not iron depleted (normal range of plasma iron concentration and total iron binding capacity). However, there was a decrease in iron uptake and iron incorporation into haem by the bone marrow cells.

In a study by Zhang et al., male Wistar rats (n=50 per group) received aluminium chloride in their drinking water for up to 150 days at 0 or 430 mg $Al.L^{-1}$ (approximatively 0 and 67-100 mg $Al.kg\ bw^{-1}.d^{-1}$ respectively). Body weight of aluminium treated rats was significantly decreased from day 60, transferrin and total iron binding capacity were significantly higher than in the control group from day 90, and soluble transferrin receptor levels and erythrocyte counts were lower than controls from day 60 (Zhang et al. 2011). The LOAEL was 67 mg $Al.kg\ bw^{-1}.d^{-1}$.

- Guinea pigs

Guinea pigs exposed over 6 months ($5d.wk^{-1}$, $6hr.d^{-1}$) to 0, 0.25, 2.5 or 25 $mg.m^{-3}$ aluminium chlorohydrate (whole body exposed) did not present haematological adverse effects (Steinhagen, Cavender, and Cockrell 1978), resulting in a NOAEL of 6.5 mg $Al.m^{-3}$ (the highest tested dose).

In the study by Stone et al., guinea pigs were exposed over 6 months ($5d.wk^{-1}$, $6hr.d^{-1}$) to 0.25, 2.5 or 25 $mg.m^{-3}$ of aluminium chlorohydrate (whole body exposed). At necropsy, peripheral blood was collected for haematological determinations (total red cells, total white cells, haematocrit, mean corpuscular volume, and total haemoglobin). The authors did not report any haematological effect following this exposure (Stone et al. 1979). The NOAEL was 25 $mg.m^{-3}$ Al chlorohydrate, corresponding to 6.5 mg $Al.m^{-3}$ (the highest tested dose).

- Dogs

Beagle dogs exposed to aluminium phosphate for 6 months through their diet (dietary concentrations of 0, 0.3, 1.0 or 3.0% of sodium aluminium phosphate) had no haematological effects (Katz et al. 1984). In this study haematology, urinalysis and blood chemistry tests were performed in addition to prothrombin and activated partial thromboplastin time measurements. The NOAEL is 88 mg $Al.kg\ bw^{-1}.d^{-1}$. The same goes for Pettersen et al., with beagle dogs exposed to aluminium phosphate over 26 weeks through the diet (0, 0.3%, 1% and 3% of sodium aluminium phosphate). In this study, haematocrit, haemoglobin concentration, erythrocyte, leukocyte and platelet counts were determined but no haematological effects related to the aluminium treatment were observed (Pettersen et al. 1990). The NOAEL is 75 mg $Al.kg\ bw^{-1}.d^{-1}$.

Table 8. Animal studies on aluminium subchronic exposure haematological toxicity

Strain	Al compound	Duration and exposure route	Doses	Endpoint	NOAEL	LOAEL	Reference
Mice							
Swiss-Webster (n= 10 per group)	Aluminium chloride	5-7 weeks Diet	3 (control) or 1000 µg Al.g^{-1} diet	No alteration in haematocrit levels at the highest dose	195 mg Al.kg bw^{-1}.d^{-1}		Oteiza et al. (1993)
Rats							
Fischer-344 (n= 20 per group)	Aluminium chlorohydrate	6 months (5d/wk, 6hr.d^{-1}) Inhalation	0, 0.25, 2.5 or 25 mg.m^{-3}	No haematological adverse effects at the highest dose	6.5 mg Al.m^{-3}		Steinhagen et al. (1978)
Fischer-344 (n≈ 17 per group)	Aluminium chlorohydrate	6 months (5d/wk, 6hr.d^{-1}) Inhalation	0, 0.25, 2.5 or 25 mg.m^{-3}	No haematological adverse effects at the highest dose	6.5 mg Al.m^{-3}		Stone et al. (1979)
Sprague-Dawley (n= 10 per group)	Aluminium nitrate	1 month Water	0, 375, 750 or 1500 mg.kg bw^{-1}.d^{-1}	Hyperaemia in the red pulp of the spleen	47 mg Al.kg bw^{-1}.d^{-1}	95 mg Al.kg bw^{-1}.d^{-1}	Gómez et al. (1986)
Sprague-Dawley (n= 10 per group)	Aluminium nitrate	100 days Water	0, 360, 720 or 3600 mg.kg bw^{-1}.d^{-1}	Haematocrit or haemoglobin levels / No effect was observed at the highest dose	468 mg Al.kg bw^{-1}.d^{-1}		Domingo et al. (1987b)
Sprague-Dawley (Control: n=8; Al	Aluminium citrate	8 months Water	0, 80 mmol.L^{-1}	Decreased haemoglobin, haematocrit & haptoglobin levels, increased reticulocyte levels, and		230 mg Al .kg bw^{-1}.d^{-1}	Vittori et al. (1999)

group: n= 10)				inhibition of CFU-E proliferation			
Wistar (n= 50 per group)	Aluminium chloride	150 days Water	0 and 67-100 mg Al.kg $bw^{-1}.d^{-1}$	Disruption of iron homeostasis		67 mg Al.kg $bw^{-1}.d^{-1}$	Zhang et al. (2011)
Guinea pigs							
Hartley (n= 20 per group)	Aluminium chlorohydrate	6 months (5d/wk, 6hr.d^{-1}) Inhalation	0, 0.25, 2.5 or 25 $mg.m^{-3}$	No haematological adverse effects at the highest dose	6.5 mg $Al.m^{-3}$		Steinhagen et al. (1978)
Hartley (n= 15 per group)	Aluminium chlorohydrate	6 months (5d/wk, 6hr.d^{-1}) Inhalation	0, 0.25, 2.5 or 25 $mg.m^{-3}$	No haematological adverse effects at the highest dose	6.5 mg $Al.m^{-3}$		Stone et al. (1979)
Dogs							
Beagle (n= 12 per group)	Aluminium phosphate	6 months Diet	0, 0.3%, 1% and 3% of sodium Al phosphate	No haematological adverse effects at the highest dose	88 mg Al.kg $bw^{-1}.d^{-1}$		Katz et al. (1984)
Beagle (n= 8 per group)	Aluminium phosphate	26 weeks Diet	0, 0.3%, 1% and 3% of sodium Al phosphate	No haematological adverse effects at the highest dose	75 mg Al.kg $bw^{-1}.d^{-1}$		Pettersen et al. (1990)

4.6.4 Bone related effects

4.6.4.1 **Human data**

No reliable human studies on bone related effects were identified following subchronic exposure to aluminium compounds.

4.6.4.2 **Animal data**

Some animal studies (rats and guinea pigs) have been identified regarding bone related effects after subchronic exposure to aluminium compounds. These studies are described below and summarised in Table 9.

- Rats

In the study conducted by Steinhagen et al., rats (Fischer-344) exposed through inhalation (whole body exposed) to aluminium chlorohydrate (0, 0.25, 2.5 or 25 $mg.m^{-3}$) over 6 months (5 d/wk, $6hr.d^{-1}$) did not present histological changes in the muscle or bone (Steinhagen, Cavender, and Cockrell 1978). The NOAEL was 6.5 mg $Al.m^{-3}$ (the highest tested dose).

Male STD Wistar rats exposed to aluminium lactate in the diet (1 000 µg $Al.g^{-1}$ diet) for 10 weeks did not show pathological changes of bones (Konishi et al. 1996). The NOAEL was 90 mg Al.kg $bw^{-1}.d^{-1}$ (the only tested dose).

In a study by Li et al., four-week-old Wistar rats were exposed to 0 or 430 mg $Al.L^{-1}$ as aluminium chloride in drinking water over 150 days. Every 30 days, 10 rats were sacrificed in each group. From day 60, the body weight of aluminium-treated rats was significantly lower than the control group. In the aluminium treated group, aluminium levels in bone were significantly higher, calcium and magnesium levels in bone were significantly lower from days 120-150 and, phosphorus levels were significantly lower from day 150 compared to the control group. Levels of zinc, iron, copper, manganese, boron, strontium, and selenium in bone also decreased significantly in the aluminium treated group, from day 60. Finally, bone mineral density of the femur metaphysis on days 120 and 150 was significantly lower in the aluminium-treated group from day 120 (Li et al. 2011). The LOAEL is 430 mg $Al.L^{-1}$ equivalent to 38.7 mg Al.kg $bw^{-1}.d^{-1}$ (the only tested dose).

Male Wistar rats were exposed to 0 or 0.4 $g.L^{-1}$ of aluminium chloride (resulting in doses of 0 and 64 mg.kg bw^{-1} $AlCl_3.d^{-1}$) in drinking water for up to 120 days. From day 60, body weights of aluminium-treated rats were significantly lower compared to control group. Aluminium levels in serum and in the femur were significantly higher following aluminium treatment compared to controls. The bone mineral densities of the proximal and the distal femoral metaphysis were significantly lower from day 120 compared to controls and the histological structure of the bone was disrupted from day 90. Aluminium chloride exposure also inhibited the Wnt/β-catenin signalling pathway as the mRNA expression of Wnt3a, Fzd2, LRP-5, β-catenin, Tcf4, cyclin D1 and c-Myc, the protein levels of Wnt3a and β-catenin and the activities of Fzd2 and LRP-5 were decreased in the aluminium-treated rats (Sun et al. 2015). The LOAEL of 64 mg.kg $bw^{-1}.d^{-1}$ of Al chloride is equivalent to 13 mg Al.kg $bw^{-1}.d^{-1}$ (the only tested dose).

In another study by Zhang et al., male Wistar rats received aluminium chloride for 120 days at doses of 0, 0.4, 0.8 or 1.6 $g.L^{-1}$ $AlCl_3$ in drinking water (resulting in 64, 128, 256 mg.kg bw^{-1} $AlCl_3.d^{-1}$). Body weights were decreased in all aluminium-treated groups compared to the control. Rats treated with aluminium had a significant higher content of aluminium in serum and in the cartilage and a significant higher level of C-telopeptide of type II collagen in serum. Serum levels of type II collagen (Col II) and alkaline phosphatase (ALP), and the mRNA expressions of TGF-b1, BMP-2, ALP and Col II were all decreased following aluminium

treatment (F. Zhang et al. 2017). Cartilage histological structure was also disrupted following aluminium treatment. The LOAEL is 64 mg.kg bw^{-1} $AlCl_3.d^{-1}$ is equivalent to 13 mg Al.kg $bw^{-1}.d^{-1}$.

Aluminium chloride was administered to male Wistar rats by gavage at doses of 0 or 8.3 mg.kg $bw^{-1}.d^{-1}$ for 60 days (dose chosen as per the dietary aluminium consumption of humans.d^{-1}). Results of this study showed that aluminium can induce changes in the mineral content and in the mineralised bone microstructure associated with alveolar bone loss (Souza-Monteiro et al. 2021). The LOAEL of 8.3 mg.kg bw^{-1} $AlCl_3.d^{-1}$ corresponds to 1.68 mg Al.kg $bw^{-1}.d^{-1}$.

- Guinea pigs

In the study conducted by Steinhagen et al., Hartley guinea pigs exposed through inhalation (whole body exposed) to aluminium chlorohydrate (0, 0.25, 2.5 or 25 mg.m^{-3}) over 6 months (5 d/wk, 6hr.d^{-1}) did not present histological changes in the muscle or bone (Steinhagen, Cavender, and Cockrell 1978). The NOAEL was 6.5 mg Al.m^{-3} (the highest tested dose).

Table 9. Animal studies on aluminium sub-chronic exposure musculo-skeletal toxicity

Strain	Al compound	Duration or exposure route	Doses	Endpoint	NOAEL	LOAEL	Reference
Rats							
Fischer-344 (n= 20 per group)	Aluminium chlorohydrate	6 months (5d/wk, 6hr.d^{-1}) Inhalation	0, 0.25, 2.5 or 25 mg.m^{-3}	No effect observed at the highest dose	6.5 mg Al.m^{-3}		Steinhagen et al. (1978)
STD Wistar (n= 4-5 per group)	Aluminium lactate	10 weeks Diet	0, 1000 µg Al.g^{-1} diet	No effect observed at the highest dose	90 mg Al.kg bw^{-1}.d^{-1}		Konishi et al. (1996)
Wistar (n=50 per group)	Aluminium chloride	150 days Water	0 or 430 mg Al.L^{-1}	Lower bone mineral density of the femur		38.7 mg Al.kg bw^{-1}.d^{-1}	Li et al. (2011)
Wistar (n=80 per group)	Aluminium chloride	120 days Water	0, 64 mg.kg bw^{-1}.d^{-1}	Lower bone mineral density and disruption of histological structure of femora		13 mg Al.kg bw^{-1}.d^{-1}	Sun et al. (2015)
Wistar (n=20 per group)	Aluminium chloride	120 days Water	0, 0.4, 0.8 or 1.6 g.L^{-1}	Inhibition of cartilage stimulatory growth factors expressions, disruption of cartilage histological structure		13 mg Al.kg bw^{-1}.d^{-1}	Zhang et al. (2017)
Wistar (n=8 per group)	Aluminium chloride	60 days Gavage	0 or 8.3 mg.kg bw^{-1}.d^{-1}	Changes in the mineral content and mineralised bone microstructure, alveolar bone loss		1.68 mg Al.kg bw^{-1}.d^{-1}	Souza-Monteiro et al. (2021)
Guinea pigs							
Hartley (n= 20 per group)	Aluminium chlorohydrate	6 months (5d/wk, 6hr.d^{-1}) Inhalation	0, 0.25, 2.5 or 25 mg.m^{-3}	No effect observed at the highest dose	6.5 mg Al.m^{-3}		Steinhagen et al. (1978)

4.6.5 Other effects

4.6.5.1 **Human data**

No reliable human studies on systemic toxicity were identified following subchronic exposure to aluminium compounds.

4.6.5.2 Animal data

Several animal studies (mice, rats, guinea pigs and dogs), reporting systemic toxicity after subchronic exposure to aluminium compounds, have been identified. These studies are described below and summarised in Table 10.

- Mice

No effects on the body weight were observed:

- in Swiss-Webster mice exposed to 25, 500 or 1000 µg Al.g^{-1} diet as aluminium lactate from Gd1 until Ld21 (NOAEL of 1000 mg.g^{-1} diet corresponding to 330 mg Al.kg bw^{-1}.d^{-1} in dams) (Donald et al. 1989);
- in Swiss-Webster mice exposed to 25 (control), 500, or 1000 µg Al.g^{-1} diet as aluminium lactate over 6 weeks (NOAEL of 1000 mg.g^{-1} diet, corresponding to 130 mg Al.kg bw^{-1}.d^{-1}) (Golub et al. 1989),
- and in Swiss-Webster mice exposed to 25 (control) or 1000 µg Al.g^{-1} diet as aluminium lactate for 90 days (NOAEL of 195 mg Al.kg bw^{-1}.d^{-1}) (Golub et al. 1992b).

A decreased body weight in lactating mice was reported in the study of Golub Keen, and Gershwin, where mice were fed with 25 (control) or 1000 µg Al.g^{-1} diet as aluminium lactate during gestation and from day 1 to day 21 of lactation (LOAEL of 250 mg Al.kg bw^{-1}.d^{-1}) (Golub, Keen, and Gershwin 1992a).

In the study by Oteiza et al., female Swiss-Webster mice exposed to aluminium chloride for 5-7 weeks, in the diet at doses of 3 (control) or 1000 µg Al.g^{-1} diet did not have alterations in body, brain and liver weight (Oteiza et al. 1993). The NOAEL of 1000 µg/g diet corresponds to 195 mg Al.kg bw^{-1}.d^{-1} (the highest tested dose).

In a study by Golub et al., Swiss-Webster mice were exposed to 6 (control) or 1025 µAl.g^{-1} diet as aluminium lactate from conception to 6 months of age. Results showed that aluminium exposed mice presented a 19% increase in spleen weights, depressed spleen cell concentrations of IL-2, INF-g and TNF-a and a deficit of CD4+ cells in T-cell populations (Golub et al. 1993). The LOAEL is 200 mg Al.kg bw^{-1}.d^{-1}.

Pregnant Swiss-Webster mice were exposed through the diet to 25 (control), 500 or 1000 µgAl.g^{-1} diet as aluminium lactate, during gestation and lactation (6 weeks) then, dams and one male and female per litter were inoculated with *Listeria monocytogenes* and were kept on the same diet for 10 days during which they were monitored. The mortality rate was significantly higher in the dams exposed to aluminium compared to the control group and the cumulative deaths were lower in mice treated with 500 µAl.g^{-1} diet compared to the ones treated with 1000 µgAl.g^{-1} diet. In the offsprings challenged after weaning, there was no difference in the mortality between the diet groups (Yoshida et al. 1989). In this same study, virgin female mice exposed to the same amount of aluminium in diets did not have a change in susceptibility to bacterial infection (no statistical significance in mortality).

- Rats

In the study by Steinhagen et al., no histological or organ weight changes were observed in the heart, liver, kidneys, reproductive and gastrointestinal tissues, adrenal, thyroid or pituitary

glands, skin and eyes, and in the body weight of rats (Fischer-344) exposed over 6 months (5d/wk, 6hr.d^{-1}) to 0.25, 2.5 or 25 mg.m^{-3} aluminium chlorohydrate (whole body exposed) (NOAEL : 25 mg.m^{-3} aluminium chlorohydrate, corresponding to 6.5 mg Al.m^{-3}) (Steinhagen, Cavender, and Cockrell 1978).

In the study by Stone et al. (1979), no effects on the body weight of Fischer-344 rats were observed following the inhalation of 0.25, 2.5 or 25 mg.m^{-3} aluminium chlorohydrate over 6 months (whole body exposed), even at the high dose exposure (Stone et al. 1979). The NOAEL was 25 mg.m^{-3} corresponding to 6.5 mg Al.m^{-3}.

In the study conducted by Gómez et al., no organ weight or histopathological changes were observed in the heart, kidney and gastrointestinal tissues and no effect on the body weight of Sprague-Dawley rats exposed to the highest dose of aluminium nitrate through water (1500 mg.kg $bw^{-1}.d^{-1}$) over one month, equivalent to 190 mg Al.kg $bw^{-1}.d^{-1}$. In the liver, a hyperaemia was reported with periportal monocytic infiltrate at the highest dose only (Gómez et al. 1986). Thus, the NOAEL for hepatic effects was considered to be 750 mg.kg bw^{-1} of aluminium nitrate equivalent to 95 mg Al.kg $bw^{-1}.d^{-1}$.

No effects on the body weight were observed in male STD Wistar rats exposed to aluminium lactate in the diet (1000 µg Al.g^{-1} diet) for 10 weeks (Konishi et al. 1996) which corresponds to a NOAEL of 90 mg Al.kg $bw^{-1}.d^{-1}$.

Following oral intake of aluminium nitrate through water at doses of 0, 360, 720 or 3600 mg.kg $bw^{-1}.d^{-1}$ over 100 days in female rats (Sprague-Dawley), Domingo et al., reported no organ weight or histopathological changes in the heart, liver, kidney and no effect on the body weight (Domingo et al. 1987b). The NOAEL of 3600 mg Al nitrate.kg $bw^{-1}.d^{-1}$ corresponds to of 468 mg Al.kg $bw^{-1}.d^{-1}$.

Rats (21 days old and 18 months old) were exposed to aluminium nitrate in water at dose of 0 or 100 mg Al.kg $bw^{-1}.d^{-1}$ (citric acid was added to the water) for 100 days. A decrease in the body weight gain was reported in the aged group (Colomina et al. 2002). The LOAEL is 100 mg Al.kg $bw^{-1}.d^{-1}$.

Male Wistar rats (n=10 per group) were administered 0, 0.4, 0.8 or 1.6 g.L^{-1} of aluminium chloride in their drinking water over a 120-day period. There was a decrease in the superoxide dismutase (SOD) activity of kidney significant only at the highest dose group and a dose dependent decrease in the glutathione peroxidase (GSH-PX) activity of kidney. A dose dependent increase in malondialdehyde, β2-microglobulin and cystatin C concentrations was also observed. Authors concluded that aluminium chloride induces oxidative stress and suppresses kidney function (Liu et al. 2016).

In a study by Zhang et al., aluminium chloride was intragastrically administered to male Wistar rats at doses of 0, 64.18, 128.36 or 256.72 mg.kg bw^{-1} of aluminium chloride for 120 days. There was dose dependent increase in the systolic and mean arterial blood pressure (significant in from the mid dose group), an increase of osmotic fragility of the erythrocyte (significant at high dose only), a decrease in the percentage of the membrane protein (significant from the mid dose for some and at high dose for all), a decrease in activities of $Na(^{+})/K(^{+})$-ATPase, $Mg(^{2+})$-ATPase, $Ca(^{2+})$-ATPase, CAT, SOD and GSH-pX (from the low dose) and an increased malondialdehyde content of erythrocyte membrane (Zhang et al. 2016). In this study, the NOAEL and LOAEL are 64.18 and 128.36 mg.kg bw^{-1} Al chloride.d^{-1} corresponding to 12.8 and 25.7 mg.kg bw^{-1} Al.d^{-1}, respectively.

Male Wistar rats, received aluminium chloride in drinking water, at doses of 0, 0.4, 0.8 or 1.6 mg/mL aluminium chloride (resulting in the doses of $AlCl_3$ at 0, 64, 128, and 256 mg.kg $bw^{-1}.d^{-1}$) for 120 days. Results showed dose-dependent histopathological lesions in the liver. Aluminium exposure reduced the electron transport chain complexes I–V activities and adenosine triphosphate (ATP) level in the liver mitochondria of aluminium-treated rats. The mitochondria DNA transcript levels (measured by measured ND1, ND2, Cyt-b, COX1, COX3

and ATPase6 mRNA expressions) also decreased in the liver following aluminium exposure. Accumulation of reactive oxygen species decreased S activity and increase in 8-OHdG levels in mitochondria were also observed in the aluminium group (Xu et al. 2017). LOAEL was 64 mg.kg bw^{-1} Al chloride.d^{-1} corresponding to 13 mg.kg bw^{-1} aluminium.d^{-1}.

Male Wistar rats were administered aluminium chloride over 60 days at doses of 0 or 8.3 mg Al.kg $bw^{-1}.d^{-1}$ through drinking water or over 42 days at doses of 0 or 100 mg Al.kg $bw^{-1}.d^{-1}$ by gavage. There was a significant increase in systolic blood pressure in the high and low dose group at the third week (but not at the end for the low dose), an increased ROS production from NAD(P)H oxidase, an increase in contractile prostanoids mainly from COX-2 following aluminium exposure, thus inducing vascular dysfunction and increasing blood pressure (Martinez et al. 2017a).

- Guinea pigs

No histological or organ weight change were observed in the heart, liver, kidneys, reproductive and gastrointestinal tissues, adrenal, thyroid or pituitary glands, skin and eyes, and in the body weight of guinea pigs exposed over 6 months, in chambers, (5d/wk, 6hr.d^{-1}) to 0.25, 2.5 or 25 mg.m^{-3} aluminium chlorohydrate (NOAEL = 25 mg.m^{-3} Al chlorohydrate corresponding to 6.5 mg Al.m^{-3}) (Steinhagen, Cavender, and Cockrell 1978).

In the study by Stone et al., no effects on the body weight of guinea pigs were observed following the inhalation of a 0.25, 2.5 or 25 mg.m^{-3} aluminium chlorohydrate (in chambers) over 6 months, even at the high dose exposure. The NOAEL was 25 mg.m^{-3} Al chlorohydrate, corresponding to 6.5 mg Al.m^{-3} (Stone et al. 1979).

- Dogs

Following dietary exposure (in the feed) to aluminium phosphate, the NOAEL for some systemic effects in dogs were 75 and 88 mg Al.kg $bw^{-1}.d^{-1}$, respectively in the study of Pettersen et al. (exposure for 26 weeks, no difference in organ weight of the heart, kidneys, thyroid, adrenals) and the one of Katz et al. (exposure for 6 months, no difference in organ weight or histopathological changes in the heart, liver, kidneys, pituitary, thyroid, adrenals and no ocular changes) (Katz et al. 1984; Pettersen et al. 1990).

Table 10. Animal studies on aluminium sub-chronic exposure systemic toxicity

Strain	Al compound	Duration and exposure route	Doses	Endpoint	NOAEL	LOAEL	Reference
Mice							
Swiss-Webster (n= 16 per group)	Aluminium lactate	Gd1-Ld21 Diet	25 (control), 500 or 1000 µg Al.g^{-1} diet	Body weight of dams / No effect observed at the highest dose	330 mg Al.kg bw^{-1}.d^{-1}		Donald et al. (1989)
Swiss-Webster (n= 5 per group)	Aluminium lactate	6 weeks Diet	25 (control), 500 or 1000 µg Al.g^{-1} diet	Body weight / No effect observed at the highest dose	130 mg Al.kg bw^{-1}.d^{-1}		Golub et al. (1989)
Swiss-Webster (n= 12 per group)	Aluminium lactate	90 days Diet	25 (control) or 1000 µg Al.g^{-1} diet	Body weight / No effect observed at the highest dose	195 mg Al.kg bw^{-1}.d^{-1}		Golub et al. (1992b)
Swiss-Webster (Control: n= 14; Al group: n= 9)	Aluminium lactate	Gd1-Ld21 Diet	25 (control) or 1000 µg Al.g^{-1} diet	Body weight of lactating mice		250 mg Al.kg bw^{-1}.d^{-1}	Golub et al. (1992a)
Swiss-Webster (n= 10 per group)	Aluminium chloride	5-7 weeks Diet	3 (control) or 1000 µg Al.g^{-1} diet	Body, brain and liver weight / No effect observed at the highest dose	195 mg Al.kg bw^{-1}.d^{-1}		Oteiza et al. (1993)
Swiss-Webster	Aluminium lactate	Gd0- PND 180 Diet	6 (control) or 1025 µAl.g^{-1} diet	Increased spleen weights, Depressed spleen cell concentrations of IL-2, IFN-g and TNF-a and a deficit of		200 mg Al.kg bw^{-1}.d^{-1}	Golub et al. (1993)

(n=10-11 per group)				CD4+ cells in T-cell populations			
Rats							
Fischer-344 (n= 20 per group)	Aluminium chlorohydrate	6 months Inhalation	0, 0.25, 2.5 or 25 $mg.m^{-3}$	Histological / weight change of heart, liver, kidneys, reproductive and gastrointestinal tissues, adrenal, thyroid, pituitary glands, skin and eyes and in the body weight / No effect observed at the highest dose	6.5 mg $Al.m^{-3}$		Steinhagen et al. (1978)
Fischer-344 (n≈ 17 per group)	Aluminium chlorohydrate	6 months Inhalation	0, 0.25, 2.5 or 25 $mg.m^{-3}$	Body weight / No effect observed at the highest dose	6.5 mg $Al.m^{-3}$		Stone et al. (1979)
Sprague-Dawley rats (n= 10 per group)	Aluminium nitrate	1 month Water	0, 375, 750, 1500 mg.kg $bw^{-1}.d^{-1}$	Weight or histopathological changes in the heart, kidney and gastrointestinal tissues and body weight	190 mg Al.kg $bw^{-1}.d^{-1}$		Gómez et al. (1986)
				Hyperaemia with periportal monocytic infiltrate in the liver	95 mg Al.kg $bw^{-1}.d^{-1}$	190 mg Al.kg $bw^{-1}.d^{-1}$	
STD Wistar (Control: n= 5; Al group: n= 4)	Aluminium lactate	10 weeks Diet	0 or 1000 µg $Al.g^{-1}$ diet	No effect on the body weight at the highest tested dose	90 mg Al.kg $bw^{-1}.d^{-1}$		Konishi et al. (1986)
Sprague-Dawley (n= 10 per group)	Aluminium nitrate	100 days Water	0, 360, 720 or 3600 mg.kg $bw^{-1}.d^{-1}$	No weight or histopathological changes in the heart, liver, kidney and the body weight at the highest tested dose	468 mg Al.kg $bw^{-1}.d^{-1}$		Domingo et al. (1987b)
(NS)	Aluminium nitrate	100 days Water	0 or 100 mg.kg $bw^{-1}.d^{-1}$	Decreased body weight		100 mg Al.kg $bw^{-1}.d^{-1}$	Colomina et al. (2002)

(n=16 per group)			+ citric acid added				
Wistar (n= 20 per group)	Aluminium chloride	120 days Gavage	0, 64.18, 128.36 or 256.72 mg.kg $bw^{-1}.d^{-1}$	Increase in the systolic and mean arterial blood pressures	12.8 mg Al.kg $bw^{-1}.d^{-1}$	25.7 mg Al.kg $bw^{-1}.d^{-1}$	Zhang et al. (2016)
Wistar (n=10 per group)	Aluminium chloride	120 days Water	0, 64, 128, and 256 mg.kg $bw^{-1}.d^{-1}$	Histopathological lesions in the liver		13 mg Al.kg $bw^{-1}.d^{-1}$	Xu et al. (2017)
Wistar (n=10 per group)	Aluminium chloride	42 days High dose Gavage	0 or 100 mg Al.kg $bw^{-1}.d^{-1}$	Increase in systolic blood pressure		8.3 mg Al.kg $bw^{-1}.d^{-1}$	Martinez et al. (2017a)
		60 days Low dose Water	0 or 8.3 mg Al.kg $bw^{-1}.d^{-1}$				
Guinea pigs							
Hartley (n= 20 per group)	Aluminium chlorohydrate	6 months Inhalation	0, 0.25, 2.5 or 25 $mg.m^{-3}$	No histological / weight change of heart, liver, kidneys, reproductive and gastrointestinal tissues, adrenal, thyroid, pituitary glands, skin and eyes and in the body weight at the highest dose tested	6.5 mg $Al.m^{-3}$		Steinhagen et al. (1978)
Hartley (n= 15 per group)	Aluminium chlorohydrate	6 months Inhalation	0, 0.25, 2.5 or 25 $mg.m^{-3}$	No effect on the body weight at the highest tested dose	6.5 mg $Al.m^{-3}$		Stone et al. (1979)
Dogs							

Beagle (n= 12 per group)	Aluminium phosphate	6 months Feed	0, 0.3%, 1% and 3% of sodium Al phosphate	No effect on organ weight or changes in the heart, liver, kidneys, pituitary, thyroid, adrenals or ocular changes at the highest dose	88 mg Al.kg $bw^{-1}.d^{-1}$		Katz et al. (1984)
Beagle (n= 8 per group)	Aluminium phosphate	26 weeks Feed	0, 0.3%, 1% and 3% of sodium Al phosphate	No effect on organ weight of the heart, kidneys, thyroid, adrenal at the highest dose	75 mg Al.kg $bw^{-1}.d^{-1}$		Pettersen et al. (1990)

4.7 Chronic toxicity

4.7.1 Neurotoxicity

4.7.1.1 Human data

Epidemiological studies assessing internal aluminium dose (at least aluminium levels in whole blood, plasma, serum or urine) and cognitive impairment are described here. A total of 21 cross-sectional and 4 longitudinal studies were identified, all of which focused on occupational exposure in different aluminium industries. Epidemiological studies provided insufficient data on aluminium concentrations in the air.

It is worth noting that most, if not all, of the studies conducted in China were carried out in the same aluminium plant, and that little information was given on the crossover of volunteers between these studies (Guo et al. 1999; He, Qiao, and Sheng 2003; Yang et al. 2015; Meng et al. 2019; Wang et al. 2020; Lu et al. 2021; Zhang et al. 2021; Shang et al. 2021; Z. Y. Zhang et al. 2022; Zhao et al. 2022).

Hosovski et al. (1990):

One-hundred-and-forty-seven (147) workers from an aluminium foundry were included in a cross-sectional study conducted in Poland (Hosovski et al. 1990). The exposed workers had a cumulative exposure of at least 6 years (12±4.5) and a job seniority of 18.9±6.9 years, which is comparable to the non-exposed workers group (n=60). Aluminium concentrations at workplaces had been measured for each worker separately during winter and summer. Concentrations were ranging from 4.6 to 11.5 $mg.m^{-3}$. Number and size of dust particles were also measured, the number of particles was of 329 to 1020/cm^3 and 65.6% of dust particles measured up to 1 µm and 26.6% 1 to 5 µm.

All workers were hospitalized for 5 days, during which time aluminium concentrations in whole blood and urine were determined by flameless atomic absorption spectrometry. Psychomotor performance was assessed using the Turners apparatus, by recording the number of errors and speed of test execution. Intellectual performance was assessed using the Wechsler test, and a quotient of verbal intelligence, performance intelligence and total intelligence was established. The use of alcohol and psychotropic drugs in the month prior to testing was considered an exclusion criterion, and no other confounding factors were considered.

Mean whole blood aluminium concentration in exposed workers was 136.85±103.15 $µg.L^{-1}$ and mean urine aluminium concentration 45.38±55.01 $µg.L^{-1}$, while in the unexposed group, whole blood aluminium concentration was 58.09±74.73 $µg.L^{-1}$ and urine aluminium concentration 7.25±7.82 $µg.L^{-1}$. The high blood aluminium levels measured both in exposed workers and in controls are probably indicative of an external contamination of the samples (or of faulty analysis).

Aluminium-exposed workers showed significant dissociation in oculomotor coordination, prolonged complex reaction times and slower psychomotor abilities. The results of the Wechsler test of intellectual ability showed impaired memory, coding, image completion and object assembling, associated with aluminium exposure.

Bast-Pettersen et al. (1994):

A cross-sectional study was conducted in a Norwegian primary aluminium plant (Bast-Pettersen et al. 1994). It included 22 workers exposed to aluminium (14 potroom workers and 8 foundry workers) and 16 controls from other departments of the same plant and never directly exposed to aluminium. All participants were 61-66 years-old and had been employed for at least 10 years in the plant (and exposed for at least 10 years to aluminium for participants from the exposed group). In both groups, exclusion criteria were: occupational exposure to other neurotoxicants, personal history of neurological disease or diabetes.

Measurements of aluminium in serum and urine and administration of psychometric tests were performed just before or soon after retirement. The methods used for aluminium analysis are not specified in the published article.

Disturbances of subjective well-being were assessed by a symptom questionnaire (Q16). A comprehensive neuropsychological exploration was performed to assess psychomotor function. It included the evaluation of static steadiness, simple visual reaction time, Wechsler adult intelligence scale (WAIS) digit symbol substitution test, trail making test, Benton visual retention test, WAIS digit span, Words learning and retention, WAIS information test, WAIS similarities test, WAIS vocabulary test, WAIS picture completion test and WAIS block design test.

Mean urine aluminium levels were 12.6 $\mu g.L^{-1}$ in potroom workers, 9.9 $\mu g.L^{-1}$ in foundry workers and 7.8 $\mu g.L^{-1}$ in controls. The corresponding values for serum aluminium were 3.6 $\mu g.L^{-1}$, 4.1 $\mu g.L^{-1}$ and 2.9 $\mu g.L^{-1}$.

Exposed workers reported more neuropsychiatric symptoms. The results also suggest increased risk of impaired visuo-spatial organisation in exposed workers but the differences with controls did not attain statistical significance, possibly due to the low numbers of exposed and control participants.

Guo et al. (1999):

A Chinese cross-sectional study compared 103 aluminium-exposed workers and 64 controls, using the WHO recommended Neurobehavioral Core Test Battery (NCTB). Exposed workers were employees of a large aluminium production plant, working in the electrolysis, smelting or welding departments for at least 5 years. Controls worked in other departments, were not exposed to aluminium and were matched on age, duration of employment, education level, drinking status and smoking status.

Urinary aluminium was measured using graphite furnace absorption spectrometry, in post-shift samples (any day of the workweek). The mean (range) levels of aluminium in the exposed and control groups were 41.8 $\mu g.g^{-1}$ creatinine (14-9-116.2 $\mu g.g^{-1}$ creatinine) and 17.7 $\mu g.g^{-1}$ creatinine (3.5-42.8 $\mu g.g^{-1}$ creatinine) respectively.

The NCTB includes a Profile of mood states (POMS) questionnaire. The mean scores of the 5 negative mood variables (tension, depression, anger, fatigue and confusion) of the POMS questionnaire were higher in workers exposed to aluminium and the difference was statistically significant for tension, depression, anger and fatigue for the older (45-60 years) participants. The scores of the psychometric tests were inconsistently impaired: significant differences between exposed workers and the referent group were observed: for the digit span test, only in 25-34 year-old participants; for the digit symbol test, only in 35-44 year-old participants; for the pursuit aiming test both in 35-44 and 45-60 year-old participants (Guo et al. 1999).

Sjögren et al. (1996) ; Iregren et al. (2001):

Iregren et al., summarised data from three different studies conducted in Sweden, in order to assess the effects of aluminium exposure on the nervous system in groups of aluminium

workers in different industries including aluminium potroom and foundry workers (n=119), aluminium welders (n=38), and workers exposed to aluminium in the production of flake powder (n=16). Data for these groups were compared with those of mild steel welders without exposure to aluminium (n=39). Both the welders and the smelters were significantly older and had been employed for longer periods. Alcohol consumption and habits did not differ between the groups; educational level was not reported for all the groups.

Measurements of aluminium concentrations in blood and urine were performed by GFAAS (detection limit < 1 $\mu g.L^{-1}$). The concentrations of aluminium in urine of the welders after the shift were calculated according to an equation determined in a previous study (Ljunggren et al. 1991). All biological samples from the smelter workers were collected at least 16 hours after their latest exposure. The samples from most of the flake powder production workers were collected after 5 exposure free days. Concentrations of neurotoxic metals manganese and lead in blood were also measured as they might confound the study results.

A questionnaire on exposure was carried out in addition to other rating scales to measure symptoms and mood. Performance was assessed in all four groups by a couple of tests including: simple reaction time, finger tapping speed, finger tapping endurance, digit span, vocabulary, tracking, and symbol digit coding and the Luria-Nebraska motor scale and a board test (cylinders) for motor function assessment. Some neuro-physiological examinations have also taken place (diadochokinesometric measurements and electroencephalography (EEG)).

Age differences between the groups were controlled by forcing age into the regression before entering the group variables simultaneously.

The median aluminium concentration in urine was 4.7 $\mu g.g^{-1}$ creatinine in the reference group and 4.2, 59.0 and 24.0 $\mu g.g^{-1}$ creatinine for the smelters, flake powder exposed workers and welders, respectively. In blood (not specified if whole blood, serum or plasma), median concentrations of aluminium were 1.0 (range LOD-11), 1.0 (LOD-18), 9.0 (LOD-21) and 3.0 (LOD-27) $\mu g.L^{-1}$ in the reference group, smelters, flake powder exposed workers and welders, respectively.

The regression analyses showed a higher prevalence of CNS symptoms for the group exposed to flake powder and the smelters compared with the steel welders. Significant group differences were found for the peg board test (cylinders), the tracking task, and the simple reaction time between aluminium smelters and mild steel welders. Workers exposed to flake powders had also a significantly different result of the tracking task compared to the reference group; their performances in the cylinder peg board test and the simple reaction time were also altered but the differences did not attain statistical significance, possibly due to a lack of power resulting of the low number of flake powder workers (n=12). In any case, there were no correlations between aluminium concentrations in urine or blood and the outcome measures. Thus, the differences between steel welders and aluminium smelters can be explained by other factors than aluminium since the groups are not comparable (Iregren et al. 2001; Sjögren et al. 1996).

Akila et al. (1999):

Akila et al., conducted a cross-sectional study among 51 asymptomatic aluminium welders, in Finland. The control group was constituted of 28 age-matched mild steel welders. The mean age of the 79 male workers was 38.4 (range 22–58). Aluminium was measured in serum and urine, using graphite furnace absorption spectrometry, with Zeeman background correction. On the basis of urinary aluminium concentrations, welders were classified into three exposure groups: reference group (n=28) <1 $\mu mol.L^{-1}$ (mean=0.46 $\mu mol.L^{-1}$) ; < 27 $\mu g.L^{-1}$ (mean=12.4 $\mu g.L^{-1}$), low exposure group (n=27) 1.1–4.0 $\mu mol.L^{-1}$ (mean=2.25 $\mu mol.L^{-1}$); 27-108 $\mu g.L^{-1}$ (mean=60.7 $\mu g.L^{-1}$) and high exposure group (n=24) >4.1 $\mu mol.L^{-1}$ (mean=9.98 $\mu mol.L^{-1}$); >

108 µg.L^{-1} (mean=269.3). Age was positively correlated with both urinary (r=0.267, p=0.017) and serum (r=0.349, p=0.002) aluminium. Alcohol consumption correlated with urinary aluminium (r=0.264, p=0.019).

A comprehensive neuropsychological exploration was performed to assess psychomotor function. Five main cognitive domains were investigated with different tests: psychomotor functions (Finger tapping speed, Santa Ana dexterity test, Simple visual reaction time (RT)), attention (WAIS: digit span task, WAIS-R: digit symbol substitution test, Stroop colour word test, Dual task), verbal abilities (WAIS Similarities, Synonyms), visuospatial skills (Embedded figures, WAIS: block design test) and memory and learning (Wechsler memory scale (WMS): paired associates, Memory for designs, Interference recall, Similarities recall, Digit symbol recall).

Aluminium welders showed no impairment on the finger tapping, Santa Ana dexterity, simple visual reaction times, any of the verbal memory tasks, the similarities subtest of Wechsler adult intelligence scale, or the Stroop task.

An exposure-dependent impairment of the performance was observed in the welders of the high exposure group for the memory for Digit symbol substitution test (p=0.025, p=0.035 after controlling for age), Item selection time (p=0.027) and Block design (p=0.036). For Embedded figure task, the effect was close to the significance threshold (p=0.055) but not significant. For memory design task, welders from the high exposure group performed lower (p=0.036) but the effect was not exposure dependent.

For the dual task, an impairment of Backward counting (p=0.016) was observed also with the higher exposure group but both in dual and single task conditions, with an exposure-dependent effect.

The authors conclude that the neuropsychological exploration showed that the effects of aluminium appeared circumscribed. Neuropsychological tasks were investigated to precise the cognitive structures impaired. It was observed that performance deficiencies were mainly detected in tasks requiring working memory, particularly those involving visuospatial information. It was also shown that such impairments were more readily found in time-limited tasks involving visually presented material, in which effective visual scanning combined with control of working memory is demanded (Akila, Stollery, and Riihimäki 1999).

Hänninen et al. (1994), Riihimäki et al. (2000):

In a Finnish cross-sectional study, the relationship between elevated internal aluminium load and central nervous system function was studied in 65 aluminium welders and a referent group of 25 mild steel welders. Aluminium was measured in serum and urine, using graphite furnace absorption spectrometry, with Zeeman background correction. Sampling was performed on Monday morning before the 1st shift of the week. In the referent group, serum aluminium ranged from 0.04 to 0.12 µmol.L^{-1} (1-3.2 µg.L^{-1}) and urine aluminium from 0.1 to 1.3 µmol.L^{-1} (2,7-35.1 µg.L^{-1}), median values were 0.08 µmol.L^{-1} (2.2 µg.L^{-1}) and 0.4 µmol.L^{-1} (10.8 µg.L^{-1}), respectively. A low and a high exposure groups of aluminium welders were defined, according to serum and urine aluminium levels: median (and range) values for serum aluminium concentrations, in the low and high exposure groups were 0.14 µmol.L^{-1} (0.07-0.24 µmol.L^{-1}; 3.8 µg.L^{-1} (1.9-6.5 µg.L^{-1})) and 0.46 µmol.L^{-1} (0.27-1.00 µmol.L^{-1}; 12.4 µg.L^{-1} (7.3-27 µg.L^{-1})), respectively. The corresponding values for urine aluminium concentrations were 1.8 µmol.L^{-1} (0.3-5.7 µmol.L^{-1}; 48.6 µg.L^{-1} (8.1-153.9 µg.L^{-1})) and 7.1 µmol.L^{-1} (3.2-27.3 µmol.L^{-1}; 191.7 µg.L^{-1} (86.4-737.1 µg.L^{-1})).

Disturbances of subjective well-being were assessed by a symptom questionnaire. A comprehensive neuropsychological exploration was performed to assess psychomotor function. Five main cognitive domains were investigated with different tests: psychomotor

functions (Finger tapping speed, Santa Ana dexterity test, Simple visual RT), attention (WAIS: digit span task, WAIS-R: digit symbol substitution test, Stroop colour word test, Bourdon Wiesma cancellation test, Dual task), verbal abilities (WAIS Similarities, Synonyms), visuospatial skills (Embedded figures, WAIS: block design test) and memory and learning (WMS: paired associates, Memory for designs, Homogeneous interference, Similarities recall, Digit symbol recall). Quantitative electroencephalography was also recorded, and P300 auditory event-related potentials were studied.

There was an exposure-related increase in reported fatigue, mild depression and memory or concentration problems. Neuropsychological testing revealed exposition-related impairments of cancellation accuracy in the Bourdon-Wiesma test, of backwards counting, of both components of the dual task, of synonyms and of memory for designs; those impairments were detectable in both the low and high exposure groups and increased with the exposure. Significant, age-adjusted correlations were observed between impairments in Digit symbol test, counting backwards, Dual task cancellation speed and Dual task counting speed, on one hand and urine aluminium concentration on the other hand. Visual EEG analysis revealed mild diffuse abnormalities only in aluminium welders. No statistically significant differences were observed between the groups in the quantitative analysis. No significant association was observed between serum or urine aluminium concentration and P300 amplitude or latency (Hänninen et al. 1994; Riihimäki et al. 2000).

Bast-Pettersen et al. (2000):

In a Norwegian cross-sectional study, 20 aluminium welders (mean age 33 years), who had been exposed to aluminium for an average of 8.1 years, were tested for tremor and simple reaction time and screened for neuropsychiatric symptoms. They were compared with 20 construction workers matched for age. Exclusion criteria in both groups were diseases affecting the CNS and exposure to solvents.

Urinary aluminium was measured using graphite furnace absorption spectrometry, with Zeeman background correction, in pre-shift and post-shift samples. Subjective symptoms were recorded by means of the self-administered Q16 questionnaire. Hand steadiness was measured by the Klove-Matthews Static Steadiness Test (SST). Reaction times were measured by two computerised test (Simple reaction time and Continuous performance test).

The median (range) urinary aluminium concentrations were 0.15 µmol/mmol creatinine (0.06-0.43 µmol/mmol creatinine; 35.8 $\mu g.g^{-1}$ creatinine; 14.3-109.9 $\mu g.g^{-1}$ creatinine). Urinary aluminium was not measured in controls.

Aluminium welders reported significantly more symptoms than controls did. Although they globally performed better than controls on the tremor test, years of exposure (but not age) was associated with poorer performance (Bast-Pettersen et al. 2000).

Letzel et al. (2000):

A longitudinal study consisting of two successive cross-sectional studies was conducted at a German aluminium powder-producing plant to evaluate possible exposure-related nervous system effects. In the first examination, 32 workers exposed to aluminium dust were compared to a control group of 30 unexposed persons; groups did not differ in age, sex, level of education or professional training. No exclusion criteria are reported. Five years later, in the second examination, only 21 of the exposed workers and 15 controls agreed to continue the study; this selection led to a difference in age and educational level between the two evaluations. Assessments mainly included biomonitoring, standardised medical history, neuropsychological tests (vocabulary test, three subtests of the Wechsler Adult Intelligence

Survey (digit span, digit symbol, and block design), the trail making test, the syndrome short test and a visual discriminative reaction task. An event-related P300 potential was also measured. The methods for aluminium measurements in plasma and urine are not presented in the article. There was no concurrent intake of aluminium-containing medications, but two individuals in the initial assessment had a history of drug abuse or brain contusion, and high alcohol consumption was reported in some individuals in both groups.

Internal aluminium levels were significantly higher in the exposed group in both assessments (sampling time and analytical method not specified). Notably, in the first examination, median urine aluminium levels were 87.6 $\mu g.g^{-1}$ creatinine in exposed workers vs 9.0 $\mu g.g^{-1}$ creatinine in the control group, with median plasma aluminium of 8.7 $\mu g.L^{-1}$ in the exposed group versus 4.3 $\mu g.L^{-1}$ in the controls. In the second examination, median urine aluminium levels were 19.8 $\mu g.g^{-1}$ creatinine in exposed workers vs 4.5 $\mu g.g^{-1}$ creatinine in the control group, with median plasma aluminium of 6.7 $\mu g.L^{-1}$ in the exposed group vs 4.3 $\mu g.L^{-1}$ in the controls (with no significant difference in this latter group). The difference between both examinations is explained by improved occupational hygiene. Regarding the psychometric tests and the P300 potentials, there was no significant exposure-related differences in any of the two cross-sectional studies. There was also no dose-response relationship between plasma or urinary aluminium concentrations, or aluminium exposure length on one hand and psychometric or P300 parameters, on the other hand (Letzel et al. 2000).

Polizzi et al. (2002):

A cross-sectional case-control study was carried out in 64 former Italian aluminium dust-exposed workers and in 32 unexposed controls. All participants were retired for at least 10 years. The control group included workers (from other industries), with a similar profile of age, education level, socio-economic status and clinical features. Subjects taking aluminium-containing drugs or drugs acting on the central nervous system, with kidney problems, or with a history of head trauma or psychological, sleep or neurological disorders, were excluded.

Serum aluminium was measured by GFAAS. Serum concentrations of copper and zinc and whole blood concentrations of iron, lead and manganese were simultaneously assessed. The cognitive assessment included a standardised occupational and medical questionnaire and the MMSE (Mini-Mental State Examination) test and, the CDT (Clock Drawing Test, testing visuospatial, abstraction, language and memory abilities). Auditory evoked event-related potentials (ERP-P300) were also measured.

There was a significant difference ($p<0.001$) between the mean serum aluminium concentrations in the workers' group (14.1 ± 3.50 $\mu g.L^{-1}$) and the control group (8.2 ± 1.17 $\mu g.L^{-1}$). It should be noted that blood iron levels were also higher in the workers' group. The results of the neuropsychological tests were also significantly different between the 2 groups, with a negative correlation between serum aluminium and the MMSE, MMSE-AE (adjusted for age and education) and CDT scores, and a positive correlation between serum aluminium and the MMSE and CDT times, confounders being taken into account. ERP-P300 latency was also found to correlate positively with serum aluminium concentration (Polizzi et al. 2002).

He et al. (2003):

In a cross-sectional study, He et al. (2003) studied neurobehavioral parameters, autonomic nervous function and lymphocyte subsets in 33 workers from a Chinese aluminium plant and 34 controls from a flour mill. Exclusion criteria were history of neurological disease, heart disease, hypertension, diabetes or renal disease, alcohol consumption ≥500 mL/week or cigarette smoking ≥ 40/j.

Urinary aluminium was measured using graphite furnace absorption spectrometry, in “morning” samples. Neurobehavioral test battery included a standardised questionnaire on mood state, and psychometric tests: Simple reaction time measurement, digital symbol test, Santa Ana dexterity test, digital span test, Benton visual retention test, and pursuit aiming.

Mean urine aluminium concentrations in the exposed workers and the control group were 40.1 $\mu g.g^{-1}$ creatinine and 26.8 $\mu g.g^{-1}$ creatinine, respectively. Reaction time was significantly slower in exposed workers. Also, the scores of the digital symbol test, the pursuit aiming were significantly lower in the aluminium-exposed group (He, Qiao, and Sheng 2003).

Buchta et al. (2003); Kiesswetter et al. (2009):

A longitudinal study, involving aluminium welders from a car-body construction industry in Germany who were not exposed to other possible neurotoxic substances, was conducted over 4 years during which three examinations were carried out, separated by 2 years, in 1999, 2001 (Buchta et al. 2003) and 2003 (Kiesswetter et al. 2009). A total of 98 aluminium welders in 1999, 97 in 2001 and 92 in 2003 were compared to a demographically similar control group of 50 subjects from the same industry (age, level of education and level of carbohydrate-deficient transferrin in plasma). At the first examination, included subjects had at least 2 years of Al-welding time. Subjects with neurological diseases not due to the exposure, cerebrovascular diseases, diabetes, head injuries, insufficient knowledge of the German language were excluded.

Aluminium concentrations were measured in personal air, as well as in plasma and in urine, in pre-shift and post-shift samples after several shifts, by GFAAS. Workers were examined during the day shift between 08:00 and 13:00 h, only if they had worked on the morning or afternoon shift the week before. Neurobehavioral assessments used a standardised interview, the Standard Progressive Matrices test (SPM) (only in the 1st examination), a verbal intelligence test (WST), and the European neurobehavioral evaluation system (EURO-NES) (these 3 tests, only for the last 2 examinations), a simple reaction time test, the block design test, the trail making test, four psychomotor performance tests (testing for steadiness, line tracing, aiming and tapping, and a recall of digits test (HAWIE) (the last test, performed in the 3 examinations).

There was no significant difference of total dust load when welding aluminium between the three examinations (p= 0.35), the same applies for the pre- and post-shift internal Al-loads in exposed welders across examinations. In welders, median (min, max) aluminium urine concentration (post-shift) was 37.87 (7.0–120.5) $\mu g.g^{-1}$ creatinine (1999), 33.57 (9.0–230.11) $\mu g.g^{-1}$ creatinine (2001) and 15.4 (0.7-94.9) $\mu g.g^{-1}$ creatinine (2003). Median plasma aluminium (post-shift) was 8.3 (2.3–42.3) $\mu g.L^{-1}$ (1999), 4.1 (0.72–11.7) $\mu g.L^{-1}$ (2001) and 4.3 (1.8-15.6) $\mu g.L^{-1}$ (2003). Median (min-max) aluminium urine concentration in control group was 5.2 (1.7-30.3) $\mu g.g^{-1}$ creatinine (1999), 6.0 (1.6-390.0) $\mu g.g^{-1}$ creatinine (2001) and 5.0 (0.2-40.3) $\mu g.g^{-1}$ creatinine (2003), and median (min-max) plasma concentration was 4.4 (1.4-31.6) $\mu g.L^{-1}$ (1999), 2.3 (0.7-5.9) $\mu g.L^{-1}$ (2001) and 3.8 (1.6-10.0) $\mu g.L^{-1}$ (2003).

Welders and controls did not report significantly more symptoms in the modified questionnaire Q16. Furthermore, no significant differences in psychomotor performance and other neurobehavioral tasks, except for reaction time, were seen between welders and non-welders. Aluminium welders were slightly slower than controls in their reactions (decision time) but quicker in their motor movements. The corresponding multivariate analysis of covariance for repeated measurements included both test parameters in one model. This model indicates a significant group difference (p= 0.015). There was a significant influence of age (p<0.001). As the only abnormal results in all 3 examinations were for simple reaction time and puzzling (the lower performance in one test component being compensated by better performance in the other test component), as these effects did not increase with exposure duration and as

confounding factors were present, the authors conclude that their study shows no adverse neurobehavioral effect of aluminium exposure.

Buchta et al. (2005); Kiesswetter et al. (2007):

In a longitudinal study (Buchta et al. 2005; Kiesswetter et al. 2007), exposure and neurobehavioral data of 44 aluminium exposed male welders and 37 controls from the same five German companies in the train and truck construction industry were examined for 4 years (1999, 2001 and 2003) and compared. Pre-shift and post-shift aluminium measurements were performed in the plasma and urine after several shifts, using graphite furnace absorption spectrometry (GFAS). Neurobehavioral assessments used standardised interview, physical examination, a verbal intelligence test (WST), the German version of Q16 questionnaire; a recall of digits test, a block design test, a computerised test battery for motor performance, a simple reaction time measurement, a German version of the standard progressive matrices test, a trail making test, and the EURO-NES.

In welders, median urinary and plasma post-shift levels were 130 $\mu g.L^{-1}$ or 97 $\mu g.g^{-1}$ creatinine (n= 31) and 11.6 $\mu g.L^{-1}$ (n= 31) in 1999, 145.5 $\mu g.L^{-1}$ or 143.9 $\mu g.g^{-1}$ creatinine (n= 25) and 14.3 $\mu g.L^{-1}$ (n= 25), in 2001, and 93.7 $\mu g.L^{-1}$ or 64.5 $\mu g.g^{-1}$ creatinine (n= 20) and 13.2 $\mu g.L^{-1}$ (n= 20) in 2003. The corresponding mean values were: 210 $\mu g.L^{-1}$ or 135.5 $\mu g.g^{-1}$ creatinine and 14.8 $\mu g.L^{-1}$ in 1999; 191.5$\mu g.L^{-1}$ or 153 $\mu g.g^{-1}$ creatinine and 18.6 $\mu g.L^{-1}$ in 2001; 155.7 $\mu g.L^{-1}$ or 113.5 $\mu g.g^{-1}$ creatinine and 17.8 $\mu g.L^{-1}$ in 2003. In the control group, median values were 5.8 $\mu g.L^{-1}$ or 4 $\mu g.g^{-1}$ creatinine in urine and 3.5 $\mu g.L^{-1}$ in plasma, in 1999; 6 $\mu g.L^{-1}$ or 4.5 $\mu g.g^{-1}$ creatinine in urine and 2.8 $\mu g.L^{-1}$ in plasma, in 2001; 8.3 $\mu g.L^{-1}$ or 8.5 $\mu g.g^{-1}$ creatinine in urine and 4.5 $\mu g.L^{-1}$ in plasma, in 2003.

In 2003, the aluminium welders who had been working in this profession for an average of 15 years had no increased symptom level. The only significant difference between welders and controls was observed for block design test scores, the welders revealing significantly lower scores than controls. It should be observed that verbal IQ (WST), performances in the SPM test, in the trail making test, in the line tracing test and in switching attention tasks were also lower in welders though the intergroup differences were not statistically significant. Regression and covariance analyses showed no correlation between biomonitoring parameters and cognitive performance variables. As only 20 welders and 12 controls were included in the 2003 analysis, these negative (statistically non-significant) results could be due to the low power of the study. The authors also discuss the possibility of a healthy worker effect, workers developing symptoms might have left the plant.

Giorgianni et al. (2014):

Giorgianni et al., looked for an association between serum aluminium level and cognitive impairment in 86 male aluminium welders from an Italian shipyard and in 90 controls from the administrative department of the same company. Serum aluminium concentration was measured using atomic absorption spectrometry. Serum concentrations of chromium, lead manganese and zinc were simultaneously measured. Neuropsychological evaluation used the WMS (form I), the Colour-Word test (Stroop test), the Attention Matrixes test. Mean ages of controls and exposed welders were 38.29±7.14 years and 38.45±6.34 years, respectively. All participants were non-smokers. Duration of aluminium exposure was 15.79±6.50 years in welders. Mean serum aluminium concentration was 24.19±9.99 $\mu g.L^{-1}$ in welders and 6.93± 1.95 $\mu g.L^{-1}$ in controls. The authors used a nonparametric test combination (NPC) to compare the stratified volunteers between welders and controls. The stratification was done at two levels, age and length of service, using 38 years and 22 years respectively as threshold values.

Decreased performances were observed in all cognitive tests for the welders' group, the WMS test and the Stroop test showing a greater sensitivity than the Test of Attention Matrixes, according to the authors. Only "partial" results of the NPC test should be considered as combined values seems to overestimate impact of aluminium exposure on neuropsychological evaluation, in the attention Matrixes test, attention deficit is observed only for individuals over 38 years old and with more than 22 years of service (Giorgianni et al. 2014).

Yang et al. (2015):

Yang et al. (2015) assessed the association of cognitive impairment and aluminium exposure in 366 aluminium potroom workers (age 40-60 years old and 21.2±6.5 years of exposure time). The exclusion criteria were the consumption of aluminium-containing or psychotropic drugs, a personal history of mental or neurological disorders or of any severe disease. People with poor vision or hearing were also excluded. Serum aluminium concentration was measured using GFAAS (LOD: 1 $\mu g.L^{-1}$). Cognitive function was assessed with the MMSE. Mild cognitive impairment (MCI) was diagnosed using MMSE scores (cut-offs not specified) followed by confirmation from "professional clinicians".

Median serum aluminium concentration was 48.99 $\mu g.L^{-1}$ (range 6.63-158.8 $\mu g.L^{-1}$). Analyses were conducted after distributing the participants in three groups based on 25th and 75th percentiles of serum aluminium concentration, 0-34.02 $\mu g.L^{-1}$, 34.03-61.42 $\mu g.L^{-1}$ and ≥ 61.43 $\mu g.L^{-1}$ respectively.

The total MMSE score decreased when serum aluminium concentration increased. There were 43 (/366) MCI cases and their rate increased with serum aluminium concentration ($p<0.001$). The association between aluminium exposure and the risk of MCI was assessed using a logistic regression model, with adjustment for possible confounders (age, education, smoking, and drinking). Cognitive impairment was significantly associated with high aluminium exposure (OR = 2.57; IC95% 1.5-4.41) (Yang et al. 2015).

Meng et al. (2019):

A large-scale case study was conducted in an aluminium factory in China. It included 853 male workers provided with protective equipment, excluding those with a history of cognitive problems or any disease that might induce them, as well as any family history of dementia or those taking aluminium-containing medication or psychotropic drugs, as well as those using cookware or consuming fried food daily; people with poor vision or hearing were also excluded.

This study comprised of a biomonitoring study measuring plasma aluminium by ICP-MS (detection limit of 0.39 $\mu g.L^{-1}$) as well as a 2-step questionnaire to assess cognitive impairment; the first stage being the MMSE and CDT tests. To increase the sensitivity and specificity of diagnosis, cognitive impairment was defined as a MMSE score of 26 or less (of 22 or less in workers whose education level is less than middle school, of 19 or less in workers whose education level is under primary school) or a CDT score of 2 or less. Participants with low MMSE or CDT scores and those complaining of memory impairment were referred to neurologists of the local university hospital for further explorations.

In all, 334 workers passed phase 2, of whom 53 (39.16%) were diagnosed with MCI, mainly on delayed recall (81.13%) and visuospatial executive ability (56.60%). For each case, 4 controls were matched by age randomly with no difference in marital status, income, smoking or drinking status; the mean age for cases and controls were between 45.04 and 44.71 years, respectively. The median (P25-P75) plasma aluminium concentration in the 53 MCI patients (18.17 (10.39, 34.96) $\mu g.L^{-1}$) was significantly higher than in the controls (12.02 (6.35, 20.86) $\mu g.L^{-1}$, $p=0.001$). People with MCI were found to have a lower level of education ($p=0.001$).

Conditional logistic regression was used to explore the influential factors of mild cognitive impairment. This showed that a high level of plasma aluminium increased the risk of cognitive problems (AOR= 2.24 95% CI 1.17-4.26 p=0.014), whereas a more advanced educational level was more of a protective factor (AOR: 0.36 95% CI 0.18-0.7 p= 0.003) (Meng et al. 2019).

Mohammed et al. (2020):

A cross-sectional study was conducted in an Egyptian aluminium foundry and included 75 exposed workers who wore gloves only, without mask or other protective equipment, and 75 "unexposed" controls from the administrative department of the same plant, to study the effect of exposure on cognitive performance. The two groups were matched in terms of age, gender, socioeconomic status, demographics and habits affecting health. People taking aluminium-containing or psychotropic drugs and those with a personal history of mental or neurological disorders were excluded. Serum aluminium level was measured (together with serum levels of lead, manganese and zinc), using atomic absorption spectrophotometry (AAS) (LOD: 1 $\mu g.L^{-1}$). Serum free tau protein was also quantified, using the Western blot technique. This protein is commonly found in the axons of neuronal cells and may be released into peripheral blood during neuronal damage. Cognitive functions were assessed using the Montreal cognitive assessment Basic (MoCA) test. The cutoff value retained for the definition of mild cognitive impairment was 24(/30). Occupational stress was also assessed using the perceived stress scale (PSS14) in its Arabic version. Quality of sleep was evaluated by the Arabic version of the Pittsburgh sleep quality index (PSQI). The Beck depression inventory (BDI) was administered to detect depression.

The exposed group had a significantly ($p<0.001$) higher serum aluminium level (mean ±SD: 560 $\mu g.L^{-1}$ ± 180) than the control group (360 $\mu g.L^{-1}$ ± 110), as did the tau protein (1.53 ± 0.58 for exposed vs. 1.03 ± 0.44 for controls, $p<0.001$).

The MoCA test showed a significantly lower performance in the exposed group (score 24.4 ± 3.4 vs 28.4 ± 1.3, $p<0.001$). Regression analysis showed that cognitive performance was negatively correlated with serum aluminium and tau protein levels ($r= -0.341$ and $p<0.003$, $r=-0.250$ and $p<0.03$ respectively). Exposed individuals were more stressed than controls, but this had no impact on cognitive performance. It should be noted that there was co-exposure to other metals, since serum lead and manganese levels were also higher in workers than in controls (Mohammed et al. 2020).

Wang et al. (2020):

Wang et al. (2020) conducted a cross-sectional study in 831 male workers (20-59 years old) exposed to aluminium in an aluminium factory (at least one year). Exclusion criteria were all causes of cognitive impairment, family history of neurodegenerative disease, long-term treatment with aluminium-containing drugs, poor vision or hearing. Plasma aluminium level was measured by ICP-MS. The participants were categorised into four quartiles based on their plasma aluminium concentrations, specifically, 0-8.28 $\mu g.L^{-1}$ (Q1), 8.28-15.26 $\mu g.L^{-1}$ (Q2), 15.26-27.02 $\mu g.L^{-1}$ (Q3), and ≥27.02 $\mu g.L^{-1}$ (Q4) subgroups. Cognitive function was measured using the MMSE and the CDT. Multidomain cognition was assessed through sub-tests of the MMSE and the CDT. There was no statistical difference in MMSE scores between groups.

When adjusted for age, education, income, marital status, type of work, and smoking and drinking habits and stratified by age (threshold of 40 years), a positive association was observed between plasma aluminium concentration and the risks of global cognitive impairment and multi-domain cognitive impairments. Considering total CDT scores the results were as follow: Q3 vs Q1 (OR=2.26, IC95% 1.25-4.11) and Q4 vs Q1 (OR=3.49, 1.85-6.59) but only for individuals older than 40 years. The same association was observed for

executive/visuospatial abilities (OR Q3 vs Q1 = 1.77, IC95% 1.03-3.04; OR Q4 vs Q1 = 2.44, IC95% 1.35-4.41) and CDT-position errors in individuals over 40 years old (OR Q3 vs Q1 = 1.75, IC95% 1.00-3.09; OR Q4 vs Q1 = 2.22, IC95% 1.22-4.10) (Wang et al. 2020).

Lu et al. (2021):

Lu et al., conducted a longitudinal study that included 2 cognitive evaluations one carried out in 2014 and then another 2 years after. A measurement of plasma aluminium concentration was performed using an ICP-MS (detection limit of 0.39 $\mu g.L^{-1}$ and standard deviation of 0.03%-0.08%) on 276 men workers in an aluminium plant in northern China. Log10 transformed plasma aluminium concentrations were used in this analysis. All workers used the same protective equipment and were exposed to aluminium metal and fluoride salt during the process of electrolytic aluminium with no other metal exposure. Information on background and health was collected by means of an employee health questionnaire, and status on smoking, alcohol consumption, age and sex, level of education and work history as well as diseases were collected. The cognitive assessment was established by an internationally recognised cognitive test questionnaire and the following tests: MMSE, VFT (Verbal Fluency Test), SRT (Simple Reaction Time), FOME (Fuld Object Memory Evaluation, evaluating delayed memory ability), DST (Digit Span Test, testing auditory linguistic memory ability), CDT, testing visuospatial, abstraction, language and memory abilities).

Participants were divided into 3 tertiles according to plasma aluminium (P-Al) concentration: T1 (<17.6 $\mu g.L^{-1}$) T2 (17.6-37.3 $\mu g.L^{-1}$) T3 (≥37.3 $\mu g.L^{-1}$). No significant differences were found among participants in terms of age, education, smoking and drinking status, or marital status. After adjusting for covariates, there was a reduction in the FOME (2014) and MMSE (2016) scores with increasing tertiles of P-Al concentrations. Also, there was negative association between P-Al concentration and most of the cognitive scores in 2014 and 2016. However, this association was statistically significant only for MMSE and FOME scores, in 2016. In 2016, each 10-fold increase in P-Al concentration was significantly associated with a 0.53-point decrease in MMSE score (p=0.002) and a 0.93-point decrease in FOME score (p=0.008). For each 10-fold increase in P-Al concentration, there was a 0.38- point decrease in MMSE score 2016-2014 (P=0.044) and a 1.20-point decrement in FOME score 2016-2014 (P=0.001). Concerning the average annual change, it was statistically different for the MMSE and FOME with the P-Al concentration increase (P<0.05): MMSE scores declined in each tertile, with annual decline rates of 0.58%, 0.61%, and 1.84%, respectively. The decrease in FOME scores only appeared in the T2 and T3 groups, which were 0.34% and 3.33%, respectively. The trend test indicated that there was a dose-response relationship between the P-Al concentration and the MMSE score (P=0.009) but no relationship with the FOME score (P>0.05) (Lu et al. 2021).

Xu et al. (2021):

A cross-sectional study was conducted in 2014 at an aluminium plant in China. Ultimately, 1,660 workers were included in this study after eliminating those who had worked for < 1 year, those taking aluminium-containing medications, those with neurological and/or mental disorders, and those with no biomonitoring results. For these 1,660 workers, plasma aluminium concentration was determined by ICP-MS with a LOD of 0.39 $\mu g.L^{-1}$. Cognitive function was assessed by the following 6 tests: the MMSE, the CDT, Digit span test (DST) forward (DSFT) and backward (DSBT), FOME, VFT, SRT. Multiple linear regression analyses were used to study the correlation between plasma aluminium concentrations and cognitive function, while taking into account age, education, marital status, smoking and alcoholism and total working hours.

All participants were male. Their average age was 40.42 ± 7.58 years; the average working duration was 17.74 ± 9.04 years. The median plasma aluminium concentration was 34.5 (P25, P75 =15.0, 42.3) $\mu g.L^{-1}$ which enabled the participants to be divided into 4 quartiles, Q1 (Al<15.00 $\mu g.L^{-1}$), Q2 (15.00 ≤ Al<34.52 $\mu g.L^{-1}$), Q3 (34.52 ≤ Al<42.25$\mu g.L^{-1}$), and Q4 (Al≥42.25 $\mu g.L^{-1}$). Similarly, participants were divided into 2 further categories: younger group (<40 years) and middle-aged group (≥40 years).

Scores of the different tests: recall, DST, DSBT, FOME, VFT, ATIME, FAS, and SLO were significantly lower in the middle-aged group than in the younger group ($p<0.05$). Multiple linear regression analysis after adjusting for age, education level, marital status, smoking status, alcohol status and total working time, showed that DST and DSBT test scores were negatively correlated ($p<0.05$) with plasma aluminium concentration in all participants (even when looking at younger and middle-aged groups). The same negative association was found in Q3 and Q4 of the younger group, whereas in the middle-aged group it was only present in Q4 ($p<0.05$).

Logistic regression analysis showed that the ORs for cognitive impairment for the DSBT and DST tests for category Q4 in all participants were 9.216 (95% CI, 5.068-16.756) and 2.309 (95% CI, 1.587-3.359), respectively, they were 7. 644 (95% CI, 3.846-15.192) and 1.695 (95% CI, 1.062-2.705), respectively, in the middle-aged group, and 15.308 (95% CI, 4.180-56.059) and 3.270 (95% CI, 1.615-6.620), respectively in the younger group (Xu et al. 2021).

Zhang et al. (2021):

Zhang et al. studied the effect of aluminium on cognition. In this study, they collected information from a public health surveillance project in Zhejiang (China) from which they selected 539 aluminium occupationally exposed participants (miners and workers from related factories): mean duration of exposure of 13.2 (± 11.3) years) and a control group of 1720 unexposed participants from another district. Cognitive function was measured by the MMSE. No aluminium measurement in blood or urine was conducted and, no information about personal or familial history of neurological diseases were brought up in the survey. Socio-demographic factors were compared between both groups, it is to be noted that the exposed group was younger than the unexposed one.

People exposed to aluminium had a significant ($p<0.001$) lower performance in the MMSE than the control group (mean score of 22.95 for unexposed vs 21.34 for exposed) and a higher risk of cognitive impairment[14]. A logistic regression model showed that aluminium-exposed group had 6.77 times more risk of cognitive impairment than the unexposed group ($p<0.001$), adjusted for age, sex, and educational level. The prevalence odds ratio remained high when adjusted for more covariates within another model (8.21, $p<0.001$). The analysis by logistic regression (covariates included age, sex, and education), showed no significant association between occupational exposure duration and cognition ($p = 0.232$) (Zhang et al. 2021).

Shang et al. (2021):

The cross-sectional study by Shang et al. aimed to assess the relationship between the plasma aluminium levels and cognitive impairment in 187 aluminium workers from departments involved in Al electrolysis (cryolite-alumina molten salt electrolysis in particular) in a Chinese factory. A total of 255 participants was considered for the study and 187 were selected according to the inclusion and exclusion criteria. People with known mental or neurological disease, or with history of neurodegenerative disease in their immediate family members, or with long-term consumption of psychotropic drugs or of aluminium-containing antacid drugs were excluded, as well as those using aluminium cookware, or with an exposure to strong

[14] Not defined in the publication. Probably MMSE score under 26.

noise. All the Al workers considered for the study were male workers, had been exposed for more than one year and had an average age of 40.16 ± 7.73 years. Cognitive function was assessed using the Chinese version of the MoCA, which asses the following performances: 1) executive/visuospatial abilities; 2) naming; 3) attention and calculation; 4) language; 5) abstraction ability; 6) recall; 7) orientation. Results were expressed as a global score, which could have a maximal value of 30, and a score fewer than 26 points was considered as MCI. Plasma aluminium levels were quantified using ICP-MS; plasma levels of eight other elements (chromium, cobalt, copper, iron, lead, lithium, manganese and zinc) were simultaneously measured.

Participants were divided into two groups based on their MoCA scores, consisting of 49 individuals classified as normal (MoCA score ≥26) and 138 individuals with mild cognitive impairment (MoCA score < 26). Median (interquartile range) plasma aluminium concentrations were 55.862 (38.701–77.012) $\mu g.L^{-1}$ for the normal group and 72.794 (42.510–102.652) $\mu g.L^{-1}$ for the MCI group. To estimate the relationship between plasma aluminium concentration and MoCA scores while adjusting for confounding factors, the study employed a multivariate generalized linear regression model and Bayesian kernel machine regression (BKMR). The results of the multivariate generalized linear model indicated a significant inverse relationship between plasma aluminium concentration and MoCA total scores (β (95% CI) -0.07 (0.108, -0.032); p<0.001), after adjustment for age, body-mass index, education level, monthly income, marital status, working duration, shift work, smoking status, drinking status, sleep quality, physical activity, and all other plasma elements concentrations (Shang et al. 2021).

Zhang Z et al. (2022a):

The study aimed to analyse the correlation between Quantitative Susceptibility Mapping (QSM) values, MoCA scores, and plasma aluminium levels in 53 Al workers issued from the previous cohort study of Shang et al. (2021). The 53 included workers were male, with an age range of 37-57 years, and were divided into two groups according to the MoCA score. Twenty-eight (28) workers were from the MCI group (MoCA score <26) and 25 from the “normal” group (MoCA score ≥26).

There was no difference in age and educational level, between the two groups. Mean plasma aluminium level was higher in the MCI group (43.8 $\mu g.L^{-1}$ vs 33.1 $\mu g.L^{-1}$). QSM values of left hippocampus, left dentate nucleus, right substantia nigra, and left putamen were higher in the MCI group compared to the “normal” group (p<0.05). No correlation was found between QSM values and plasma Al levels, suggesting that the pathological MCI mechanism is not related to plasma aluminium concentration and aluminium deposition in brain tissue. The authors concluded that, although QSM might be a valuable diagnostic marker for the diagnosis of MCI, no correlation was identified between plasma aluminium levels and QSM in Al workers (Zhang et al. 2022).

Zhao et al. (2022):

In a cohort study including 352 workers from a Chinese electrolytic aluminium workshop (19-55 years old), Zhao et al. (2022) investigated neurocognitive impairment using neuropsychological tests. Exclusion criteria were: age ≥ 60 years, exposure duration < 1 year, education level lower than primary school, familial history of neurodegenerative disease, personal history of neurological or mental disease, long-term use of psychotropic drugs, consumption of aluminium-containing drugs or use of aluminium cookware, exposure to strong noise and hearing deficiency. The tests performed included MMSE, VFT, FOME (evaluating delayed memory ability), DST(testing auditory linguistic memory ability), CDT (testing visuospatial, abstraction, language and memory abilities). Plasma aluminium concentration

was measured using GFAAS. Individuals were distributed into 4 quartiles according to plasma aluminium level (Q1 <17.7 µg.L^{-1}; Q2 17.7-27.85 µg.L^{-1}; Q3 27.85-41.04 µg.L^{-1}; Q4 ≥ 41.04 µg.L^{-1}).

Participants from Q3 and Q4 groups performed poorly to cognitive function tests compared to Q1 participants (DST, DSB, VFT for Q3vsQ1 and DST, DSF, DSB, VFT for Q4vsQ1). After adjustment for age, years of employment, education, income, smoking and drinking status, a significant association was observed between plasma aluminium concentration and a global score of cognitive impairment; it was statistically significant only for Q4 compared to Q1 participants, OR=6.172 (IC95% 2.31-16.488). With each 1µg.L^{-1} rise in plasma aluminium concentration, there was a 1.051-fold increase in the risk of cognitive impairment (95% CI: 1.031 to 1.072) (Zhao et al. 2022).

Zhang et al. (2022):

Zhang et al. studied a cohort of 392 male workers from an electrolytic workshop in China. Participants have worked for 15±9 years in aluminium plant. All participants had been exposed for more than one year. People with long-term consumption of aluminium-containing antacid drugs were excluded, as well as those using aluminium cookware, or those exposed to aluminium less than one year, or those with high blood pressure or hypotension. Plasma aluminium levels were determined by ICP-MS. Thirty minutes after their blood pressure measurement, participants were interviewed to collect the cognitive function test data. Cognitive functions were assessed using several tests as the MMSE, the VFT, the Average Reaction Time (ATIME), the FOME (evaluating delayed memory ability), the DST (testing auditory breadth and auditory linguistic memory ability), the CDT (testing visuospatial construction, abstract thinking, language and memory abilities). The authors conducted a generalised linear regression model to analyse the relationship between plasma aluminium levels, cognitive functions and blood pressure.

The participants were divided into four groups based on median and quartiles of plasma Al levels: Q1 (<18.08 µg.L^{-1}), Q2 (18.08-28.21 µg.L^{-1}), Q3 (28.21-40.88 µg.L^{-1}), Q4 (> 40.88 µg.L^{-1}). When aluminium concentration was used as a continuous variable, after adjustment for age, education level, marital status, smoking and drinking status, BMI, duration of employment, and family history of hypertension, for every fold increase, the MMSE, VFT, and FOM scores decreased by 1.275, 4.289 and 0.879 units respectively. When the Q4 group was compared to the Q1 group, plasma aluminium increase was associated with an increased ATIME. Plasma aluminium increase was also associated with an increasing risk of hypertension (odds-ratio, OR = 1.630, 95% CI: 1.103–2.407), and with an elevated systolic (OR = 1.578, 95% CI: 1.038–2.399) and diastolic blood pressure (OR = 1.842, 95% CI: 1.153–2.944) (Zhang et al. 2022).

Zhang et al. (2023):

In this study by Zhang et al., the relationship between cognitive impairment and occupational exposure to aluminium, as indicated by plasma levels, was examined. The participants were 54 subjects who were native Chinese male individuals, aged 37-57 years and who have worked in an aluminium factory for a minimum of 10 years. Exclusion criteria were left-handedness, history of major illness, contraindication of MRI scanning, and medical history of current serious medical problems

MoCA and verbal memory evaluated with the Rey Auditory Verbal Learning Test (AVLT) and blood sampling were done before MRI scanning. Out of the 54 subjects, 28 with MoCA scores <26 were assigned to the MCI group whereas the 26 other participants were assigned to the control group with normal cognition (MoCA scores >26). Respective work durations were of 25.07±10.38 years for MCI participants and 27.88±5.03 years for the control group. Plasma

aluminium levels were measured at 48.90±9.21 µg.L^{-1} for patients and 32.51±6.05 µg.L^{-1} for the control group, and there was no difference between the two groups.

After adjusting for confounding factors, the study observed an inverse relationship between plasma aluminium concentration and MoCA (r=-0.278; p=0.036) and AVLT (r=-0.287; p=0.035) scores. Cerebral MRI data were obtained for each participant and analysed using nonnegative matrix factorization. In MCI participants, the grey-mater volume of the default mode network (DMN) was lower than that in controls. Positive correlations were observed between DMN and MoCA scores, as well as between DMN and AVLT scores (Zhang et al. 2023).

Zhao et al. (2023):

Zhao et al., investigated the relationship between plasma aluminium levels, lifestyle and cognitive function of 476 male workers from an electrolytic aluminium workshop and a repair workshop in an aluminium factory in China. Inclusion criteria were: age between 20 and 60 years and good physical condition. Exclusion criteria were: long-term use of aluminium-containing drugs, use of drugs affecting neurological functions during the past week, history of personal or familial neurological or mental disease, high frequency of cooking oil strips. Plasma aluminium concentration was measured by ICP-MS. Cognitive condition was determined using the MoCA. MCI was defined as a MoCA score under 26. Subjects were 43.69±7.41 years old. Only 126 individuals had worked in aluminium industry for at least 10 years. Among them 49 were included in the MCI group and 77 considered as having normal cognitive performances. Despite this discrepancy, all 476 workers were categorised in four quartiles according to their plasma aluminium concentration, respectively Q1 <14.95 µg.L^{-1}, Q2 14.95-32.96 µg.L^{-1}, Q3 32.96-56.62 µg.L^{-1} and Q4 >56.62 µg.L^{-1}.

In this study, plasma aluminium concentration was associated with an increased risk of cognitive impairment for Q2, Q3 (not significant) and Q4 compared with Q1 participants. Derived OR (IC95%) were 2.102 (1.092-4.051), 1.866 (0.955-3.644) and 3.679 (1.928-7.020), respectively. The model was adjusted for income and marital status, education level, smoking status, drinking status, physical activity, daily reading time, daily mobile phone use, daily sleep duration (Zhao et al. 2023).

Meta-analyses

A first meta-analysis was performed in 2007 by Meyer-Baron et al. It included the 9 studies by Hosovski et al. (1990), Bast Pettersen et al. (1994 and 2000), Sjögren et al. 1996, Akila et al. (1999), Guo et al. (1999), He et al. (2003), Buchta et al. (2003 and 2005). These nine studies globally concerned 449 exposed workers and 315 control subjects. The mean urinary aluminium concentrations in the exposed groups ranged from 13 to 133 µg.L^{-1}. Six neuropsychological tests yielding 10 performance variables were analysed. A significant overall effect size was characterized for the digit symbol test (measuring speed-related components of cognitive and motor performances). The meta-analysis results also suggest an exposure-response relationship for this variable. This would constitute an argument for impairments of cognitive functions associated with occupational exposure to aluminium, even when urinary aluminium level is under 135 µg.L^{-1}. However, the authors pertinently noted that one significant effect size out of 10 analyses could be a chance result, and that uncertainties remain concerning the confounding factors that should and can be considered (Meyer-Baron et al. 2007).

A second meta-analysis was published in 2021 by Bagepally et al. It includes 23 studies, 1781 exposed and 1186 unexposed individuals. It shows statistically significant impairments of global cognitive scores, memory and working memory, associated with occupational aluminium exposure, but do not try to characterise a NOAEL or a LOAEL for these effects, using indicators of external exposure or biomarkers of exposure (Bagepally et al. 2021).

Vlasak et al. conducted a third meta-analysis of 18 studies of aluminium exposure association with performances in seven cognitive functions. It included 1357 exposed and 1119 control individuals, however, the same longitudinal studies that are described in two separate papers are counted twice which might induce biased results. Results of the meta-analysis are reported using Hedges' g as aggregated effect size to consider small sample sizes of some integrated studies. Overall, exposed workers had impaired performances in the following cognitive outcomes: reaction time, working memory and processing speed. No association could be found between urine aluminium levels (corrected for creatinine or not) and cognitive performance while a linear association with blood aluminium levels is observed (Vlasak, Dujlovic, and Barth 2024).

4.7.1.1.1 Neurodegenerative diseases

Amyloid plaques and neurofibrillary tangles are significant neuropathological indicators of Alzheimer's disease. The presence of aluminium in senile plaques, primarily composed of aggregated β-amyloid peptides, and the occurrence of neurofibrillary tangles in the presence of aluminium offer some support for the link between Alzheimer's disease and aluminium presence in the brain (Bryliński et al. 2023). Considering the conflicting results of studies testing for an association between aluminium in brain and the risk of Alzheimer’s disease, the simultaneous observation of these neuropathological features and aluminium in the brain does not establish the causal role of aluminium in Alzheimer's disease.

In a meta-analysis of three epidemiological studies (Virk and Eslick 2015), aluminium occupational exposure was not associated with Alzheimer’s disease (OR, 1.00; 95% CI, 0.59 to 1.68). In another meta-analysis of eight epidemiological studies (Wang et al. 2016), including also the three previous studies, an association of aluminium exposure with Alzheimer’s disease was found (OR, 1.71; 95% CI, 1.35 to 2.18). When separating exposure through drinking water and occupational exposure, this association was observed only with exposure through drinking water (OR, 1.95; 95% CI, 1.47 to 2.59) while no association with occupational exposure was found (OR, 1.25; 95% CI, 0.80 to 1.94).

Most of the epidemiological studies testing for the association between aluminium concentration in drinking water and the risk of Alzheimer’s disease and/or dementia suffer multiple methodological flaws. The main of these are that: 1) exposure to aluminium from water is generally not evaluated from individual repeated sampling of water really consumed by the participants, but from data issued from water distributing companies; they inconstantly take into accounts that the participants did not live at the same place during their whole life; 2) they generally only consider aluminium exposure through water, when it usually represents less than 5 % of the total exposure in the general population; 3) they generally do not take into account the other substances in drinking water (when positive and negative associations are respectively reported with the concentrations of fluorides or silicium in water and the risk of dementia). According to EFSA and WHO, exposure to aluminium through the food, including drinking water, does not constitute a risk for developing Alzheimer’s disease (EFSA 2008; JECFA 2012).

4.7.1.1.2 Autism spectrum disorder

Autism spectrum disorder have initially been suggested to be associated with aluminium exposure through vaccines based on ecological studies. The Global Advisory Committee on Vaccine Safety (GACVS 2012) had assessed those studies. They presented limitations such as uncertainties regarding autism spectrum disorder prevalence in different countries or in vaccines schedule. More recently, a meta-analysis comprising 18 case-control studies with aluminium measurement in hair, blood and/or urine was published (Sulaiman, Wang, and Ren 2020). It shows equivocal associations between aluminium levels in biological matrices and autism spectrum disorder. While levels of aluminium in hair and urine were positively associated with autism spectrum disorder, aluminium levels in blood were negatively associated. Overall, these studies address association and cannot be used for causality assessment of the association of aluminium exposure with autism spectrum disorder.

Table 11. Epidemiological studies

Study	Population	Industry	Analytical method	BM	BM results in control group	BM results in workers	NOAEL / LOAEL	Results
Hosovski et al. (1990) Cross-sectional	Yugoslavia 87 Al-exposed workers 60 controls	Al foundry Al concentration in the workplace: 4.6 to 11.5 $mg.m^{-3}$	Flameless AAS	Blood-Al	Mean: 58.09±74.73 $\mu g.L^{-1}$	Mean: 136.85±103.15 $\mu g.L^{-1}$	Blood-Al LOAEL: 136.85 $\mu g.L^{-1}$ U-Al LOAEL: 45.38 $\mu g.L^{-1}$	Memory disorder, decreased performance in complex reaction tests, complicated manipulations and oculomotor coordination. No confounder considered except for alcohol and psychotropic drugs consumption within one month before the study. Probable massive external contamination of the blood samples
				U-Al	Mean: 7.25±7.82 $\mu g.L^{-1}$.	Mean: 45.38±55.01 $\mu g.L^{-1}$		
Bast-Pettersen et al. (1994) Cross-sectional	Norway 22 Al-exposed workers (potroom, foundry) 16 controls (other department)	Primary aluminium plant	Not reported	S-Al	Mean: 2.9 $\mu g.L^{-1}$.	Mean: 3.6 $\mu g.L^{-1}$ in potroom workers Mean: 4.1 $\mu g.L^{-1}$ in foundry workers		Exposed workers reported more neuropsychiatric symptoms. Increased risk of impaired visuo-spatial organisation in exposed workers but the differences are not significant with the control group
				U-Al	Mean: 7.8 $\mu g.L^{-1}$	Mean: 12.6 $\mu g.L^{-1}$ in potroom workers Mean: 9.9 $\mu g.L^{-1}$ in foundry workers		
Sjögren et al. (1996) Iregren et al. (2001)	Sweden 173 Al exposed workers	Al foundry and potroom workers, Al welders,	GFAAS	Blood-Al	Median: 1.0 (range LOD-11) $\mu g.L^{-1}$	Median: 1.0 (LOD-18), 9.0 (LOD-21) and 3.0 (LOD-27) $\mu g.L^{-1}$ in		No correlation between Al in urine and the outcomes measures. Groups not comparable.

Cross sectional	39 mild steel welders	workers in production of Al flake powder				smelters, flake powder exposed workers and welders, respectively		
				U-Al	Median: 4.7 $\mu g.g^{-1}$ creatinine	Median: 4.2, 59.0 and 24.0 $\mu g.g^{-1}$ creatinine for the smelters, flake powder exposed workers and welders, respectively		
Akila et al. (1999) Cross-sectional	Finland 51 aluminium welders 28 age-matched steel welders	Aluminium welders	GFAAS	S-Al	Not reported	Not reported		Effects of Al are only significant at high exposure group for Digit symbol substitution test, Item selection time, Block design, Backward counting.
				U-Al	<1 $\mu mol.L^{-1}$ (mean=0.46 $\mu mol.L^{-1}$) < 27 $\mu g.L^{-1}$ (mean=12.4 $\mu g.L^{-1}$)	Low exposure group: 1.1–4.0 $\mu mol.L^{-1}$ (mean=2.25 $\mu mol.L^{-1}$); 27-108 $\mu g.L^{-1}$ (mean=60.7 $\mu g.L^{-1}$) High exposure group: >4.1 $\mu mol.L^{-1}$ (mean=9.98 $\mu mol.L^{-1}$); > 108 $\mu g.L^{-1}$ (mean=269.3 $\mu g.L^{-1}$)		

Hänninen et al. (1994) ; Riihimäki et al. (2000) Cross-sectional	Finland 65 Al welders Control: 25 mild steel welders	Aluminium welders	GFAAS	S-Al	Median: 0.08 µmol.L^{-1} (2.2 µg.L^{-1}) Range: 0.04 to 0.12 µmol.L^{-1} (1-3.2 µg.L^{-1})	Median (range): Low exposure group: 0.14 µmol.L^{-1} (0.07-0.24 µmol.L^{-1}); 3.8 µg.L^{-1} (1.9-6.5 µg.L^{-1}) High exposure group: 0.46 µmol.L^{-1} (0.27-1.00 µmol.L^{-1}); 12.4 µg.L^{-1} (7.3-27 µg.L^{-1})		Exposition related impairments in cancellation accuracy (Bourdon-Wiesma test), backward counting, both components of dual task, synonyms, and memory for designs. Age-adjusted correlations between U-Al and impairments in Digit symbol test, backward counting, dua task cancellation speed and counting speed. No statistically significant differences between the groups in EEG quantitative analysis. No significant association was observed between serum or urine aluminium concentration and P300 amplitude or latency.
				U-Al	Median: 0.4 µmol.L^{-1} (10.8 µg.L^{-1}) Range: 0.1 to 1.3 µmol.L^{-1} (2.7-35.1 µg.L^{-1})	Low exposure group: 1.8 µmol.L^{-1} (0.3-5.7 µmol.L^{-1}); 48.6 µg.L^{-1} (8.1-153.9 µg.L^{-1}) High exposure group: 7.1 µmol.L^{-1} (3.2-27.3 µmol.L^{-1}); 191.7 µg.L^{-1} (86.4-737.1 µg.L^{-1})		
Bast-Pettersen et al. (2000)	Norway 20 Al welders 20 constructi	Aluminium welders	GFAAS	U-Al pre and post shift	Not measured	Median (range): 0.15 µmol/mmol creatinine (0.06-0.43 µmol/mmol creatinine); 35.8 µg.g^{-1} creatinine;		Welders reported significantly more symptoms than controls and years of exposure were associated with poorer performance on the tremor test

Cross-sectional	on workers = control					14.3-109.9 µg.g^{-1} creatinine)		
Letzel et al. (2000) Longitudinal study	Germany 32 (E1) and 21 (E2) workers 30 (E1) and 15 (E2) controls	Al powder plant	Not reported	P-Al	Median: 1st examination: 4.3 µg.L^{-1} 2nd examination: 4.3 µg.L^{-1}	Median: 1st examination: 8.7 µg.L^{-1} 2nd examination: 6.7 µg.L^{-1}	NOAEL: 8.7 µg.L^{-1} NOAEL: 87.6 µg.g^{-1} creatinine	No significant exposure-related differences regarding performances in the psychometric tests or P300 potentials.
				U-Al	Median: 1st examination: 9.0 µg.g^{-1} creatinine 2nd examination: 4.5 µg.g^{-1} creatinine	Median: 1st examination: 87.6 µg.g^{-1} creatinine 2nd examination: 19.8 µg.g^{-1} creatinine		
Polizzi et al. (2002) Cross sectional study	Italy 64 al-exposed workers 32 controls All participants retired for 10	Foundries	GFAAS	S-Al	Mean: 8.2 ± 1.17 µg.L^{-1}	Mean: 14.1 ± 3.50 µg.L^{-1}	LOAEL: 14.1 µg.L^{-1}	Negative correlation between serum aluminium and the MMSE, MMSE-AE and CDT scores Positive correlation between serum aluminium and the MMSE and CDT times ERP-P300 latency positively correlated with serum aluminium concentration

	years or more							
Buchta et al. (2003) and Kiesswetter et al. (2009) Longitudinal study (4 years)	Germany 98, 97, 92 Al welders 50 controls	Al welders of car-body construction industry	GFAAS	P-Al (post-shift)	Median (min, max): 1st: 4.4 (1.4-31.6) µg.L-1 2nd: 2.3 (0.7-5.9) µg.L-1 3rd: 3.8 (1.6-10.0) µg.L-1	Median (min, max): 1st: 8.3 (2.3–42.3) µg.L-1 2nd: 4.1 (0.72–11.7) µg.L-1 3rd: 4.3 (1.8-15.6) µg.L-1	P-Al NOAEL: 8.3 µg.L-1 U-Al NOAEL: 37.87 µg.g-1 creatinine	No differences in neurological symptoms report and in performances in psychometric tests, except that welders were slightly slower in their decision time but quicker in their motor movements.
				U-Al (post-shift)	Median (min, max): 1st: 5.2 (1.7-30.3) µg.g-1 creatinine 2nd: 6.0 (1.6-390.0) µg.g-1 creatinine 3rd: 5.0 (0.2-40.3) µg.g-1 creatinine	Median (min, max): 1st: 37.87 (7.0–120.5) µg.g-1 creatinine 2nd: 33.57 (9.0–230.11) µg.g-1 creatinine 3rd: 15.4 (0.7-94.9) µg.g-1 creatinine		
Buchta et al. (2005) and Kiesswetter et al. (2007)	Germany 44 Al-welders 37 controls	5 companies in the train body and truck trailer construction industry	GFAAS	P-Al (post-shift)	Median: 1st: 3.5 µg.L-1 2nd: 2.8 µg.L-1 3rd: 4.5 µg.L-1	Median: 1st: 11.6 µg.L-1 2nd: 14.3 µg.L-1 3rd: 13.2 µg.L-1	P-Al LOAEL: 11.6 µg.L-1 U-Al LOAEL: 97 µg.g-1 creatinine	Observed significant difference between welders and controls only for block design test scores. Lowered performances (intergroup differences were not statistically significant) in welders group for verbal IQ, SPM test, trail making test, line tracing test and switching attention tasks.
				U-Al	Median:	Median:		

Longitudinal study (4 years)				(post-shift)	1st: 5.8 µg.L^{-1} or 4 µg.g^{-1} creatinine 2nd: 6 µg.L^{-1} or 4.5 µg.g^{-1} creatinine 3rd: 8.3 µg.L^{-1} or 8.5 µg.g^{-1} creatinine	1st: 130 µg.L^{-1} or 97 µg.g^{-1} creatinine 2nd: 145.5 µg.L^{-1} or 143.9 µg.g^{-1} creatinine 3rd: 93.7 µg.L^{-1} or 64.5 µg.g^{-1} creatinine		
Giorgianni et al. (2014) Cross-sectional	Italy 86 Al-welders Control group (from the same plant): 90	Welders in a shipyard using MIG (metal inert gas) technique	Spectrophotometry technique of absorption fitted with a graphite oven	S-Al (Monday morning)	Mean: 6.93± 1.95 µg.L^{-1}	Mean: 24.19±9.99 µg.L^{-1}	LOAEL: 24.19 µg.L^{-1}	Impaired scores of exposed workers in all cognitive tests, especially WMS test, Stroop test and attention matrices test
Mohammed et al. (2020) Cross-sectional	Egypt 75 Al exposed workers 75 controls from the same plant	Foundry (exposed to various metals)	Atomic Absorption Spectrometry (AAS)	S-Al	Mean ±SD: 0.36 mg.L^{-1} ± 0.11	Mean ±SD: 0.56 mg.L^{-1} ± 0.18	LOAEL: 560 µg.L^{-1}	Significant decline in cognitive performance in the exposed group negatively correlated to S-Al and tau protein level. Probable massive external contamination of the blood samples
Guo et al. (1999)	China	Large aluminium production	GFAAS	U-Al post-shift	Mean (range): 17.7 µg.g^{-1} creatinine (3.5-	Mean (range): 41.8 µg.g^{-1} creatinine (14-9-	LOAEL: 41.8 µg.g^{-1} creatinine	Significant higher score of some negative mood variables of the POMS questionnaire in workers and inconsistent impairment in

Cross-sectional	103 Al-exposed workers 64 controls	plant (electrolysis, smelting or welding departments)			42.8 µg.g^{-1} creatinine)	116.2 µg.g^{-1} creatinine)		some psychometric tests (age dependent) in the group of workers
He et al. (2003) Cross-sectional	China 33 workers from a Chinese Al plant 34 controls from a flour mill.	Chinese aluminium plant	GFAAS	U-Al pre shift	Mean: 26.8 µg.g^{-1} creatinine	Mean: 40.1 µg.g^{-1} creatinine	LOAEL: 40.1 µg.g^{-1} creatinine	Reaction time was significantly slower for exposed workers and scores of the digital symbol test and pursuit aiming test were significantly lower in this group.
Yang et al. (2015) Cross-sectional	China 366 Al potroom workers	Al potroom	GFAAS	S-Al	-	Median (range): 48.99 µg.L^{-1} (6.63-158.8 µg.L^{-1})		Total MMSE score decrease with S-Al increase Risk of mild cognitive impairment (MCI) increase with S-Al increase
Meng et al. (2019) Cross-sectional	China 853 Al-exposed workers from which only 334 were fully evaluated	Al factory	ICP-MS	P-Al	Median (P25-P75): (12.02 (6.35, 20.86) µg.L^{-1})	Median (P25-P75) in the 53 MCI patients: 18.17 (10.39, 34.96) µg.L^{-1})		High P-Al increased the risk of cognitive problems, advanced education was a protective factor

	1336 matched controls							
Wang et al. (2020) Cross-sectional	China 831 Al-exposed workers	Al factory	ICP-MS	P-Al	-	Four quartiles: Q1:0-8.28 µg.L^{-1} Q2: 8.28-15.26 µg.L^{-1} Q3: 15.26-27.02 µg.L^{-1} Q4: ≥27.02 µg.L^{-1}		Positive association between P-Al and cognitive impairments
Lu et al. (2021) Longitudinal study (2 years)	China 276 Al-exposed workers	Al factory	ICP-MS	P-Al	-	3 tertiles: T1: <17.6 µg.L^{-1} T2: 17.6-37.3 µg.L^{-1} T3: ≥37.3 µg.L^{-1})		Observed dose-response negative relationship between P-Al and MMSE score and FOME score
Xu et al. (2021) Cross-sectional study	China 1660 exposed workers	Al plant	ICP-MS	P-Al	-	Median: 34.5 (P25, P75 =15.0, 42.3) µg.L^{-1}		P-Al negatively correlated with DST and DSBT test scores.
Zhang et al. (2021) Cross-sectional	China 539 Al-exposed workers	Aluminium niners and workers from remated factories	No measurement	-	-	-		Exposed people had a significant lower MMSE score (p<0.001) and a higher risk of cognitive impairment (OR 2.21)

	1720 unexposed							
Shang et al. (2021) Cross-sectional	China 187 aluminium workers	Aluminium factory	ICP-MS	P-Al	-	Median (IQR): Normal group: 55.862 (38.701–77.012) $\mu g.L^{-1}$ MCI group: 72.794 (42.510–102.652) $\mu g.L^{-1}$ for the MCI group.		Significant inverse relationship between P-Al and MocA total scores
Zhang Z et al. (2022) Cross-sectional	China 53 Al-exposed workers	Al factory	ICP-MS	P-Al	-	Mean level: Normal group: 33.1 $\mu g.L^{-1}$ MCI group: 43.8 $\mu g.L^{-1}$		28 workers had mild MCI P-Al was higher in workers with MCI QSM exploration showed higher values in several brain regions for the MCI group No correlation between P-Al and QSM values.
Zhao et al. (2022) Cross-sectional	China 352 al-exposed workers	Al factory	GFAAS	P-Al	-	Four quartiles: Q1 <17.7 $\mu g.L^{-1}$; Q2 17.7-27.85 $\mu g.L^{-1}$; Q3 27.85-41.04 $\mu g.L^{-1}$; Q4 ≥ 41.04 $\mu g.L^{-1}$		Association between P-Al increase and decrease of global score of cognitive impairment
Zhang Y et al. (2022) Cross-sectional	China 392 Al-exposed workers	Al factory	ICP-MS	P-Al	-	Four groups based on median and quartiles of plasma Al levels: Q1 (< 18.08 $\mu g.L^{-1}$), Q2 (18.08-28.21		Decrease of MMSE, VFT and FOM scores with P-Al increase

						µg.L^{-1}), Q3 (28.21-40.88 µg.L^{-1}), Q4 (≥ 40.88 µg.L^{-1})		
Zhang et al. (2023) Case-control	China 28 Al-exposed workers with MCI 26 controls	Al factory	Not reported	P-Al	32.51±6.05 µg.L^{-1}	48.90±9.21 µg.L^{-1} for patients with MCI		Inverse relationship between P-Al and MocA and ALVL scores Lower grey matter volume in MCI patients at cerebral MRI examination
Zhao et al. (2023) Cross-sectional	China 476 Al-exposed workers	Al factory	ICP-MS	P-Al	-	Four quartiles: Q1 <14.95 µg.L^{-1}, Q2 14.95-32.96 µg.L^{-1}, Q3 32.96-56.62 µg.L^{-1} and Q4 >56.62 µg.L^{-1}		P-Al increase associated with increased risk of cognitive impairment

Blood-Al: blood aluminium concentration; P-Al: plasma aluminium concentration; S-Al: serum aluminium concentration; U-Al: urinary aluminium concentration.

Urinary aluminium levels reported in the various studies with NOAELs or LOAELs are presented in the histogram below (Figure 7) along with the number of samples (the study by Hosovski et al. 1990 is excluded as it shows limitations and urinary aluminium levels are not in $\mu g.g^{-1}$ creatinine).

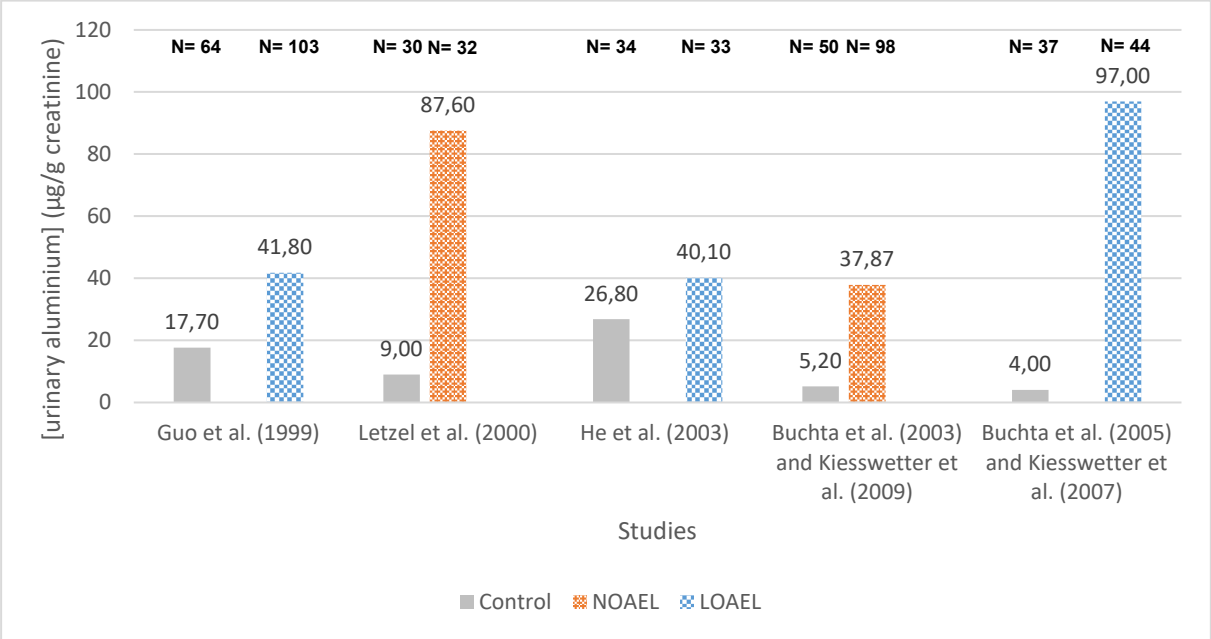


Figure 7. NOAEL and LOAEL extrapolated from median urinary concentrations measured in exposed workers in relation to cognitive impairment.

4.7.1.2 Animal data

No neurotoxicity studies have been found in animals following chronic exposure to aluminium compounds.

4.7.2 Respiratory toxicity

4.7.2.1 Human data

Numerous studies have documented respiratory effects linked to occupational exposure to aluminium, with diverse activities implicated such as aluminium smelting, electrolytic refineries, aluminium powder production, and aluminium welding. The spectrum of respiratory disorders includes wheezing, dyspnoea, impaired lung function, asthma, and pulmonary fibrosis. However, the attribution of these disorders to aluminium exposure remains uncertain or even improbable in many studies due to confounding factors, particularly co-exposures to other toxic chemicals, especially irritants. For instance, co-exposure to hydrogen fluoride and other fluorides were reported in electrolytic refineries in cases of potroom asthma or pulmonary fibrosis; co-exposure to ozone and ultra-fine particles in workers exposed to welding fumes; co-exposure to crystalline silica in cases of fibrosis in workers exposed to bauxite (Krewski et al. 2007; ATSDR 2008). Conflicting data are reported concerning the pulmonary effects of finely ground aluminium powder: some publications report on cases of pulmonary fibrosis in exposed workers, when other studies show no evidence of fibrosis after prolonged exposure to aluminium fine particles. It is believed that these differences could be explained by the type of lubricant used to prevent surface oxidation of aluminium particles during milling. Stearic acid is the most commonly used lubricant; it reacts with aluminium forming a protective superficial film of aluminium stearate; no fibrogenic effect is reported when using this process. In contrast, the previous and now discontinued use of mineral oil, as a lubricant for aluminium milling has

been associated with pulmonary fibrosis. Sporadic cases of pneumoconiosis associated with aluminium occupational exposure are also reported (Korogiannos, Babatsikou, and Tzimas 1998; Kraus et al. 2000; Hull and Abraham 2002). Their small number and the co-exposures to other chemical agents limit their interpretation.

4.7.2.2 Animal data

Limited data are available on respiratory effects of aluminium and its compound following chronic inhalation (ATSDR 2008). Identified studies are described below and summarised in Table 12.

- Mice

No organ weight or histological changes were observed in the lungs of Swiss mice exposed over lifetime (2-2.5 years) to 1.2 mg Al.kg $bw^{-1}.d^{-1}$ as aluminium sulphate in drinking water (Schroeder and Mitchener 1975b) or in mice exposed to 979 mg Al.kg $bw^{-1}.d^{-1}$ as aluminium potassium sulphate in the feed for 20 months (Oneda et al. 1994).

- Rats

No organ weight or histological changes of the lungs were observed in Long-Evans rats exposed over 2 years to 0.6 mg Al.kg $bw^{-1}.d^{-1}$ as aluminium sulphate in drinking water (Schroeder and Mitchener 1975a).

Rats (Fischer- 344) exposed over 12-24 months (5d/wk and $6hr.d^{-1}$) to aluminium chlorohydrate (whole body) at doses of 0.25, 2.5 or 25 $mg.m^{-3}$ presented a 108-274% increase in relative lung weight at 2 years at the highest exposure dose (LOAEL= 25 $mg.m^{-3}$ Al chlorohydrate, corresponding to 6.5 mg $Al.m^{-3}$). No effects on lungs weight were observed at the dose of 2.5 $mg.m^{-3}$ (NOAEL corresponding to 0.65 mg $Al.m^{-3}$) (Stone et al. 1979).

In a study by Pigott et al., no lung fibrosis was observed in rats (Wistar) following exposure (whole body) to 2.18 or 2.45 $mg.m^{-3}$ alumina fibres (Saffil fibres or Saffil aged fibres, median diameter ranging between 3.0-3.3 µm) over 86 weeks (5 d/wk and $6hr.d^{-1}$) (Pigott, Gaskell, and Ishmael 1981).

- Guinea pigs

Guinea Pigs (Hartley) exposed, whole body, to aluminium chlorohydrate at doses of 0.25, 2.5 or 25 $mg.m^{-3}$ over 12-21 months (5d/wk and $6hr.d^{-1}$) showed a 21% increase in relative lung weight at 2 years at the lowest exposure dose (LOAEL corresponding to 0.065 mg $Al.m^{-3}$) (Stone et al. 1979).

Table 12. Animal studies on aluminium chronic exposure respiratory toxicity

Strain	Al compound	Duration and route of exposure	Doses	Endpoint	NOAEL	LOAEL	Reference
Mice							
Swiss (n= 54 per group)	Aluminium sulphate	Lifetime Water	0 or 5 mg.L^{-1}	Weight and histological changes in lungs	1.2 mg Al.kg $bw^{-1}.d^{-1}$		Schroeder and Mitchener (1975b)
B6C3F1 (n= 60 per group)	Aluminium potassium sulphate	20 months Feed	0, 1, 2.5, 5, 10% APS (w/w)	Weight and histological changes in lungs	979 mg Al.kg $bw^{-1}.d^{-1}$		Oneda et al. (1994)
Rats							
Long- Evans (n=52 of each sex per group)	Aluminium sulphate	2 years Water	0 or 5 mg.L^{-1}	Weight and histological changes in lungs	0.6 mg Al.kg $bw^{-1}.d^{-1}$		Schroeder and Mitchener (1975a)
Fischer- 344 (n≈ 17 per group)	Aluminium chlorohydrate	12-24 months Inhalation	0, 0.25, 2.5 or 25 mg.m^{-3}	Increase in relative lung weight at 2 years	0.65 mg Al.m^{-3}	6.5 mg Al.m^{-3}	Stone et al. (1979)
Wistar (n= 50 per group)	Alumina fibres (Aluminium oxide)	86 weeks Inhalation	2.18 or 2.45 mg.m^{-3}	Lung fibrosis	2.45 mg.m^{-3}		Pigott et al. (1981)
Guinea pigs							
Hartley (n= 15 per group)	Aluminium chlorohydrate	12-21 months Inhalation	0, 0.25, 2.5 or 25 mg.m^{-3}	Increase in relative lung weight at 2 years		0.065 mg Al.m^{-3}	Stone et al. (1979)

4.7.3 Haematological effects

4.7.3.1 Human data

Elevated aluminium body burden is associated with a reduced erythrocyte lifespan and interferes with haemoglobin synthesis; these factors contribute to the microcytic hypochromic anaemia that develops after prolonged Al exposure in patients with compromised kidney function (Willhite et al. 2014). No human studies were identified regarding haematological effects following chronic environmental or occupational exposure to aluminium compounds of people with normal renal function.

4.7.3.2 Animal data

In a study by Stone et al., rats (Fischer-344) and guinea pigs exposed to 0.25, 2.5 or 25 $mg.m^{-3}$ of aluminium chlorohydrate over 12-24 and 12-21 months respectively did not present haematological effects. The NOAEL of 25 $mg.m^{-3}$ Al chlorohydrate corresponds to 5.4 $mg\ Al.m^{-3}$ (Stone et al. 1979).

4.7.4 Bone related effects

4.7.4.1 Human data

No human studies were identified related to musculoskeletal effects following chronic exposure to aluminium compounds.

4.7.4.2 Animal data

No animal studies were identified regarding musculoskeletal effects following chronic inhalation or chronic oral exposure to aluminium compounds.

4.7.5 Other effects

4.7.5.1 Human data

No human studies on systemic toxicity were identified following chronic exposure to aluminium compounds.

4.7.5.2 Animal data

Studies reporting systemic effects following chronic exposure to aluminium and its compounds were documented in the ATSDR (2008) report. The studies are described below and summarised in Table 13.

- Mice

Swiss mice exposed over lifetime to aluminium sulphate via water (5 ppm aluminium) did not show histological changes in the heart, kidney or liver and no effects were observed on the body and organs weights (NOAEL of 1.2 mg Al.kg $bw^{-1}.d^{-1}$) (Schroeder and Mitchener 1975b).

Swiss-Webster mice were exposed to aluminium lactate for 2 years (from conception to month 24) at 7 (control) or 100 µg $Al.g^{-1}$ diet. A 20% decrease in body weight gain was reported in females at the dose of 100 mg Al.kg $bw^{-1}.d^{-1}$ as aluminium lactate (LOAEL). However, alterations in body weights were not observed in another group of mice similarly exposed (Golub et al. 2000).

- Rats

Rats (Long-Evans) exposed for 2.5 years to aluminium sulphate via water (5 ppm aluminium) did not show histological changes in the heart, kidney or liver nor effects on the body weight (NOAEL of 0.6 mg Al.kg $bw^{-1}.d^{-1}$) (Schroeder and Mitchener 1975a).

Fischer-344 rats exposed to the highest dose of aluminium chlorohydrate, whole body, (0, 0.25, 2.5 and 25 $mg.m^{-3}$) had a significant decrease in their body weight at 12 and 24 months of exposure (LOAEL of 25 $mg.m^{-3}$ Al chlorohydrate, equivalent to 6.5 mg $Al.m^{-3}$ and NOAEL of 2.5 $mg.m^{-3}$ Al chlorohydrate equivalent to 0.65 mg $Al.m^{-3}$) (Stone et al. 1979).

Finally, Sprague-Dawley rats exposed from conception to sacrifice (at 1 year or 2 years) to 0, 50 or 100 mg Al.kg $bw^{-1}.d^{-1}$ as aluminium nitrate through water (+ citric acid to increase aluminium absorption), did not show any adverse body weight effect (Roig et al. 2006). The NOAEL was 100 mg Al.kg $bw^{-1}.d^{-1}$.

- Guinea pigs

No effect on the body weight was observed in guinea pigs exposed to 0.25, 2.5 or 25 $mg.m^{-3}$ of aluminium chlorohydrate (whole body) over 12-21 months (NOAEL=25 $mg.m^{-3}$ Al chlorohydrate , equivalent to 6.5 mg $Al.m^{-3}$) (Stone et al. 1979).

Table 13. Animal studies on aluminium chronic exposure systemic toxicity

Strain	Al compound	Duration and route of exposure	Doses	Endpoint	NOAEL	LOAEL	Reference
Mice							
Swiss (n= 54 per group)	Aluminium sulphate	Lifetime Water	0 or 5 mg.L^{-1}	Histological changes in heart, kidney, liver and the body weight	1.2 mg Al.kg $bw^{-1}.d^{-1}$		Schroeder and Mitchener (1975b)
Swiss-Webster (n= 18 per group)	Aluminium lactate	Conception- 24 months Diet	7 (control) or 100 µg $Al.g^{-1}$ diet	20% decrease in body weight gain in female mice		100 mg Al.kg $bw^{-1}.d^{-1}$	Golub et al. (2000)
Rats							
Long- Evans (n=52 of each sex per group)	Aluminium sulphate	2 years Water	0 or 5 mg.L^{-1}	Histological changes in heart, kidney, liver and the body weight	0.6 mg Al.kg $bw^{-1}.d^{-1}$		Schroeder and Mitchener (1975a)
Fischer- 344 (n≈ 17 per group)	Aluminium chlorohydrate	12-24 months Inhalation	0, 0.25, 2.5 or 25 $mg.m^{-3}$	Decrease in the body weight	0.65 mg $Al.m^{-3}$	6.5 mg $Al.m^{-3}$	Stone et al. (1979)
Sprague-Dawley (n= 15-21 per group)	Aluminium nitrate + citric acid	Conception- 1 or 2 years olds Water	0, 50 or 100 mg Al.kg $bw^{-1}.d^{-1}$	No effect on the body weight at the highest tested dose	100 mg Al/ $bw.d^{-1}$		Roig et al. (2006)
Guinea pigs							
Hartley (n= 15 per group)	Aluminium chlorohydrate	12-21 months Inhalation	0, 0.25, 2.5 or 25 $mg.m^{-3}$	No effect on the body weight at the highest tested dose	6.5 mg $Al.m^{-3}$		Stone et al. (1979)

4.8 Toxicity on reproduction and developmental toxicity

4.8.1 Human data

No reliable studies have been identified regarding the reproductive effects and developmental toxicity of aluminium or its compounds in humans.

4.8.2 Animal data

ATSDR (2008) and EFSA (2008) reported some studies regarding reproductive effects and developmental toxicity of aluminium compounds in animals. Identified studies are described below and summarised in Table 14, Table 15 and Table 16.

- Mice

An increased incidence of resorptions was reported in female BALB/c mice treated with 200 or 300 mg.kg $bw^{-1}.d^{-1}$ of aluminium chloride, through gavage, on Gds 7-16 (Cranmer et al. 1986). The control group received a saline solution intraperitoneally (ip). The LOAEL for increased resorption is 200 mg.kg $bw^{-1}.d^{-1}$ $AlCl_3$ equivalent to 41 mg Al.kg $bw^{-1}.d^{-1}$.

In female Swiss-Webster mice exposed to aluminium lactate through diet (25 (control), 500 or 1000 µg $Al.g^{-1}$ diet), during gestation and lactation (Gd1-Ld21), an altered gestational length was observed in the 500 and 1000 µg $Al.g^{-1}$ groups, where some pups were born on Gd 17, 19 or 20 whereas all pups were born on Gd18 in the control group. The LOAEL for reproductive effects was equivalent to 155 mg Al.kg $bw^{-1}.d^{-1}$. Furthermore, no effects were observed on the pregnancy rate, litter size, birth weight, peri and post-natal pup mortality, even in the group with the highest exposure approximatively equivalent to 310 mg Al.kg $bw^{-1}.d^{-1}$ (NOAEL for developmental toxicity). In this study, mice fed with aluminium lactate from conception through weaning had a decrease in forelimb strength (age of 39 days), an increase in hind limb grip strength (age of 25 days) and an increase in foot splay in weanling (age of 21 and 35 days) at the dose of 500 µg $Al.g^{-1}$ diet (Donald et al. 1989). The LOAEL for neurodevelopmental toxicity was of 500 µg $Al.g^{-1}$ diet, corresponding to 155 mg Al.kg $bw^{-1}.d^{-1}$.

Pregnant Swiss mice exposed through gavage during Gd 6 to 15 to aluminium hydroxide at doses of 0, 66.5, 133 or 266 mg.kg $bw^{-1}.d^{-1}$ corresponding to 0, 23, 46 or 92 mg Al.kg $bw^{-1}.d^{-1}$ did not present maternal toxicity or signs of embryotoxicity including morphological abnormalities (Domingo et al. 1989). The NOAEL was thus reported to be 92 mg Al.kg $bw^{-1}.d^{-1}$ (the highest tested dose).

Swiss-Webster mice were exposed to aluminium lactate at doses of 25 (control) or 1000 µg $Al.g^{-1}$ diet, through the diet, from conception through gestation, or from conception to lactation, or during lactation only (Golub, Keen, and Gershwin 1992a). There was a significant decrease in pup body weight, crown-rump length and forelimb grip strength in the gestation exposed group. There was an increase in hind limb grip strength and in tail withdrawal times in gestation and lactation exposed groups. An increase in negative geotaxis latency was observed in the lactation exposed groups. The LOAEL was 1000 $µg.g^{-1}$ diet, equivalent to 250 mg Al.kg $bw^{-1}.d^{-1}$. In this study, no reproductive effects (no effects on litter size, birth weight, crown-rump length, or sex ratio) were seen in female mice dams exposed to aluminium lactate during gestation and lactation. The NOAEL for reproductive toxicity is equivalent to 250 mg Al.kg $bw^{-1}.d^{-1}$ (the highest tested dose).

In another study, Swiss (CD-1) mice were exposed during Gd 6 to 15, by gavage, to either aluminium lactate (627 mg.kg bw^{-1} delivering 57.4 mg Al.kg $bw^{-1}.d^{-1}$) or aluminium hydroxide

(166 mg.kg bw^{-1} delivering 57.4 mg Al.kg bw^{-1}.d^{-1}) or aluminium hydroxide and lactic acid (570 mg.kg bw^{-1}) or lactic acid or distilled water. It was shown that dams had a reduced body weight gain (not related to food consumption) following exposure to either aluminium lactate or aluminium hydroxide + lactic acid. In addition, exposure to aluminium lactate induced a significant decrease of foetal body weight, cleft palate and delayed foetal ossification (Colomina et al. 1992). The LOAEL for aluminium lactate was 57.4 mg Al.kg bw^{-1}.d^{-1} and the NOAEL for aluminium hydroxide 57.4 mg Al.kg bw^{-1}.d^{-1}.

Aluminium hydroxide (dose of 300 mg.kg bw^{-1}.d^{-1} delivering 103 mg Al.kg bw^{-1}.d^{-1}) was also administered to Swiss mice, by gavage, with or without ascorbic acid (85 mg.kg bw^{-1}.d^{-1}) from Gd 6 to Gd 15. The study included a control group receiving distilled water. A significant reduction in maternal food consumption was reported during all the gestational period in the aluminium hydroxide and aluminium hydroxide + ascorbic acid groups. No developmental effects were observed among the groups including the percentage of post implantation loss, foetal body weight, and the incidence of minor anomalies and major malformations (Colomina et al. 1994). The NOAEL was 103 mg Al.kg bw^{-1}.d^{-1}.

Swiss-Webster mice were exposed to aluminium lactate in the diet at 7 (control), 500 or 1000 µg Al.g^{-1} diet from conception until weaning. At 500 µg Al.g^{-1} diet, there was a decrease in forelimb and hind limb grip strengths and startle response compared to controls (Golub et al. 1995). The LOAEL was 500 µg.g^{-1} diet, or 155 mg Al.kg bw^{-1}.d^{-1}.

In a study by Golub and Germann, where Swiss-Webster mice were exposed through diet, from conception till PND 35 to aluminium lactate at doses of 7 (control), 500 or 1000 µg Al.g^{-1} diet, there was no effect of aluminium exposure on the performance of the Delayed Spatial Alternation task (Golub and Germann 1998). The NOAEL was 1000 µg.g^{-1} diet, or330 mg Al.kg bw^{-1}.d^{-1} (the highest tested dose).

In a study where five groups of CD-1 mice were exposed by gavage to aluminium nitrate nonahydrate at a single dose of 995 mg.kg bw^{-1} (71 mg Al.kg bw^{-1}), at one of the Gds 8 to 12, a reduction of body weight gain and a reduced foetal body weight were observed in all aluminium treated groups compared to controls. In addition, reduced ossification was common due to the exposure to aluminium (in all groups compared to controls). Some female death and abortions were also reported (Albina et al. 2000). The LOAEL was 71mg Al.kg bw^{-1} in this study.

Furthermore, a chronic exposure to aluminium lactate through diet (at 7 (control) or 1000 µg Al.g^{-1} diet) over 2 years, from conception until month 24 of age caused a decrease in forelimb and hind limb strength and a decreased thermal activity in aluminium-treated Swiss-Webster mice (Golub et al. 2000). The LOAEL was 1000 µg.g^{-1} diet equivalent to 100 mg Al.kg bw^{-1}.d^{-1}.

Swiss Webster mice were exposed to aluminium lactate through diet at doses of 7 (control), 100, 500, or 1000 µg Al.g^{-1} diet from conception to PND 35. From the dose of 500 µg Al.g^{-1} diet, females showed an impaired performance on the water maze test and males had shorter latency to fall in wire suspension test. At 1000 µg Al.g^{-1} diet there was a decrease in hind limb grip strength compared to controls (Golub and Germann 2001). The LOAEL was 500 µg.g^{-1} diet or 130 mg Al.kg bw^{-1}.d^{-1} and the NOAEL was 100 µg.g^{-1} diet, or 26 mg Al.kg bw^{-1}.d^{-1}.

Pregnant Swiss-Webster mice were exposed to 0, 300 or 600 mg Al.kg bw^{-1}.d^{-1} as aluminium chloride through water from Gd 1 until PND 15. For each experimental group, pups were culled to 8 per dam but stayed with their mothers until PND 22. In male offspring, a significant and dose-dependent deficit was reported in the locomotor activity (PND 22), learning capacity (PND 25) and cognitive behaviours (PND 30-36). In addition, delays in opening of the eyes and appearance of body hair fuzz, and deficits in the sensory motor reflexes of the pups during weaning period were reported (Abu-Taweel, Ajarem, and Ahmad 2012). The LOAEL was 300 mg Al.kg bw^{-1}.d^{-1}.

- Rats

Fischer-344 rats inhaling 0, 0.065, 0.65 or 6.5 mg Al.m^{-3} as aluminium chlorohydrate over 6 months had no histological changes in their reproductive tissues (Steinhagen, Cavender, and Cockrell 1978). The NOAEL was 6.5 mg Al.m^{-3}.

Aluminium chloride was given to Wistar rats, through diet, at doses of 0, 160 or 200 mg Al.kg bw^{-1}.d^{-1}, from Gd 8 until parturition. There was no difference between the aluminium treated groups and the control group regarding food consumption and weight gain of pregnant rats. Aluminium affected postnatal pups' survival but not in a dose dependent manner. The age of appearance of eye opening and mean body weight of pups did not differ between groups except for the body weight that was reduced on the first day postpartum in the treated groups compared to controls (Bernuzzi, Desor, and Lehr 1986). The LOAEL was 160 mg Al.kg bw^{-1}.d^{-1}.

Male Sprague-Dawley rats were exposed to aluminium nitrate nonahydrate through gavage, over 60 days prior to mating, at the following doses: 0, 180, 360 or 720 mg.kg bw^{-1}.d^{-1}. Female rates were exposed to similar doses for 14 days prior to mating (with male rat with the same exposure dose), during gestation, delivery and lactation. No reproductive toxicity was observed in male and female rats (Domingo et al. 1987a). NOAEL regarding male and female fertility was considered to be 720 mg.kg bw^{-1}.d^{-1} of aluminium nitrate nonahydrate, equal to 52 mg Al.kg bw^{-1}.d^{-1}.

Domingo et al., administered aluminium nitrate by gavage at doses of 0, 180, 360 or 720 mg.kg bw^{-1}.d^{-1} (delivering 0, 13, 26 or 52 mg Al.kg bw^{-1}.d^{-1}) to pregnant Sprague Dawley rats (10 per group) from Gd14 to Gd21. Number of litters and number of live pups per litter were lower in all aluminium treated groups compared to controls. However, the decrease was not significantly dose dependent. At the highest dose of aluminium nitrate, the mean pup body weight was lower (Domingo et al. 1987c). The LOAEL was 13 mg Al.kg bw^{-1}.d^{-1}.

In another study, aluminium nitrate was administered to rats (Sprague Dawley, 10 per group), by gavage, from gestational day 6 to gestational day 14, at doses of 0, 180, 360 or 720 mg.kg bw^{-1}.d^{-1} (delivering 0, 13, 26 or 52 mg Al.kg bw^{-1}.d^{-1}), then, rats underwent caesarean section on Gd20. Results showed that all groups exposed to aluminium nitrate had a significantly reduced body weight gain of dams compared to controls. The number of runt foetuses was higher, in an aluminium dose dependent manner. In addition, foetal body weight was reduced in all aluminium treated group where severe signs of delayed ossification, increase congenital malformations and minor anomalies were observed (Paternain et al. 1988). The LOAEL was 13 mg Al.kg bw^{-1}.d^{-1}.

Bernuzzi et al. administered aluminium chloride (0, 100, 300 or 400 mg.kg bw^{-1}.d^{-1} delivering 0, 20, 60 and 80mg Al.kg bw^{-1}.d^{-1}) or aluminium lactate (0, 100, 300 or 400 mg.kg bw^{-1}.d^{-1} delivering 0, 9, 18 and 36 mg Al.kg bw^{-1}.d^{-1}), through diet, to pregnant Wistar rats from Gd1 to parturition. In the mid and high doses of aluminium chloride and in the high dose of aluminium lactate, a reduction of maternal body weight gain, higher postnatal mortalities and significant reduction of pup weights at birth and during postnatal development were observed compared to controls. Litter size at birth was similar in all the groups (Bernuzzi, Desor, and Lehr 1989a). The NOAEL was 20 mg Al.kg bw^{-1}.d^{-1} in rats treated with aluminium chloride and 18 mg Al.kg bw^{-1}.d^{-1} for those treated with aluminium lactate. The LOAEL were 60 and 36 mg Al.kg bw^{-1}, respectively for aluminium chloride and aluminium lactate.

In another study, aluminium lactate was administered through diet at 0 or 400 mg Al.kg bw^{-1}.d^{-1} to pregnant Wistar rats during Gd1-Gd7 or Gd1-Gd14 or Gd1-partution. The results showed no effect of aluminium on the litter size, mortality rate or weight of pups. Maternal body weight was significantly decreased on Gd16 and Gd19 in the group of rats treated during the whole

gestational period (Muller et al. 1990). The NOAEL for developmental effects was 400 mg Al.kg $bw^{-1}.d^{-1}$.

Wistar rats were administered, by gavage, aluminium chloride onGD6 to GD15 at doses delivering 0, 66, 132 or 264 mg Al.kg $bw^{-1}.d^{-1}$ (divided in two equal administrations.d^{-1}). Dams were killed on day 20 of gestation. No maternal toxicity nor embryotoxicity were reported in all groups (Gomez et al. 1990). The NOAEL was 264 mg Al.kg $bw^{-1}.d^{-1}$.

Female rats (Sprague-Dawley) were exposed for 15 days prior to mating, then during gestation, lactation and post-weaning period to 0, 50 or 100 mg Al.kg $bw^{-1}.d^{-1}$ as aluminium nitrate nonahydrate in drinking water (citric acid was added at 335 or 710 mg.kg $bw^{-1}.d^{-1}$) (Colomina et al. 2005). At 100 mg Al.kg $bw^{-1}.d^{-1}$, a decrease in the body weight of pups was observed from postnatal day 12 through 21. A delay in vaginal opening was reported from the dose of 50 mg Al.kg $bw^{-1}.d^{-1}$ and a delay in testes descent was reported from 100 mg Al.kg $bw^{-1}.d^{-1}$. The LOAEL for developmental toxicity was of 50 mg Al.kg $bw^{-1}.d^{-1}$. In this study, a decrease in forelimb strength of pups was observed at 100 mg Al.kg $bw^{-1}.d^{-1}$. The LOAEL for neurodevelopmental effects was 100 mg Al.kg $bw^{-1}.d^{-1}$ for these effects and the NOAEL 50 mg Al.kg $bw^{-1}.d^{-1}$. Nevertheless, Sprague Dawley rats did not have alterations in performance of water maze test when exposed to 100 mg Al.kg $bw^{-1}.d^{-1}$ as aluminium lactate (NOAEL) from conception to sacrifice (at 1 year or 2 years old) (Roig et al. 2006). In this study, citric acid was added to the water and aluminium was administered at doses of 0, 50 or 100 mg Al.kg $bw^{-1}.d^{-1}$.

Wistar rats were exposed to aluminium chloride during gestational and lactation stages and then after weaning in their drinking water (0 or 3 $g.L^{-1}$ $AlCl_3$) until the age of 4 months. There was a significant increase of glial fibrillary acidic protein (GFA-P) -immunoreactive astrocytes in brain of aluminium treated rats who also had a significant reduced locomotor activity compared to controls. Also, rats exposed to aluminium preferred to spend more time in the lit compartment of a dark/light box, which indicates increased anxiety; this was not seen in rats only exposed to aluminium at adult age in this same study (Erazi et al. 2010). The LOAEL was 3000 mg aluminium chloride.L^{-1}, or 600 mg Al..L^{-1}.

In a study conducted according to GLP with a design based on OECD Test Guideline 426, Sprague Dawley pregnant rats were exposed to aluminium citrate through drinking water, starting gestational day 6, during gestation, lactation, and to offspring during post-weaning, through to PND 364, at doses delivering 30, 100 or 300 mg Al.kg $bw^{-1}.d^{-1}$. The study also included two control groups receiving either sodium citrate solution or deionised water. The concentration of aluminium in diet was reported to be less than 9 $\mu g.kg^{-1}$. On PND 4, there was a normalisation to 4 males and 4 females per litter assigned per number to each of four sacrifice day groups (day 23, day 64, day 120, day 364) associated with milestone observations and sacrifice. In the offspring, white precipitates were observed in the urinary tracts (test item precipitation) resulting in hydronephrosis, ureteral dilation and stone formation, this effect was considered related to aluminium-treatment and was most prominently observed in the high dose group, particularly in male pups, which resulted in higher mortality and morbidity rate in male pups of the high dose group. The high dose group was considered to be the maximum tolerated dose. In the middle dose group, urinary tract lesions, decreased body weight in males at PND 120, elevated fluid consumption and, an exaggerated response to tail pinch and narrower foot splay in females were observed. There was also a decrease in hindlimb and forelimb grip strength in pups (significant in the mid- and high dose) that was dose related, although some of the effects may be secondary to body weight changes. No significant effects were reported for auditory startle response, T-maze tests or the Morris water maze test. The authors concluded a LOAEL of 100 mg Al.kg $bw^{-1}.d^{-1}$ and a NOAEL of 30 mg Al.kg $bw^{-1}.d^{-1}$ (Poirier et al. 2011).

Sun and al., conducted a study on male Wistar rats, exposed orally, for 120 days, to 0, 64.18, 128.36 or 256.72 mg.kg $bw^{-1}.d^{-1}$ of aluminium chloride in drinking water. Aluminium treated male rats had decreased levels of testosterone and luteinizing hormone (LH) when exposed to ≥ 128.36 mg.kg $bw^{-1}.d^{-1}$ compared to controls. In all aluminium treated groups follicle-stimulating hormone (FSH) level did not show significant change compared to controls however, androgen receptor protein expression and mRNA expression were lower than in control group (Sun et al. 2011). The LOAEL was 64.18 mg.kg $bw^{-1}.d^{-1}$ of aluminium chloride, equivalent to 13 mg Al.kg $bw^{-1}.d^{-1}$.

Female Wistar rats were administered 0, 64.18, 128.36, or 256.72 mg .kg $bw^{-1}.d^{-1}$ of aluminium chloride through their drinking water over 120 days. It was shown that aluminium exposed female rats, in the three aluminium exposure groups, had a significant decrease in serum levels of oestrogens, progesterone, FSH and LH in an Al dose-dependent manner, compared to the control group (Wang et al. 2012). The LOAEL was 64.18 mg.kg $bw^{-1}.d^{-1}$ of aluminium chloride, equivalent to 13 mg Al.kg $bw^{-1}.d^{-1}$.

Pregnant Wistar rats were divided into four groups: from the first day after birth, they received water containing 0, 0.2, 0.4 or 0.6% of aluminium chloride. Eight litters per group were kept and were exposed to aluminium chloride through lactation from parturition to weaning (3 weeks) and then were administered water containing 0, 0.2, 0.4, 0.6% of aluminium chloride until 3 months age. Pups exposed to aluminium chloride had higher levels of aluminium in blood and hippocampus than controls and, aluminium caused pathological changes in neuronal and synaptic ultrastructure and impaired spatial memory ability in rats (Zhang et al. 2013). The LOAEL was 0.2 % aluminium chloride in drinking water, or400 mg $Al.L^{-1}$.

Wistar male rats were orally exposed to 0, 64.18, 128.36 or 256.72mg.kg $bw^{-1}.d^{-1}$ of aluminium chloride for 120 days. Findings of this study (Zhu et al. 2014) showed that aluminium caused adverse effects on testicular function; exposed rats had a decrease in Zn and Fe testes content (mid and high dose), sperm count (mid and high dose) and enzyme activities of testicular ACP (acid phosphatase), LDH-x (lactate dehydrogenase isoenzyme) (mid and high dose), SDH (succinate dehydrogenase) and LDH (lactate dehydrogenase) (high dose) with an increase in Al and Cu contents (mid and high dose) and an increase in sperm malformation rate (in all the aluminium-treated groups, 31.24% in the highest exposed group vs 14.93% in the control group). LOAEL was of 64.18 mg.kg $bw^{-1}.d^{-1}$ of aluminium chloride, equivalent to 13 mg Al.kg $bw^{-1}.d^{-1}$.

In 2014, Fu et al. exposed female Wistar rats to 0, 64, 128 or 256 mg.kg $bw^{-1}.d^{-1}$ of aluminium chloride in drinking water over 120 days. Results showed that $AlCl_3$-treated rats had a disruption in their ovary structure (at high dose), a decrease in the activities of ALP, ACP, SDH, Na^+-K^+-ATPase, $Mg2^+$-ATPase and Ca^{2+}-ATPase (from low dose), lower contents of Zn, Fe (from mid dose), lower protein expression of FSHR and LHR (from low dose) and an increase of Cu content (from mid dose) in the ovaries compared to controls. The authors concluded that sub-chronic exposure to aluminium chloride could damage the ovarian structure, suppress energy supply in the ovary, inhibit ovulation and corpus luteum development, resulting in sterility (Fu et al. 2014). LOAEL was 64 mg.kg $bw^{-1}.d^{-1}$ of aluminium chloride, equivalent to12.96 mg Al.kg $bw^{-1}.d^{-1}$.

In a study by Martinez et al., Wistar male rats were orally exposed to aluminium chloride. The study included 2 experiments: experiment 1 with a control group and rats exposed over 60 days to 1.5 or 8.3 mg Al.kg $bw^{-1}.d^{-1}$ through drinking water and, experiment 2 with a control group and rats exposed over 42 days to 100 mg Al.kg $bw^{-1}.d^{-1}$. In these experiments aluminium was detected in germinative cells and even low concentrations in testes could alter spermatogenesis and sperm quality. In fact, aluminium increased oxidative stress in the reproductive organs and caused inflammation in testis (Martinez et al. 2017b). The LOAEL was 1.5 mg Al.kg $bw^{-1}.d^{-1}$.

Male Wistar rats were orally exposed, by gavage, to aluminium chloride at concentrations of 0, 6.7×10^{-5}, 3.35×10^{-4}, 10, and 40 mg.kg $bw^{-1}.d^{-1}$ for 112 days. In this study, rats exposed to doses from 6.7×10^{-5} mg.kg $bw^{-1}.d^{-1}$ had lower testis, parenchymal and epididymal weight and lower testosterone concentrations than control rats. No significant difference was reported between the low and the high exposure groups for these parameters. A significant lower sperm motility was observed in the highest dose group (40 mg.kg $bw^{-1}.d^{-1}$). Aluminium exposure did not alter the histology of testis and epididymis and sperm morphology (Mouro et al. 2018).

In another study, male Wistar rats (n=4 per group) were administered, through gavage for 90 days, 0 or 4.2 mg.kg $bw^{-1}.d^{-1}$ of aluminium chloride or 1 g ethanol.kg $bw^{-1}.d^{-1}$ or both. Rats exposed orally to aluminium or ethanol had a loss of normal distribution of spermatogenic cells in the seminiferous tubules and few fragmented sperms in the lumen. More adverse effects were observed in rats exposed concomitantly to ethanol and aluminium and, the authors concluded that ethanol increases the impact of aluminium on testis (Ghosh, Kant Sharma, and Yadav 2021a). LOAEL was 4.2 mg.kg $bw^{-1}.d^{-1}$ of aluminium chloride, or 0.85 mg Al.kg $bw^{-1}.d^{-1}$.

In another study of Gosh et al., female Wistar rats (n=4 per group) were also exposed orally and for 3 months, through gavage, to 0 or 4.2 mg.kg $bw^{-1}.d^{-1}$ of aluminium chloride with or without 1 g ethanol .kg $bw^{-1}.d^{-1}$. A significant increase of atretic follicles with degenerated ova and vacuolation was seen in the ovary of aluminium treated rats in addition to the rupture of zona pellucida in oocyte. In this study, authors also observed that ethanol increased the impact of aluminium on the ovary (Ghosh et al. 2021b). LOAEL was 4.2 mg.kg $bw^{-1}.d^{-1}$ of aluminium chloride, equivalent to 0.85 mg Al.kg $bw^{-1}.d^{-1}$.

Multigeneration studies:

Hirata-Koizumi et al., conducted a multigeneration GLP-compliant study to evaluate the effect of aluminium on reproduction and development. Twenty-four male and 24 female Crl:CD (SD) rats were given, through water, 0, 120, 600 or 3000 mg.L^{-1} of aluminium sulphate from the age of 5 weeks for 10 weeks prior to mating, during mating and gestation (Generation F0). Males were then sacrificed, and females were also exposed through weaning and then sacrificed. At weaning, 24 male and 24 female pups were considered as generation F1 and were given the aluminium sulphate for 10 weeks prior to mating, during mating and gestation, and, for the females, through weaning, same exposure scheme as F0. Aluminium exposure from the diet and drinking water were reported. At the three aluminium sulphate concentrations, a decrease in water consumption was observed and linked to the pH of water. It was associated with a decrease of food consumption in the 600 and 3000 mg.L^{-1} groups and a decrease of body weight in the 3000 mg.L^{-1} group. There was a decrease in preweaning body weight gain in the F1 & F2 pups in the 3000 mg.L^{-1} group in addition to a decrease in the liver and spleen weight at weaning. In addition, at 3000 mg.L^{-1} there was a slight delay in the vaginal opening. On another hand, aluminium did not cause changes in other reproductive and developmental parameters and no developmental neurobehavioral toxicity was reported. The NOAEL was considered to be 600 mg.L^{-1} equivalent to 41 mg.kg $bw^{-1}.d^{-1}$ of aluminium_sulphate. Considering the intake from food and drinking water, NOAEL was 8.06 mg Al.kg $bw^{-1}.d^{-1}$ (Hirata-Koizumi et al. 2011b). The LOAEL was considered to be 3000 mg.L^{-1} (188 mg.kg $bw^{-1}.d^{-1}$) of aluminium sulphate equivalent to 31.2 mg Al.kg $bw^{-1}.d^{-1}$ considering intake from food and water.

Another two-generation GLP-compliant study was conducted by Hirata-Koizumi et al. and included 24 male and 24 female Crl:CD(SD) rats (F0) who were exposed to either 0, 50, 500 or 5000 mg.L^{-1} of aluminium ammonium sulphate through drinking water at 5 weeks of age for 10 weeks. Afterwards female rats were mated with males from the same dosage group. F0 male rats were killed after parturition and F0 females were necropsied after weaning of their offsprings but were administrated aluminium ammonium sulphate during mating, gestation and

lactation periods. At weaning, 24 male and 24 female pups were identified to be generation F1 and were exposed as generation F0, to aluminium ammonium sulphate for 10 weeks before mating, during mating and gestation and during weaning for females. Aluminium exposure from diet was reported. A decrease in water consumption was reported in all treated groups but was related to the low pH of drinking water. At 5000 $mg.L^{-1}$ there was a transient body weight decrease in parental rats. Female and male reproductive performance were not affected by aluminium treatment (oestrous cycle, copulation, fertility index, precoital interval, gestation length, number of implantations, number of pups delivery, delivery index, sperm parameters), changes in reproductive organs were not reported and, in F1 and F2 pups there were no malformations, sex ratio or viability difference with the control group. A decrease in body weight was reported in male and female F1 pups on PND 21 and 14 & 21, respectively and on PND 26 in F2 pups (the reduced preweaning body weight gain might be due to decrease in water consumption). However, there was no difference in body weight at birth between control groups and aluminium treated groups. Vaginal opening was delayed in F1 female pups at 5000 $mg.L^{-1}$; no differences were reported regarding time of preputial separation in F1 male pups. In F1 and F2 weanlings, there was a decrease in liver, spleen and thymus weight at 5000 $mg.L^{-1}$ without histopathological changes. There was no aluminium treatment effect on locomotor activity, righting reflex and negative geotaxis reflex. The authors considered the NOAEL to be 500 $mg.L^{-1}$ of aluminium ammonium sulphate equivalent to 33.5 $mg.kg\ bw^{-1}.d^{-1}$ expressed as aluminium 3.81 $mg.kg\ bw^{-1}.d^{-1}$. Considering diet aluminium income, the calculated total aluminium level was 5.35 $mg\ Al.kg\ bw^{-1}.d^{-1}$ (Hirata-Koizumi et al. 2011a). The LOAEL was considered to be 5000 $mg.L^{-1}$ of aluminium ammonium sulphate; considering combined income from food and drinking water, LOAEL was 305 $mg.kg\ bw^{-1}.d^{-1}$ and 36.3 $mg\ Al.kg\ bw^{-1}.d^{-1}$.

- Gerbils

A recent study aimed at assessing the effect of prenatal aluminium exposure on gerbils' prostate. Pregnant gerbils (*Meriones unguiculatus*) were orally exposed, by gavage, to 0 or 100 $mg.kg\ bw^{-1}.d^{-1}$ of aluminium chloride (delivering 20.2 $mg\ Al.kg\ bw^{-1}.d^{-1}$; 1/35 LD50) during Gd17 to GD24. Following birth, males and female gerbils were separated and euthanized at either PN1 or PN90 (8 pups per group). A decrease in the body weight of PN1 males and females, a reduced anogenital distance of PN1 females, changes in the prostate developmental patterns of PN1 animals causing an increase in proliferative status and a decrease in the immunostaining of androgen receptor were reported in the aluminium exposed groups. These effects were permanent as some were also observed in the adult gerbils (Gomes et al. 2019). The LOAEL was 20.2 $mg\ Al.kg\ bw^{-1}.d^{-1}$.

The authors conducted another study aiming to assess the effect of aluminium neonatal exposure on the male and female paraurethral gland of gerbils. Male and female gerbils (8 per group) were exposed, by gavage, to 0 or 10 $mg.kg\ bw^{-1}.d^{-1}$ of aluminium chloride (delivering 2.02 $mg\ Al.kg\ bw^{-1}.d^{-1}$; 1/345 LD50), from day PND1 to PND14. Aluminium caused morphological changes in the ventral male paraurethral gland (intensified prostate branching morphogenesis with greater length, number and area of prostatic epithelial buds and, increased immunostaining of the androgen receptor) and in the female paraurethral gland (up regulation of the androgen receptor and oestrogen receptor α) and altered the prostate hormonal regulation of males and females (Gomes et al. 2020). The LOAEL was 2.02 $mg\ Al.kg\ bw^{-1}.d^{-1}$.

Male and female gerbils (*Meriones unguiculatus*) orally exposed over 30 days to 10 $mg.kg\ bw^{-1}.d^{-1}$ to aluminium chloride showed toxic effects on their paraurethral gland and gonads (Da Silva Lima et al. 2020). In another study, with the same exposure design, male gerbils had a paraurethral gland increased cell proliferation, glandular hyperplasia, increased secretory activity and greater androgen receptor immunoreactivity when euthanized one day after the

aluminium treatment. When gerbils were euthanized 30 days after the end of the treatment, a partial recovery of the prostate was observed in males, however, in females, 30 days recovery wase not enough for paraurethral glands healing (Da Silva Lima et al. 2022). LOAEL for both studies was of 10 mg.kg $bw^{-1}.d^{-1}$ of aluminium chloride, equivalent to 2.024 mg Al.kg $bw^{-1}.d^{-1}$.

- Rabbits

Four New Zealand rabbit groups were given through gavage, ascorbic acid (40 mg.kg $bw^{-1}.d^{-1}$) or aluminium chloride (34 mg.kg $bw^{-1}.d^{-1}$) or ascorbic acid & aluminium chloride. Results showed that rabbits exposed to 34 mg.kg $bw^{-1}.d^{-1}$ of aluminium chloride over 16 weeks had a significant decrease in feed intake, body weight, relative weights of testes and epididymis, means of semen ejaculated volume, sperm concentration, total sperm output, sperm motility, total sperm ejaculate and libido (Yousef, El-Morsy, and Hassan 2005). LOAEL was 34 mg.kg $bw^{-1}.d^{-1}$ of aluminium chloride equivalent to 6.8 mg Al.kg $bw^{-1}.d^{-1}$.

- Guinea pigs

Hartley guinea pigs inhaling 0.065, 0.65 or 6.5 mg $Al.m^{-3}$ as aluminium chlorohydrate over 6 months had no histological changes in their reproductive tissues (Steinhagen, Cavender, and Cockrell 1978). The NOAEL is 6.5 mg $Al.m^{-3}$.

- Dogs

Male (n=4) and female (n=4) beagle dogs were fed diets containing 0, 3 000, 10 000 or 30 000 mg basic sodium aluminium phosphate per kg over 26 weeks. This exposure is equivalent to 4, 10, 27 or 75 and 3, 10, 22 or 80 mg Al.kg $bw^{-1}.d^{-1}$ for male and female dogs respectively. In the high dose group, males had a decrease in food consumption and in body weight associated with testicular changes. NOAEL for male dogs was considered to be 27mg Al.kg $bw^{-1}.d^{-1}$ (Pettersen et al. 1990).

Table 14. Animal studies on aluminium reproductive toxicity

Strain	Duration and exposure route	Dose	Al Compound	Endpoint	NOAEL	LOAEL	Reference
Mice							
BALB/c (n≈ 6 per group)	Gd7-Gd16 Gavage	0 (ip), 200, 300 mg.kg $bw^{-1}.d^{-1}$	Aluminium chloride	Increased incidence of resorptions		41 mg Al.kg $bw^{-1}.d^{-1}$	Cranmer et al. (1986)
Swiss-Webster (n= 16 per group)	Gd1-Ld21 In diet	25 (control), 500 or 1000 µg $Al.g^{-1}.diet^{-1}$	Aluminium lactate	Altered gestational length from 500 µg $Al.g^{-1}$ diet		155 mg Al.kg $bw^{-1}.d^{-1}$	Donald et al. (1989)
Swiss-Webster (Control: n=14, Al group: n=9)	Gestation and lactation In diet	25 (control) or 1000 µg $Al.g^{-1}$ diet	Aluminium lactate	No effects on litter size, birth weight, crown-rump length, or sex ratio	250 mg Al.kg $bw^{-1}.d^{-1}$		Golub et al. (1992a)
Rats							
Fischer-344 (n=20 per group)	6 months (5d/wk and $6hr.d^{-1}$) Inhalation	0, 0.065, 0.65 or 6.5 mg $Al.m^{-3}$	Aluminium chlorohydrate	Histological changes in reproductive tissues	6.5 mg $Al.m^{-3}$		Steinhagen et al. (1978)
Sprague-Dawley (number not reported)	Males: 60 days prior mating Females 14 days prior to mating till end of lactation Gavage	0, 180, 360 or 720 mg.kg $bw^{-1}.d^{-1}$	Aluminium nitrate nonahydrate	No reproductive toxicity (male and female fertility)	52 mg Al.kg $bw^{-1}.d^{-1}$		Domingo et al. (1987a)
Wistar (n=10 per group)	120 days Drinking water	0, 64.18, 128.36 or 256.72 mg.kg $bw^{-1}.d^{-1}$	Aluminium chloride	Lower androgen receptor protein expression and mRNA expression		13 mg Al.kg $bw^{-1}.d^{-1}$	Sun et al. (2011)

Wistar (n=10 per group)	120 days Drinking water	0, 64.18, 128.36, or 256.72 mg.kg $bw^{-1}.d^{-1}$	Aluminium chloride	Decrease in serum levels of oestrogen, progesterone, FSH and LH		13 mg Al.kg $bw^{-1}.d^{-1}$	Wang et al. (2012)
Wistar (n= 10 per group)	120 days Drinking water	0, 64.18, 128.36 or 256.72 mg.kg $bw^{-1}.d^{-1}$	Aluminium chloride	Increase in sperm malformation rate		13 mg Al.kg $bw^{-1}.d^{-1}$	Zhu et al. (2014)
Wistar (n= 20 per group)	120 days Drinking water	0, 64, 128 or 256 mg.kg $bw^{-1}.d^{-1}$	Aluminium chloride	Lower protein expression of FSHR and LHR and lower energy supply in the ovary		12.96 mg Al.kg $bw^{-1}.d^{-1}$	Fu et al. (2014)
Wistar (n= 6 per group)	60 days Drinking water	1.5 or 8.3 mg Al.kg $bw^{-1}.d^{-1}$	Aluminium chloride	Alteration of spermatogenesis and sperm quality		1.5 mg Al.kg $bw^{-1}.d^{-1}$	Martinez et al. (2017b)
	42 days Gavage	100 mg Al.kg $bw^{-1}.d^{-1}$					
Wistar (n= 5 per group)	112 days Gavage	0, 6.7×10^{-5}, 3.35×10^{-4}, 10, and 40 mg.kg $bw^{-1}.d^{-1}$	Aluminium chloride	Lower testis, parenchyma and epididymal weight and lower testosterone concentrations		6.7×10^{-5} mg.kg $bw^{-1}.d^{-1}$	Mouro et al. (2018)
Wistar (n=4 per group)	90 days Gavage	0 or 4.2 mg.kg $bw^{-1}.d^{-1}$	Aluminium chloride	Loss of normal distribution of spermatogenic cells in the seminiferous tubules and few fragmented sperms in the lumen		0.85 mg Al.kg $bw^{-1}.d^{-1}$	Gosh et al. (2021)
Wistar (n=4 per group)	3 months Gavage	0 or 4.2 mg.kg $bw^{-1}.d^{-1}$	Aluminium chloride	Atretic follicles with degenerated ova and vacuolation, rupture of zona pellucida in oocyte		0.85 mg Al.kg $bw^{-1}.d^{-1}$	Gosh et al. (2021)
Gerbils							
Meriones unguiculatus (n= 20 for	30 days Gavage	0 or 10 mg.kg $bw^{-1}.d^{-1}$	Aluminium chloride	Toxic effect on paraurethral gland and gonads		2.024 mg Al.kg $bw^{-1}.d^{-1}$	Da Silva Lima et al. (2020)

each sex per group)							
Meriones unguiculatus (n= 20 for each sex per group)	30 days Gavage	0 or 10 mg.kg $bw^{-1}.d^{-1}$	Aluminium chloride	Toxic effect on paraurethral gland		2.024 mg Al.kg $bw^{-1}.d^{-1}$	Da Silva Lima et al. (2022)
Rabbits							
New Zealand (n= 6 per group)	16 weeks Gavage	34 mg.kg $bw^{-1}.d^{-1}$	Aluminium chloride	Reduced semen quality		6.8 mg Al.kg $bw^{-1}.d^{-1}$	Yousef et al. (2005)
Guinea pigs							
Hartley (n= 20 per group)	6 months (5d/wk, 6hr.d^{-1}) Inhalation	0, 0.065, 0.65 or 6.5 mg $Al.m^{-3}$	Aluminium chlorohydrate	Histological changes in reproductive tissues	6.5 mg $Al.m^{-3}$		Steinhagen et al. (1978)
Dogs							
Beagle (n= 4 for each sex per group)	26 weeks In diet	4, 10, 27 or 75 and 3, 10, 22 or 80 mg Al.kg $bw^{-1}.d^{-1}$ for male and female	Aluminium phosphate	Decrease in food consumption and in bw associated with testicular changes	27 mg Al.kg $bw^{-1}.d^{-1}$	75 mg Al.kg $bw^{-1}.d^{-1}$	Pettersen et al. (1990)

Table 15. Animal studies on aluminium developmental toxicity

Stain	Duration and exposure route	Dose	Al Compound	Endpoint	NOAEL	LOAEL	Reference
Mice							
Swiss Webster F0 (n= 16 per group) F1 (n= 4/ litter)	Gd1-Ld21 In diet	25, 500 or 1000 mg Al.kg^{-1} diet	Aluminium lactate	No effects on birth weight, peri and post-natal pup mortality	310 mg Al.kg bw^{-1}.d^{-1}		Donald et al. (1989)
Swiss F0 (n= 20 per group)	Gd6 to Gd15 Gavage	0, 23, 46 or 92 mg Al.kg bw^{-1}.d^{-1}	Aluminium hydroxide	No signs of embryotoxicity including morphological abnormalities	92 mg Al.kg bw^{-1}.d^{-1}		Domingo et al. (1989)
Swiss (DD1) F0 (n= 10-13 per group)	Gd6 to Gd15 Gavage	0 or 57.4 mg Al.kg bw^{-1}.d^{-1}	Aluminium lactate	Reduced foetal body weight, cleft palate and delayed foetal ossification		57.4 mg Al.kg bw^{-1}.d^{-1}	Colomina et al. (1992)
Swiss (DD1) F0 (n= 10-13 per group)	Gd6 to Gd15 Gavage	0 or 57.4 mg Al.kg bw^{-1}.d^{-1}	Aluminium hydroxide		57.4 mg Al.kg bw^{-1}.d^{-1}		Colomina et al. (1992)
Swiss (number not reported)	Gd6 to Gd15 Gavage	0, 103 mg Al.kg bw^{-1}.d^{-1}	Aluminium hydroxide	No developmental effects	103 mg Al.kg bw^{-1}.d^{-1}		Colomina et al. (1994)
CD-1 F0 (n= 10-14 per group)	One day between Gd8-Gd12 Gavage	0 or 71 mg Al.kg bw^{-1}	Aluminium nitrate	Reduced foetal body weight, reduced ossification		71mg Al.kg bw^{-1}	Albina et al. (2000)
Rats							

Wistar	Gd 8 until parturition In diet	0, 160 or 200 mg Al.kg $bw^{-1}.d^{-1}$	Aluminium chloride	Reduced pup weight on PND1		160 mg Al.kg $bw^{-1}.d^{-1}$	Bernuzzi et al. (1986)
Sprague Dawley	Gd14 to Gd21 Gavage	0, 13, 26 or 52 mg Al.kg $bw^{-1}.d^{-1}$)	Aluminium nitrate	Reduced number of litters and live pups per litter		13 mg Al.kg $bw^{-1}.d^{-1}$	Domingo et al. (1987c)
Sprague Dawley F0 (n= 10 per group) F1 (n= more than half of the foetuses)	Gd6 to Gd 14 Gavage	0, 13, 26 or 52 mg Al.kg $bw^{-1}.d^{-1}$	Aluminium nitrate	Higher number of runt foetuses, reduced bw, delayed ossification, increase of congenital malformations and minor anomalies		13 mg Al.kg $bw^{-1}.d^{-1}$	Paternain et al. (1988)
Wistar F0 (n= 6 to 12 per group)	Gd1 to parturition In the diet	0, 20, 60 and 80mg Al.kg $bw^{-1}.d^{-1}$	Aluminium chloride	Reduction of pup weight, higher postnatal mortalities	20 mg Al.kg $bw^{-1}.d^{-1}$	60 mg Al.kg $bw^{-1}.d^{-1}$	Bernuzzi et al. (1989a)
Wistar F0 (n= 6 to 10 per group)	Gd1 to parturition In the diet	0, 9, 18 and 36 mg Al.kg $bw^{-1}.d^{-1}$	Aluminium lactate	Reduction of pup weight, higher postnatal mortalities	18 mg Al.kg $bw^{-1}.d^{-1}$	36 mg Al.kg $bw^{-1}.d^{-1}$	Bernuzzi et al. (1989a)
Wistar rats F0 (n= 6 to 9 per group)	Gd1-Gd7 or Gd1-Gd14 or Gd1-partution In the diet	0 or 400 mg Al.kg $bw^{-1}.d^{-1}$	Aluminium lactate	No effect of on the litter size, mortality rate or weight of pups	400 mg Al.kg $bw^{-1}.d^{-1}$		Muller et al. (1990)
Wistar F0 (n= 18-19 per group)	Gd6 to 15 Gavage	0, 66, 132 or 264 mg Al.kg $bw^{-1}.d^{-1}$	Aluminium chloride	No embryotoxicity		264 mg Al.kg $bw^{-1}.d^{-1}$	Gomez et al. (1990)
Sprague Dawley F0 (n= 11 to 17 per group)	15-day premating to post-weaning In water	0, 50 or 100 mg Al.kg $bw^{-1}.d^{-1}$ + citric acid	Aluminium nitrate nonahydrate	Delay in vaginal opening	50 mg Al.kg $bw^{-1}.d^{-1}$		Colomina et al. (2005)

F1 (n= 8 per litter)							
Crl:CD (SD)	Multigenerational GLP-compliant study In water	0, 120, 600 or 3000 mg.L^{-1}	Aluminium sulphate	Decrease in preweaning bw, decrease in liver & spleen weight at weaning, delayed vaginal opening	8.06 mg Al.kg bw^{-1}.d^{-1}	31.2 mg Al.kg bw^{-1}.d^{-1}	Hirata-Koizumi et al. (2011b)
Crl:CD (SD)	Multigenerational GLP-compliant study In water	0, 50, 500 or 5000 mg.L^{-1}	Aluminium sulphate	Delayed vaginal opening in F1 female, decrease in liver, spleen and thymus weight	3.81 mg.kg bw^{-1}.d^{-1}	36.3 mg Al.kg bw^{-1}.d^{-1}	Hirata-Koizumi et al. (2011a)
Gerbils							
Meriones unguiculatus F0 (n=10 per group) F1 (n=8 per group)	Gd 17 to 24 Gavage	0 or 20.2 mg Al.kg bw^{-1}.d^{-1}	Aluminium chloride	Decrease in bw of PN1, changes in the prostate developmental patterns of PN1		20.2 mg Al.kg bw^{-1}.d^{-1}	Gomes et al. (2019)
Meriones unguiculatus (n= 8 of each sex per group)	PND 1 to 14 Gavage	0 or 2.02 mg Al.kg bw^{-1}.d^{-1}	Aluminium chloride	Morphological changes in the ventral male prostate and female prostate		2.02 mg Al.kg bw^{-1}.d^{-1}	Gomes et al. (2020)

Table 16: Animal studies on aluminium neurodevelopmental toxicity

Strain	Duration and exposure route	Dose	Al Compound	Endpoint	NOAEL	LOAEL	Reference
Mice							
Swiss Webster (F0= 16 per group) F1 (n= 4/ litter)	From conception to Ld21 In diet	25 (control), 500 or 1000 µg Al.g^{-1} diet	Aluminium lactate	Decreased forelimb, increased hindlimb grip strength, increased foot splay in weanlings		155 mg Al.kg bw^{-1}.d^{-1}	Donald et al. (1989)
Swiss-Webster F0 (n= 9-14 per group) F1 (n= 2 pups per litter)	G: Gd1 -Gd19 or G+ D: Gd1 - Ld21 or L: Ld1-Ld21 In diet	25 (control) or 1000 µg Al.g^{-1} diet	Aluminium lactate	Decrease forelimb grip strength (G), increase in hindlimb grip strength and tail withdrawal times (gestation and lactation groups), increase in negative geotaxis latency (L)		250 mg.kg bw^{-1}.d^{-1}	Golub et al. (1992a)
Swiss-Webster (n= 8 males and females per group)	From conception to weaning In diet	7 (control), 500 or 1000 µg Al.g^{-1} diet	Aluminium lactate	Decrease in forelimb and hindlimb grip strength and in the startle response		155 mg Al.kg bw^{-1}.d^{-1}	Golub et al. (1995)
Swiss Webster (n= 8 per group)	From conception to PND 35 In diet	7 (control), 500, or 1000 µg Al.g^{-1} diet	Aluminium lactate	Performance of the Delayed spatial Alternation task	330 mg Al.kg bw^{-1}.d^{-1}		Golub and Germann (1998)
Swiss Webster (n= 18 per group)	Conception – month 24 of age In diet	7 (control) or 1000 µg Al.g^{-1} diet	Aluminium lactate	Decreased forelimb and hindlimb strength, decreased thermal activity		100 mg Al.kg bw^{-1}.d^{-1}	Golub et al. (2000)
Swiss Webster (n = 20 per group)	From conception to PND 35 In diet	7 (control), 100, 500, or 1000 µg Al.g^{-1} diet	Aluminium lactate		26 mg Al.kg bw^{-1}.d^{-1}	130 mg Al.kg bw^{-1}.d^{-1}	Golub and German (2001)

Swiss-Webster (n= 21 pups per group)	From Gd1 to PND15 In water	0, 300 or 600 mg Al.kg $bw^{-1}.d^{-1}$	Aluminium chloride	Deficit in locomotor activity, learning capacity and cognitive behaviours		300 mg Al.kg $bw^{-1}.d^{-1}$	Abu Taweel et al. (2012)
Rats							
Sprague Dawley F0 (n= 11-17 per group) F1 (n= 1 male & 1 female of each litter)	15 days premating and from Gd1 to Ld21 In water	0, 50 or 100 mg Al.kg $bw^{-1}.d^{-1}$ (+citric acid added)	Aluminium nitrate	Decreased forelimb grip	50 mg Al.kg $bw^{-1}.d^{-1}$	100 mg Al.kg $bw^{-1}.d^{-1}$	Colomina et al. (2005)
Sprague Dawley (n=17-21 per group)	Conception- 1 or 2 years old In water	0, 50 or 100 mg Al.kg $bw^{-1}.d^{-1}$ (+citric acid added)	Aluminium lactate	Performance of water maze test	100 mg Al.kg $bw^{-1}.d^{-1}$		Roig et al. (2006)
Wistar (n= 10 per group)	From conception to 4 months age In water	0 or 3 $g.L^{-1}$ $AlCl_3$	Aluminium chloride	Increased GFA-P astrocytes in brain, increased anxiety, reduced locomotor activity		600 mg $Al.L^{-1}$	Erazi et al. (2010)
Sprague Dawley F0 (n= 20 per group) F1 (n=4 of each sex per litter)	From Gd6 to PND 364 In water	0, 30, 100 or 300 mg Al.kg $bw^{-1}.d^{-1}$	Aluminium citrate	Decrease in hindlimb and forelimb grip strength (+other effects)	30 mg Al.kg $bw^{-1}.d^{-1}$	100 mg Al.kg $bw^{-1}.d^{-1}$	Poirier et al. (2011)

Wistar (n= 8 per group)	From parturition to 3-month age In water	0, 0.2, 0.4 or 0.6% of $AlCl_3$	Aluminium chloride	Pathological changes in neuronal and synaptic ultrastructure and impaired spatial memory ability		400 mg $Al.L^{-1}$	Zhang et al. (2013)

4.9 Macrophagic myofasciitis

Macrophagic myofasciitis (MMF) is an inflammatory condition characterised by specific muscle lesions infiltrated by macrophages containing aluminium crystal inclusions and was reported for the first time in 1982 (Mrak 1982). This lesion generally results from aluminium adjuvant depots after vaccine injection. Though the duration of this phenomenon after vaccination is not known and could be variable from an individual to another, there is no indication that it is pathologic.

More recently, French authors published from 1998 to 2023, clinical and experimental studies with the aim to establish an association between MMF and a systemic syndrome diversely associating diffuse myalgias, arthralgias, fatigue, muscle weakness, fever and cognitive alterations' (Gherardi et al. 1998; Eickhoff and Myers 2002; HCSP 2013; J.-P. Goullé and Grangeot-Keros 2020). However, the published studies suffer several methodologic flaws: inclusion criteria of the patients in the cohort are not presented; the relative frequencies of the signs and symptoms constituting the syndrome, as well the sex ratio of the patients in the cohort are broadly fluctuating from a publication to another. The cohort is constituted of patients with a biopsy of the deltoid showing a MMF and also complaining for the systemic syndrome described above. There is (as ethically expected) no control group with no systemic complaint and results of a deltoid biopsy.

Finally, MMF as a local reaction after intramuscular injection of an aluminium-adjuvanted vaccine is a largely documented phenomenon. There is no demonstration that it is or can be causally associated with a systemic syndrome or illness. Strong arguments against a causal link are that this association has been quasi-exclusively described in France and by the same authors and rarely in children, though the latter constitute the fraction of the population with the bigger exposure to aluminium adjuvanted vaccines (Gherardi et al. 1998; Eickhoff and Myers 2002; HCSP 2013; J.-P. Goullé and Grangeot-Keros 2020).

Evaluations by Afssaps (2004) Scientific Committee and by HCSP (2013) both concluded that there is no evidence that MMF following intramuscular injection of aluminium-adjuvanted vaccines is causally associated with one or more systemic manifestations (Afssaps 2004; HCSP 2013).

In 2022, the US Centers for Disease Control and Prevention (CDC) acknowledged an observational study in which a possible association between exposure to vaccine aluminium and the subsequent development of persistent asthma in a cohort of children was identified (Daley et al. 2023). This finding is considered by the CDC to be a health signal but does not call into question the assessment of the risk of exposure to aluminium after following the vaccination schedule (Mitkus et al. 2011).

4.10 Genotoxicity

Since the aluminium salts are able to induce an oxidative stress, they could possibly induce mutagenicity in vivo using this mechanism of action.

4.10.1 *In vitro* studies

In studies documented in EFSA's report, aluminium ion (Al^{3+}) was proved to interact with DNA *in vitro* by binding to phosphate oxygen. Several aluminium compounds showed negative results in bacterial mutagenicity assays and in mammalian cells in vitro and, others produced DNA damage (EFSA 2008). These studies are reported below.

Aluminium lactate at concentration of 1.8 - 5.5 µmol/plate gave negative response in the reverse mutation test using various *Salmonella typhimurium* strains (Gava et al. 1989). Negative results were also observed for aluminium fluoride at 0.02-119 µmol/plate (Shimizu et al. 1985), aluminium silicate at 0.96 - 38.5 µmol/plate (Zeiger et al. 1987), sodium aluminium silicate at 0.36 - 108.1 µmol/plate (Prival, Simmon, and Mortelmans 1991), aluminium chloride hexahydrate at 0-100 nmol/plate (Marzin and Phi 1985), aluminium sulphate up to 5000 µg/plate (ECHA, Registration dossier) and aluminium chloride at concentrations of 0.3 and 3.0 $mg.L^{-1}$ in an assay carried out in suspension culture (Ahn and Jeffery 1994).

In other studies, bacterial tryptophan reverse mutation assay using *Escherichia coli WP2* strain, showed negative responses with aluminium chloride, aluminium fluoride, calcium aluminosilicate and sodium aluminium silicate to induce gene mutations (Seo, and Lee 1993; Shimizu et al. 1985; Prival, Simmon, and Mortelmans 1991).

No mutagenic activity was induced by aluminium oxide, aluminium chloride or aluminium sulphate at concentrations of 1-10 mM in the rec-assay using *Bacillus subtilis* strains (ATSDR 2006).

In L5178Y mouse lymphoma assay, no forward mutations were detected with aluminium chloride at concentrations up to 625 µg aluminium chloride/ml (Oberly, Piper, and McDonald 1982).

The induction of micronuclei in human lymphocytes was increased following exposure to aluminium sulphate (exposure for 48 h after PHA stimulation) (Migliore et al. 1999) and to aluminium chloride (with a decrease at high dose correlated to an increase of apoptosis) (Banasik et al. 2005). Paz et al. have also observed a significant increase in the quantity of micronucleus in human lymphocytes (from the peripheral blood) exposed to aluminium chloride at concentrations of 5 µM, 10 µM and 20 µM (Paz et al. 2017).

Effects of aluminium chloride (1, 2, 5, 10 and 25 µg/ml) on DNA damage and apoptosis in human lymphocytes were assessed using a comet assay. The results showed a dose-dependent increase in DNA damage up to the dose of 10 µg/mL of aluminium chloride and decline at 25 $\mu g.mL^{-1}$ due to increase in apoptosis (Lankoff et al. 2006). The authors then evaluated the effect of aluminium on DNA repair and found that aluminium chloride treated cells had a decreased capacity of DNA repair compared to controls (Lankoff et al. 2006). Lima et al. have also observed aluminium induced DNA damage in human lymphocytes in addition to structural chromosomal aberrations (Lima et al. 2007).

In the study by Tenan et al. (2021), on V79 hamster lung fibroblasts exposed to aluminium, dose-dependent increases in DNA double strand breaks, and chromosome numerical abnormalities (aneuploidy) as well as arrest in the G2/M phase of the cell cycle, were observed. Additionally, during mitosis, abnormal multipolar mitotic spindles were detected (SCCS 2023).

4.10.2 *In vivo* studies

In vivo genotoxicity studies in rodents showed a clastogenic potential of aluminium (EFSA 2008).

In a study by Manna and Das (1972), mice intraperitoneally injected with aluminium chloride exhibited a significant increase in chromosome aberrations in the bone marrow. However, no clear dose-response relationship was observed (ATSDR 2008; EFSA 2008).

As stated in EFSA (2008), the administration of aluminium sulphate (17, 22, 28, 43, 85 or 172 mg $Al^{3+}.kg\ bw^{-1}$) or aluminium potassium sulphate (28 or 43 mg $Al^{3+}.kg\ bw^{-1}$) to rats by gavage, daily over 21 days, led to a dose-dependent inhibition of cell division and an increase in chromosome aberrations, in the bone marrow (Roy, Sharma, and Talukder 1991). Furthermore, a dose-dependent induction of micronuclei was observed in the bone marrow of mice injected intraperitoneally with aluminium sulphate (2 doses, 24 hours apart). Aluminium

sulphate also induced sister chromatid exchanges in the bone marrow of mice injected intraperitoneally, in a dose related manner (Roy, Dhir, and Sharma 1992).

In a study by Paz et al., Swiss mice (n= 8 per group) were orally administered hydrated aluminium chloride at 0, 49, 98 or 161 mg Al.kg bw^{-1} to assess aluminium's possible genotoxic activity using micronucleus test. The study included a negative control and a positive control group. An increase of micronucleus number was observed in all aluminium concertation groups and significant alterations in all the evaluated organs were identified and verified by the presence of irreversible lesions (Paz et al. 2017).

In another study, Sprague Dawley rats (n= 8 per group) were gavaged with 0 or 2000 $mg.L^{-1}$ aluminium (as aluminium chloride) 5 days/week for 90 days with or without N-nitroso-N-methyl urea (NMU) induction of breast cancer. A higher number of micronucleus count in peripheral blood erythrocytes was observed following the exposure to +2000Al/−NMU and −Al/+NMU treatments indicating that treatment containing only aluminium can independently cause genotoxicity in rats. Furthermore, comets were observed after 10 and 15 days in the Comet Assay in rats receiving the +2000AL/-NMU treatment (García-Alegría et al. 2020).

As stated in the recent opinion by SCCS, in the study by Mandriota et al. (2020), normal mouse mammary epithelial cells after long-term culture in the presence of aluminium chloride formed tumours and metastases when injected into syngeneic and immunocompetent BALB/cByJ mice. Aluminium chloride rapidly increased chromosomal structural abnormalities in the cultured cells (SCCS 2023).

In the study of Jalili et al., acute exposure to aluminium chloride (25 mg.kg bw^{-1} through gavage) induced slight but non-significant oxidative DNA damage in peripheral blood lymphocytes of Sprague-Dawley rats (n= 5 per group). No increase of micronuclei in both bone marrow cells and in colon was observed (Jalili et al. 2020).

EFSA (2008) stated that aluminium had genotoxic effects at high level of exposure, not relevant for human exposure through the diet. Nevertheless, an in vivo mammalian erythrocyte micronucleus test combined with in vivo mammalian alkaline comet assay with aluminium oxide has been requested by ECHA, but the test has not been performed yet. The results of this study may better clarify the assessment on the potential of aluminium salts to induce genotoxicity, as stated by SCCS in its latest opinion (SCCS 2023).

4.11 Carcinogenicity

4.11.1 Human data

According to the International agency for research on cancer (IARC), there is sufficient evidence in humans for the carcinogenicity of aluminium production using the Söderberg process. This activity is associated with elevated incidences of cancers of bladder and lung. These cancer hazards associated with aluminium production mainly result from exposure to polycyclic aromatic hydrocarbons (PAHs) rather than from exposure to aluminium or its related compounds (INRS 2021).

Based on the quantification of aluminium in breast cancer tissues, a potential link between antiperspirants and breast cancer was suggested by some authors, alongside observations of a high incidence of breast cancer in the upper outer quadrant, adjacent to the area of typical application of deodorants and/or antiperspirants (Darbre 2005; Exley et al. 2007). Epidemiological studies had assessed the association between exposure to aluminium through cosmetics containing aluminium and the risk of breast cancer but none of them established a causal link between aluminium exposure and breast cancer. It has been suggested that a

reverse causal effect cannot be excluded, implying that the breast tumour could accumulate aluminium (Linhart et al. 2017).

The SCCS has conducted safety assessments of aluminium exposure through cosmetic products on four occasions since 2014 (in 2014, 2020, 2023, and 2024). It concluded that despite the known genotoxic effects of aluminium, which may potentially contribute to the development of breast cancer, the existing data from both animal and epidemiological studies are presently insufficient to definitively establish a causal relationship between aluminium exposure and the risk of developing breast cancer.

4.11.2 Animal data

No reliable studies regarding cancer effects were identified in animals following acute or intermediate duration inhalation of aluminium or its compounds.

Oneda et al. did not report an increase of tumours incidence or other proliferative lesions in B6C3F1 mice ingesting aluminium potassium sulphate through diet at doses of 1.0, 2.5, 5.0 and 10.0% (w/w) over 20 months (the study included a control group). In this study, hepatocellular carcinoma's incidence was significantly decreased in the group of high-dose males (Oneda et al. 1994).

Following oral exposure of Swiss CD mice to aluminium potassium sulphate in drinking water (5 ppm Al, equivalent to 1.2 mg Al.kg $bw^{-1}.d^{-1}$) from weaning through their lifetime (mean lifespans were of 533 days), a significant increase in the incidence of gross tumours was observed in females (46.3% in the aluminium exposed group vs 29.8% in the control group). In addition, the incidence of lymphoma leukaemia was also significantly increased in females (10/41 vs 3/47) (Schroeder and Mitchener 1975b). No significant increase of tumour incidence was observed in male mice.

In another study, Long-Evans rats were exposed to aluminium potassium sulphate in their drinking water (5 ppm Al, equivalent to 0.6 mg Al.kg $bw^{-1}.d^{-1}$) from weaning through their lifetime (2 years). Only males presented an increase in the incidence of gross tumours (52% in the aluminium exposed group vs 15% in the control group). Of the tumours, six were malignant in the aluminium exposed group vs 2 in the control group (Schroeder and Mitchener 1975a). No significant increase of tumour incidence was observed in female rats.

In both studies, only one dose of aluminium was used and, the type of tumours and the organs where they were found were not mentioned. Thus, it could not be determined if this incidence increase was dose dependent. The levels of aluminium in the base diet were mentioned but the diet was low in trace elements.

In a study by Pigott et al., male and female rats (Wistar) did not show an increase in cancer rate following whole-body inhalation of 2.18-2.45 mg $Al.m^{-3}$ as alumina fibres (≈ 96% aluminium oxide, Saffil fibres & aged Saffil fibres with a median diameter ranging between 3.0-3.3 µm) over 86 weeks (5 d/wk and $6hr.d^{-1}$) (Pigott, Gaskell, and Ishmael 1981).

Four groups of female Sprague Dawley rats (n= 8 per group) were exposed to 0 or 2000 $mg.L^{-1}$ aluminium (as aluminium chloride) by gavage 5 days/week for 90 days with or without N-nitroso-N-methylurea (NMU) induction of breast cancer: −Al/−NMU; +2000Al/+NMU; +2000Al/−NMU; −Al/+NMU. The dose of aluminium is equivalent to 10 mg Al.kg $bw^{-1}.d^{-1}$. The group +2000Al/−NMU had a significantly higher aluminium concentration in the mammary gland. In the aluminium-treated groups, there was a moderate intraductal cell proliferation (hyperplasia) but no cancer development; cell proliferation was minimal in the –Al/+NMU group (García-Alegría et al. 2020).

4.12 Sensitive population

People suffering from kidney failure are the main population at risk because of the decreased glomerular filtration leading to an increase in internal exposure at the same external dose and are therefore more sensitive to aluminium toxicity (Krewski et al. 2007; ATSDR 2008).

4.13 Synthesis of the toxicological profile

■ Acute toxicity

No relevant studies demonstrating the effects of acute inhalation or ingestion of aluminium or its compounds in humans have been identified.

Several cases of aluminium-related encephalopathy have been reported in patients undergoing otoneurosurgery with bone reconstruction using aluminium-containing cement (Hantson et al. 1995; Lévêque et al. 1996; Reusche et al. 2001). Cases of acute encephalopathy with high plasma aluminium levels have also been reported, following post-surgical bladder irrigation with alum. However, in most of these latter cases, aluminium was probably not the sole or main cause of neurological symptoms, as severe hydroelectrolytic disturbances were obviously or probably associated (Phelps et al. 1999).

In laboratory animals, LD50s have been reported for several aluminium compounds in rats, ranging from 162 mg Al.kg bw^{-1} (aluminium bromide) to over 730 mg Al.kg bw^{-1} (aluminium sulphate). A 4-hour inhalation exposure in rats to 1000 $mg.m^{-3}$ was not lethal, but multifocal microgranulomas in the lungs and hilar lymph nodes were detected (Thomson et al. 1986).

■ Irritation and sensitization

Anhydrous aluminium chloride is classified as skin corrosive (category 1B) in the harmonized CLP classification. Several CLP notifications have been received by ECHA concerning the skin and/or eye irritation effect of other aluminium compounds, including aluminium citrate, aluminium hydroxide, aluminium lactate, aluminium nitrate, aluminium phosphate, aluminium silicate, aluminium sodium dioxide and aluminium sulphate.

The SCCS has stated that there are no sufficient data in humans to suggest that aluminium compounds used in antiperspirants cause allergies, and that, given their widespread use, this effect, if it exists, appears to be rare. Animal data do not indicate any skin sensitization effect of aluminium compounds used in antiperspirants (SCCS 2023).

■ Subchronic and chronic toxicity

Numerous studies have documented respiratory effects associated with occupational exposure to aluminium. The spectrum of respiratory disorders includes wheezing, dyspnoea, impaired lung function, asthma and pulmonary fibrosis. However, the attribution of these disorders to aluminium exposure remains uncertain or even improbable in many studies, due to confounding factors including co-exposure to other toxic chemicals, particularly irritants. For example, co-exposures to hydrogen fluoride and other fluorides have been reported in electrolytic refineries in cases of potroom asthma or pulmonary fibrosis; co-exposure to ozone and ultrafine particles in workers exposed to welding fumes; co-exposure to crystalline silica in cases of fibrosis in workers exposed to bauxite (Krewski et al. 2007; ATSDR 2008). Contradictory data are reported concerning the pulmonary effects of finely ground aluminium powder: Some publications reported cases of pulmonary fibrosis in exposed workers, while other studies showed no evidence of fibrosis after prolonged exposure to fine aluminium

particles. Sporadic cases of pneumoconiosis associated with occupational exposure to aluminium have also been reported (Korogiannos, Babatsikou et Tzimas 1998; Kraus et al. 2000; Hull et Abraham 2002). Their low number and co-exposure to other chemical agents limit their interpretation.

The main toxic effects of aluminium reported after exposure in the workplace are cognitive impairments, characterised in several epidemiological studies by reduced performance in psychomotor and/or attention tests. The epidemiological studies either contained no data, or insufficient data, on airborne aluminium concentrations (no personal measurements or airborne dust concentrations). However, aluminium concentrations in blood (serum or plasma) or urine were reported, and differences in the concentration of the biomarker of exposure (BME) between exposed and unexposed workers were observed in relation to cognitive disorders, enabling NOAELs and/or LOAELs to be identified from these studies.

Several studies have been carried out on laboratory animals (mice, rats, gerbils, guinea pigs and dogs) to investigate the effects of sub-chronic or chronic oral or respiratory exposure to various aluminium compounds. Some of these studies showed neurotoxic effects after oral administration. Pulmonary effects have also been reported by inhalation. Haematological effects have also been reported in some studies following digestive administration. Divergent results have been observed concerning bone effects.

■ Reproductive and developmental effects

Several studies have investigated the effects of exposure to aluminium compounds on reproduction and development in laboratory animals (mice, rats, gerbils, rabbits, guinea pigs and dogs).

Reported toxicological effects on reproduction include increased incidence of resorptions, altered gestation length, reduced sperm quality, toxicity to paraurethral glands and gonads, and decreased serum levels of oestrogen, progesterone, FSH and LH. Other studies have shown no effect of aluminium exposure on the histology of reproductive tissues and fertility in males and females.

Various studies have observed developmental effects following aluminium exposure, such as reduced litter size, reduced pup weight, higher postnatal mortality, changes in postnatal prostate development patterns, delayed vaginal opening and increased congenital malformations (notably, cleft palate) and minor anomalies (notably, delayed ossification). Effects on neurodevelopment have also been demonstrated in several studies. Other studies, however, found no effects on birth weight, peri- and post-natal pup mortality, no signs of embryotoxicity, including morphological abnormalities, and no delay in vaginal opening.

■ Genotoxicity

Since aluminium salts are capable of inducing oxidative stress, they could potentially induce mutagenicity in vivo via this mechanism of action. In vitro and in vivo studies indicate that aluminium compounds can induce genotoxic effects, mainly at high exposure levels. EFSA noted that these levels are not relevant for human exposure via food. However, additional tests, such as the mammalian erythrocyte micronucleus assay and the mammalian cell Comet assay with aluminium oxide, are needed to further clarify the genotoxic potential of aluminium salts.

■ Carcinogenicity

According to the International agency for research on cancer (IARC), there is sufficient evidence in humans for the carcinogenicity of aluminium production using the Söderberg

process. This activity is associated with elevated incidences of cancers of bladder and lung. The cancer hazards associated with aluminium production mainly result from exposure to polycyclic aromatic hydrocarbons (PAHs) rather than from exposure to aluminium or its related compounds (INRS 2021).

Based on the quantification of aluminium in breast cancer tissues, a potential link between antiperspirants and breast cancer has been assumed. However, despite its potential genotoxic effects, existing data from animal and epidemiological studies are currently insufficient to definitively establish a cause-and-effect relationship between exposure to aluminium and the risk of developing breast cancer.

- **Sensitive populations**

People suffering from kidney failure are the main population at risk of aluminium over-impregnation and are therefore more sensitive to aluminium toxicity (Krewski et al. 2007; ATSDR 2008).

5 Overview of existing reference value for general population

- **US EPA**

In 2006, US EPA has derived a provisional oral reference dose (pRfD) of 1 mg/Al.kg $bw^{-1}.d^{-1}$ and a provisional inhalation reference concentration (pRfC) of 5 $\mu g.m^{-3}$ (respirable fraction). The oral point of departure (PoD) was obtained from a mice study (Golub et al. 1995) where a LOAEL[15] of 100 mg.kg $bw^{-1}.d^{-1}$ was considered for neurotoxicity in the offspring exposed in utero from conception and through weaning (decreased forelimb strength, increased hindlimb grip strength, and increased hindlimb foot splay distance). US EPA considered that increased grip strength has unclear toxicological significance, and increased grip strength and foot splay distance, did not persist after 2 weeks of no further exposure. An uncertainty factor (UF) of 3 for the use of a LOAEL instead of a NOAEL ($UF_{L/B}$), an UF_A of 10 by default for interspecies differences and an UF_H of 3 for interindividual differences as the effects were observed in a sensitive sub-group, which lead to a pRfD of 1mg.kg $bw^{-1}.d^{-1}$ (U.S. EPA 2006).

In the same publication, the pRfC derivation was based on human observations in a cohort of aluminium workers (Hosovski et al. 1990). Workers were exposed at concentrations of 4.6-11.5 mg $Al.m^{-3}$ (time-weighted average) for 12 years. US EPA did consider 4.6 mg $Al.m^{-3}$ as a LOAEC for psychomotor and cognitive impairment. An adjustment to continuous exposure duration was done considering respiratory rates of 20 $m^3.d^{-1}$ in the general population and 10 m^3 per workshift in workers and continuous exposure in the general population instead of exposure for 5 days a week in workers resulting in a $LOAEC_{ADJ}$ of 1.64 mg $Al.m^{-3}$. The pRfC was obtained after application of an UF_H of 10, an UF_L of 10 for the use of a LOAEC instead of a NOAEC (usually a default value of 3 would have been used) and an UF_D of 3 for the lack of inhalation studies leading to an overall UF of 300. Thus, the calculated pRfC was of 5.5 $\mu g.m^{-3}$ rounded to 5 $\mu g.m^{-3}$.

In 2023, US EPA proposed a pRfD for aluminium phosphate salts, this assessment is motivated by the impact of aluminium on inorganic phosphate salts. Since no human or animal data were available specifically for aluminium phosphate salts toxicity, they considered an alternative analogue approach, using the study of Golub et al. (1995). However, in this assessment, the lowest tested dose of 26 mg.kg $bw^{-1}.d^{-1}$ was considered to be the NOAEL. Thus, using a default 100 UF, they derived a pRfD of 0.3 mg.kg $bw^{-1}.d^{-1}$. No additional UF was considered, specifically regarding study duration, since "*a developmental study is selected as the principal study, and the severity of observed toxic effects doesn't appear to increase when exposure duration increases*" (U.S. EPA 2023). It is worth noting that aluminium phosphate salts are insoluble aluminium compounds.

- **ATSDR**

ATSDR (2008) has recommended a minimal risk level (MRL) of 1 mg.kg $bw^{-1}.d^{-1}$ for chronic exposure. This MRL was derived from a mice study (Golub et al. 2000) where mice were treated from conception to 2 years of age. Neurological effects were described as decreased forelimb and hindlimb strength leading to a LOAEL of 100 mg Al.kg $bw^{-1}.d^{-1}$ according to ATSDR. This LOAEL was divided by an UF of 300 corresponding to an UF_A and UF_H (interspecies and interindividual variability) both of 10 by default, an UF_L of 3 for the use of a LOAEL instead of a NOAEL; a modifying factor of 0.3 was also applied, considering that

[15] LOAEL of 155 mg.kg $bw^{-1}.d^{-1}$ in Toxicological profile because of different methodologies to convert the dose in ppm.

aluminium lactate (aluminium compound used for treatment) has a higher bioavailability than aluminium supposedly retrieved in food and drinking diet. This led to a MRL of 10 µg.kg $bw^{-1}.d^{-1}$ (ATSDR 2008).

- **EFSA**

EFSA (2008) derived a tolerable weekly intake health-based guidance value (TWI) of 1 mg Al.kg bw^{-1} per week (corresponding to 0.14 mg.kg $bw^{-1}.d^{-1}$) (EFSA 2008). Two PoD were considered to derive this TWI. From the study by Golub et al. (1995) (mice treated from conception and through weaning), EFSA retained a LOAEL of 50 mg Al.kg $bw^{-1}.d^{-1}$ based on grip strength reduction. In a second study in mice exposed through conception to PND35 (Golub and Germann 2001), EFSA identified a LOAEL of 50 mg Al.kg $bw^{-1}.d^{-1}$ for reduced body weight gain (only observed at 11 weeks) and a NOAEL of 10 mg Al.kg $bw^{-1}.d^{-1}$. Considering an UF of 300 applied to the LOAEL from the first study (UF_A and UF_H of 10, UF_L of 3) and an UF of 100 applied to the NOAEL in the second study (UF_A and UF_H of 10), EFSA derived two reference values of respectively 167 µg Al.kg $bw^{-1}.d^{-1}$and 100 µg Al.kg $bw^{-1}.d^{-1}$, that is 1.2 and 0.7 mg Al.kg $bw^{-1}.wk^{-1}$ which was averaged to 1 mg Al.kg $bw^{-1}.wk^{-1}$.

- **JECFA**

In 2012, JEFCA considered a neurodevelopmental study in rats (Poirier et al. 2011) to derive a provisional TWI (PTWI). Rats were treated with aluminium citrate through GD6 to PND364 through drinking water. As a result, water consumption had a significant impact on the aluminium dose, which varied during the different life stages of the rats (e.g. during gestation, the dose was 10-14 below the target dose, up to 50% above during lactation, 30% below during weaning and then 15-45% above for the remainder of the study). Decrease in hindlimb and forelimb grip strength was observed alongside renal effects at 100 mg Al.kg $bw^{-1}.d^{-1}$. A NOAEL of 30 mg Al.kg $bw^{-1}.d^{-1}$ was proposed by the authors of the study. As the effects on grip strength were more pronounced in young animals, exposure in utero or during lactation is likely more significant than exposure during later stages when the exposure dose decreased due, to reduced drinking water consumption. JECFA also considered that the aluminium compound used, aluminium citrate, is more bioavailable than other compounds. Therefore, a NOAEL of 30 mg.kg $bw^{-1}.d^{-1}$ was assumed. Based on the evidence, an UF of 100 was used for interspecies and interindividual differences. No other UF was judge necessary. The derived reference value was of 300 µg Al.kg $bw^{-1}.d^{-1}$ approximatively corresponding to PTWI of 2 mg Al.kg bw^{-1} per week (corresponding to 0.29 mg.kg $bw^{-1}.d^{-1}$) (JECFA 2012).

A summary of existing TRV recommended by national and international organisms is done in Table 17.

Table 17. Summary of existingTRV for oral and inhalation route

Reference value	**Organism**	US EPA	US EPA	ATSDR	EFSA	JECFA
	Year	2006	2006	2008	2008	2012
	Name	p-RfD	p-RfC	MRL	TWI	PTWI
	Value	1 mg.kg $bw^{-1}.d^{-1}$	5 µg.m^{-3}	5 µg.m^{-3}	1 mg.kg bw^{-1}/ week corresponding to 0.14 mg.kg $bw^{-1}.d^{-1}$	2 mg.kg bw^{-1}/ week corresponding to 0.29 mg.kg $bw^{-1}.d^{-1}$
Critical effect		Neuromuscular effects (decreased forelimb grip strength)	Psychomotor and cognitive	Neuromuscular effects (decreased forelimb and hindlimb strength)	Neuromuscular effects (grip strength reduction and reduced body weight gain)	Renal effects (hydronephrosis, urethral dilatation, obstruction and/or presence of calculi) and Neuromuscular effects (decreased hindlimb and forelimb grip strength)
Key study	**Reference**	Golub et al. (1995)	Hosovski et al. (1990)	Golub et al. (2000)	1) Golub et al. (1995) 2) Golub & Germann (2001)	Poirier et al.(2011)
	Study population	Mice (SW)	Human, workers	Mice (SW)	Mice (SW)	Rats (SD)
	Exposure (duration, route)	From conception to weaning, diet	12 years, occupational	From conception to 2 years, diet	1) From conception to weaning, diet. 2) Conception to 35 days age, diet	From gestational day 6 to 364 days, drinking water
Point of departure		100 mg.kg $bw^{-1}.d^{-1}$ (LOAEL)	4.6 mg Al.m^{-3} (LOAEC)	100 mg.kg $bw^{-1}.d^{-1}$ (LOAEL)	1) LOAEL: 50 mg.kg $bw^{-1}.d^{-1}$ 2) LOAEL: 50 mg.kg $bw^{-1}.d^{-1}$ NOAEL: 10 mg.kg $bw^{-1}.d^{-1}$	
Temporal adjustment		NA	1.64 mg.m^{-3} (LOAECADJ) (10 m3/20 m3 and 5 days/7 days)	NA	NA	NA
Allometric scalling		NA	NA	NA	NA	NA
Uncertainty factor (UF)		100 (UF_A: 10; UF_H: 3; $UF_{L/B}$: 3)	300 (UF_H: 10; $UF_{L/B}$: 10; UFD: 3)	300 (UF_A: 10; UF_H: 10; $UF_{L/B}$: 3), modifying factor of 0.3 for bioavailability difference	1) 300 (UF_A: 10; UF_H: 10; $UFL_{/B}$: 3) 2) 100 (UF_A: 10; UF_H: 10)	100 (UF_A: 10; UF_H: 10)
Confidence level		Low	Low-Medium	NA	NA	NA

NA: not applicable

6 Derivation of toxicological reference values

6.1 Oral long term TRV for aluminium and its inorganic compounds

6.1.1 Choice of the critical effect

Exposure to aluminium via the oral route can result in numerous health effects, including neurotoxic, neurodevelopmental, bone and hematological effects. Neurotoxic effects appear in both humans and laboratory animals, at the lowest doses tested by the oral route in animals, and via multiple routes in workers, including oral and respiratory.

Therefore, the HRV committee consider neurotoxic effects as the critical effect.

Given the existence of new studies demonstrating neurotoxic effects of the cognitive performance type at lower doses (Cao et al. 2016), the HRV committee does not retain the existing long-term oral TRVs. The HRV committee therefore decided to propose a new long-term oral TRV.

6.1.2 Choice of key study and point of departure

No human study conducted on the general population on the neurotoxic effects of aluminium after oral exposure was identified from the literature search. Cognitive effects have been documented in human occupational studies of aluminium workers. The available data allow the characterization of dose-response effects with IBE measurements but not with external exposure measurements.

Recent studies observed cognitive neurotoxic effects following oral exposure in animals and characterised the dose-response relationship: Cao et al. 2016 and Yan et al. 2017.

Cao et al. exposed male rats (n = 30/group) to aluminium chloride for 3 months by gavage at doses of 0, 10, 30 and 90 mg Al.kg $bw^{-1}.d^{-1}$. A significant reduction in learning and memory performances in Morris water maze was observed in rats exposed at 30 mg Al.kg $bw^{-1}.d^{-1}$ (LOAEL). The NOAEL is 10 mg Al.kg $bw^{-1}.d^{-1}$.

In the Yan et al. study, rats were exposed to aluminium chloride from lactation (3 weeks) to 14 weeks via drinking water at doses of 0, 36, 73 and 108 mg Al.kg $bw^{-1}.d^{-1}$ (n = 15/sex/dose). A significant decrease in learning and memory capacity was observed (Morris pool) at 36 mg Al.kg $bw^{-1}.d^{-1}$ (LOAEL) (Yan et al. 2017).

Reported data dose not gave the basis for a benchmark dose approach.

As the study by Cao et al. was judged to be of good quality (Klimisch 1) and identified the lowest NOAEL for impaired cognitive performance, the HRV committee retains it as a key study and identified the NOAEL of 10 mg.kg $pc^{-1}.d^{-1}$ as the PoD.

6.1.3 Allometric scaling

To reduce the uncertainty of inter-species variability, an allometric adjustment was performed. A Human Equivalent Dose (HED) was calculated using the following equation:

$$Dose_{HED} = Animaldose \times (\frac{AnimalBW}{HumanBW})^{\frac{1}{4}}$$

Mean rats body weight (Sprague Dawley) is of 450 g (from an abacus). The human body weight used for the calculation is 70 kg.

$NOAEL_{HED}$ = 2.83 mg.kg $bw^{-1}.d^{-1}$

6.1.4 Application of uncertainty factors

The oral long-term TRV was calculated based on the $NOAEL_{HED}$ and using the following uncertainty factors (UF) (Anses, to be released):

- inter-species variability (UF_A): 2.5, to account for toxicodynamic variability and residual toxicokinetic uncertainties, an allometric adjustment having been made;
- inter-individual variability (UF_H): 10 by default;
- subchronic-to-chronic transposition (UF_S): √10, to take account of the transposition from a subchronic study to a long-term TRV;
- use of point of departure (UF_L): 1, the PoD being a NOAEL, no additional factor is needed;
- insufficient data (UF_D): 1, aluminium is a chemical agent whose effects are well documented.

An overall uncertainty factor of 79 is therefore used to derive the oral long-term TRV.

6.1.5 Proposed oral long-term TRV and confidence level

TRV = NOAELHED / UF = 0.036 mg.kg $bw^{-1}.d^{-1}$ rounded up to 40 µg.kg $bw^{-1}.d^{-1}$

The overall **medium-high** confidence level (score 3.5/5) of this long-term oral TRV was estimated using a tool established by Anses, based on:

- the nature and quality of the corpus of data (score 5/5, the quantity of data for the oral route is deemed sufficient),
- the choice of critical effect and mode of action (score 5/5, cognitive effects are observed in animal studies as well as in exposed workers),
- the choice of key study (rated 4.3/5, the selected study only exposes rats for 3 months),
- the choice of point of departure (rated 3/5; a NOAEL/LOAEL pair is chosen, as the BMD approach is not possible on the basis of the data reported),
- the choice of uncertainty factors (score of 1/5, coefficients and uncertainty factor are set by default for allometric adjustment and uncertainty linked to inter-individual variability).

6.2 Respiratory short term TRV for aluminium and its compounds

No human studies have been identified on the effects of aluminium following short-term exposure by the respiratory or ingestion routes. Animal studies on the effects of aluminium by inhalation reveal potential effects on the respiratory system: increased alveolar macrophages, granulomatous lesions in the lungs and increased lung weights (Mazzoli-Rocha et al. 2010, Thomson et al. 1986, Drew et al. 1974). However, the pulmonary effects observed in animals in these studies may be related to dust overload rather than aluminium-specific effects.

In the absence of respiratory data, and given the impossibility of extrapolating from one route to another, it was not possible to derive a short-term respiratory TRV.

6.3 Respiratory long term TRV for aluminium and its inorganic compounds

6.3.1 Choice of the critical effect

Pulmonary effects were observed in workers, for which a risk of bias is raised by the co-exposures that probably caused the observed effects. In rats subchronically exposed by inhalation to aluminium chlorohydrate, only pulmonary effects (increased lung weight, increased alveolar macrophages, granulomatous lesions) were observed (Steinhagen and Cavender, 1978; Stone et al., 1979). These effects could be attributable to both aluminium and the chlorohydrate moiety. It is therefore not possible to distinguish the proportion attributable to aluminium.

Exposure to aluminium via the oral or respiratory routes can result in numerous systemic health effects, including neurotoxic, neurodevelopmental, bone and haematological effects. Neurotoxic effects appear in both humans and laboratory animals at the lowest doses tested, via the oral route in laboratory animals, and via the respiratory route in workers Thus, **the HRV committee retains neurotoxic effects as the critical effect.**

6.3.2 Choice of construction hypothesis

For most non-carcinogenic effects, it is considered by default and in the current state of knowledge that toxicity is only expressed above a dose threshold. Thus, **the HRV committee considers that neurotoxic effects result from a dose-threshold mechanism.**

6.3.3 Analysis of existing long-term respiratory TRVs

In 2006, US EPA proposed a provisional long-term respiratory TRV (pRfC) based on a decrease in cognitive and psychomotor performance scores observed in workers occupationally exposed for 12 years (Hosovski et al. 1999) (Appendix 2) (US EPA 2006). However, the exposure value presented by the authors, ranging from 4.6 to 11.5 $mg.m^{-3}$, does not clearly indicate whether this is a concentration of aluminium or dust, especially as the number and size of dust particles are mentioned without specifying the fraction of aluminium in the air. In addition, the very high concentrations of blood aluminium in exposed individuals, as well as in controls, suggest a high level of contamination of the samples and therefore a major risk of bias in the analysis of the results of this study. The pRfC is estimated with an IF of 300, taking into account inter-individual variability (UF_H = 10), the use of a LOAEL ($UF_{L/B}$ = 10) and moderate confidence in the database (lack of data confirming effect levels (NOAEL and additional LOAEL), lack of available data for neurodevelopmental effects via inhalation and the need for a well-designed two-generation reproduction study) (UF_D = 3).

In view of the limitations described above, the HRV committee does not retain the US EPA's provisional respiratory TRV, nor the key study identified. The HRV committee therefore decided to propose a new long-term respiratory TRV.

6.3.4 Choice of key study and point of departure

No epidemiological studies in the general population provide information on the neurotoxic effects of aluminium after inhalation or oral exposure. Data on airborne aluminium concentrations from epidemiological studies of workers are inadequate to characterize their inhalation exposure to aluminium. Indeed, there are many different sources and forms of

exposure to aluminium in the workplace. Available studies generally present aluminium levels averaged over several categories of workers, or an airborne dust concentration that is not relevant to this assessment. No animal studies investigating the neurotoxicity of aluminium via the respiratory route have been identified.

Thus, in the absence of relevant studies in humans and (sub)chronic studies in animals highlighting the critical effect, a route-to-route extrapolation is proposed to derive a respiratory TRV from the PoD of the oral TRV described above. Such a route-to-route extrapolation is possible when the critical effect is a systemic one.

The kinetic models available (Poddalgoda et al. 2021; Hethey et al. 2021) do not include the respiratory route and cannot therefore be used to perform route-to route extrapolation.

Thus, the following route-to-route extrapolation is based on the key study identified for the oral TRV (Cao et al. 2016), where aluminium is administered by gavage as aluminium chloride, which is one of the most bioavailable. In the absence of absorption data specific to this compound, the maximum oral and respiratory absorption rates of the different inorganic aluminium compounds are taken into account, i.e., 0.3% and 3% respectively.

$$NOAEC_{HEC} = \frac{NOAEL_{HED} \times Absorption_{orale} \times BW}{Respiratory\ volume \times Absorption_{resp.}}$$

Where $NOAEL_{HED}$ = 2,83 mg.kg $bw^{-1}.d^{-1}$, body weight (BW) = 70 kg and respiratory volume = 20 $m^3.d^{-1}$.

$$NOAEC_{HED} = 0.99\ mg.m^{-3}$$

The HRV committee retains a $NOAEC_{HED}$ of 0.99 $mg.m^{-3}$ as PoD after extrapolation from the oral to the respiratory route.

6.3.5 Application of uncertainty factors

The respiratory long-term TRV was calculated based on the $NOAEC_{HED}$ and using the following uncertainty factors (UF) (Anses, forthcoming):

- inter-species variability (UF_A): 2.5, to account for toxicodynamic variability and residual toxicokinetic uncertainties, an allometric adjustment having been made;
- inter-individual variability (UF_H): 10 by default;
- subchronic-to-chronic transposition (UF_S): √10, to take account of the transposition from a subchronic study to a chronic exposure;
- use of point of departure ($UF_{L/B}$): 1, the PoD being a NOAEC, no additional factor is needed;
- insufficient data (UF_D): 1, aluminium is a chemical agent whose effects are well documented.

An overall uncertainty factor of 79 is therefore used to derive the oral long-term TRV.

6.3.6 Proposed respiratory long-term TRV and confidence level

A long-term threshold respiratory TRV was calculated by dividing the adjusted PoD by the overall UF.

TRV = $NOAEC_{HED}$ / UF = 0.0125 $mg.m^{-3}$ rounded to 12 $\mu g.m^{-3}$

The overall **medium** confidence level (score 2.7/5) of this long-term oral TRV was estimated using a tool established by Anses, based on:

- the nature and quality of the corpus of data (score 1/5, the quantity of data for the respiratory route is deemed insufficient),
- the choice of critical effect and mode of action (score 5/5, cognitive effects are observed in animal studies as well as in exposed workers),
- the choice of key study (rated 3/5, the selected study exposes rats for 3 months by gavage),
- the choice of point of departure (rated 3/5, a NOAEL/LOAEL pair is chosen, as the BMD approach is not possible on the basis of the data reported),
- the choice of uncertainty factors (score of 1/5, coefficients and uncertainty factor are set by default for allometric adjustment and uncertainty linked to inter-individual variability).

Although it has proposed a long-term respiratory TRV in response to the request, the HRV committee does not recommend its use, as it only takes into account the respiratory route, which is never isolated and rarely predominant: even when there are sources of airborne emissions of aluminium compounds into the environment in the form of smoke or dust, these are ultimately deposited on soil, surfaces and plants and accumulate there. The main ways in which people become contaminated are by putting dust-contaminated hands or objects to the mouth and by eating locally-grown plants. As the oral route accounts for the vast majority of exposure, the assessment of exposure to aluminium by the respiratory route is unsuitable; compliance with the respiratory TRV cannot guarantee the absence of overexposure of all or part of the population concerned.

The HRV committee therefore does not recommend its use and stresses the need to use an internal TRV, which it has therefore derived.

6.4 Internal TRV for aluminium and its compounds

In order to qualify and quantify risk for human health based on biomonitoring studies of the French population, a human biomonitoring guidance value is required for aluminium and its inorganic compounds.

6.4.1 Choice of the biomarker of exposure

Urinary aluminium is selected by the experts as the relevant BME for biological monitoring of exposure to aluminium, on the basis of an analysis of the advantages and disadvantages of the various BMEs identified. In the case of impaired renal function, urinary aluminium cannot be used as BME because this pathological condition affects the interpretation of biomonitoring results (see section 4.2.2).

6.4.2 Choice of the critical effect

The main systemic effect occurring at the lowest urinary concentrations, reported in epidemiological studies of aluminium-exposed workers, is a decline in cognitive performance objectified as a decrease in neurobehavioral performance compared with unexposed individuals (Hosovski et al. 1990; Bast-Pettersen et al. 1994; Hänninen et al. 1994; Guo et al. 1999; Riihimäki et al. 2000; Bast-Pettersen et al, 2000; He et al. 2003; Buchta et al. 2005; Kiesswetter et al. 2007). In addition, several general population studies have explored the association between aluminum exposure and cognitive performance (neurobehavioral tests). However, only aluminium levels measured in drinking water are reported, without corresponding measurements of aluminium in biological matrices.

The choice of the critical effect is also supported by experimental studies. Indeed, several oral experimental studies in animals have shown neurotoxic effects such as impaired learning and

memory, reduced forelimb and hindlimb grip strength, reduced startle response, reduced locomotor activity and total number of activities, reduced negative geotaxis test and hippocampal cell damage and density.

Thus, the HRV committee has identified neurotoxic effects (reduced cognitive performance as measured by neurobehavioral tests) as a critical effect for the development of an internal TRV for urinary aluminium.

6.4.3 Choice of construction hypothesis

For most non-carcinogenic effects, it is considered by default and in the current state of knowledge that toxicity is only expressed above a dose threshold. Thus, **the HRV committee considers that neurotoxic effects result from a dose-threshold mechanism.**

6.4.4 Choice of the key study and identification of point of departure (PoD)

No epidemiological studies were identified in the literature search for the general population. Among several studies, only two longitudinal studies, judged to be of good quality, on separate cohorts of workers establishing an association between urinary aluminium concentrations and impairment of cognitive performances make it possible to determine NOAELs and LOAELs:

- NOAEL of 38 $\mu g.g^{-1}$ creatinine (post-shift, after several shifts) from a study of aluminium welders in car manufacturing (98 workers and 50 controls) (Buchta et al. 2003 and confirmed by the Kiesswetter et al. 2009),

- LOAEL of 97 $\mu g.g^{-1}$ creatinine (post-shift, after several shifts) from a study of train and truck construction workers (44 workers and 37 controls) (Buchta et al., 2005 and confirmed by the Kiesswetter et al. 2007).

Contrastingly, the longitudinal study conducted by Letzel et al. (2000) did not identify any discernible effects on the cognitive performance of workers compared to controls (32 workers and 30 controls on the first examination, 21 workers and 15 controls on the second one). Although plasma aluminium concentration among workers was comparable to that observed by Buchta et al. (2003), the urinary concentration was notably higher at 87.6 $\mu g.g^{-1}$ creatinine (sampling time not specified).

Experts also identified studies exhibiting lowest LOAELs. These LOAELS were not considered usable because results on cognitive effects were equivocal:

- LOAEL of 41.8 $\mu g.g^{-1}$ creatinine post-shift (timing from the start of the shift and day of the work-week not specified) (Guo et al. 1999). Cognitive performances were impaired in an inconsistent manner across age group;
- LOAEL of 40.1 $\mu g.g^{-1}$ creatinine in “morning” urine samples (day of the work-week, not specified) (He et al. 2003). In this study, exposed workers had a significantly better reaction time than controls despite a significantly lower scores in digital symbol test and pursuit aiming test.

In conclusion, in the absence of any epidemiological study in the general population, the HRV committee selects the longitudinal study by Buchta et al. in 2003, confirmed by Kiesswetter et al. in 2009, as the key studies, and the NOAEL of 38 $\mu g.g^{-1}$ creatinine (post-shift, after several shifts) as the PoD.

6.4.5 Application of uncertainty factors

The internal TRV was calculated using UF described below:

- inter-species variability (UF_A): 1, because the internal TRV is based on human data;
- inter-individual variability (UF_H): 2, by considering that the population of workers present in the key study is representative of all workers in terms of inter-individual

variability and by considering that the ratio between the inter-individual uncertainty of 10 for the general population and 5 by default for workers.
- subchronic to chronic transposition (UF_S): 1, because workers from the reference study were chronically exposed (4 years of follow-up, 3 evaluations)
- use of point of departure ($UF_{L/L}$): 1, the retained PoD is a NOAEL;
- Insufficient data (UF_D): 1, aluminium is a chemical agent whose effects are well documented.

The overall UF for deriving the internal TRV is 2.

6.4.6 Proposed internal TRV value

The internal TRV for aluminium is derived from the NOAEL of 38 $\mu g.g^{-1}$ creatinine with an uncertainty factor of 2, rounded to 20 $\mu g.g^{-1}$ creatinine.

An internal TRV of 20 $\mu g.g^{-1}$ creatinine is proposed for urinary aluminium based on neurotoxicity.

6.4.7 Support for the internal TRV

6.4.7.1 Analytical methods for aluminium determination

Samples can be analysed after dilution (water, Triton®, EDTA, nitric acid) or after microwave-assisted acidic mineralisation. Nitric acidification is sufficient, for most of the metals present in urine, to ensure good preservation for a few weeks at +4°C.

After sample homogenisation, aliquots are dispensed into clean tubes and either refrigerated (for preservation of less than two weeks) or frozen (at - 20°C, when the preservation time could be of more than 2 weeks) for subsequent analysis. If the sample is frozen, defrosting is followed by homogenisation and centrifugation. The sample must be properly mixed before dosing as, for example, aluminium phosphate tends to precipitate in urine (WHO 1996; Labat 2010; San Martín, Bauçà, and Martinez-Morillo 2022).

Aluminium determination remains a challenge, regardless of the techniques used or matrices studied, because of the ubiquity of this element and the contamination risks associated with it. In fact, the majority of analytical errors are due to contamination of the sample by aluminium from ambient air, laboratory equipment or reagents used for sampling and sample preparation. It is essential to use high-purity standards and reagents, and type 1 grade ultrapure water.

Blank determination from pre-washed sample containers is recommended to ensure that the cleaning protocols and pre-analytical steps avoided aluminium contamination. The laboratory's environment should be kept as clean as possible.

Numerous analytical methods exist for aluminium concentration measurements in biological materials. Nevertheless, due to their insufficient detection limits or significant number of interferences, some of these techniques are no longer used. These include UV-visible absorption spectroscopy, fluorescence spectroscopy, flame atomic absorption spectrometry, X-ray fluorescence spectrometry, and neutron activation analysis. At present, inductively coupled plasma mass spectrometry (ICP-MS) is the method of choice for measurement of aluminium, as it has shown to offer the best limits of quantification (LOQ), selectivity and robustness (San Martín, Bauçà, and Martinez-Morillo 2022).

The main analytical methods for the measurement of aluminium are described below. It should be noted that the aim of this section is not to recommend an analytical method for the measurement of aluminium, but to inform on specific metrological parameters and to present the advantages and limitations of each method.

Electrothermal atomic absorption spectrometry (ETAAS) or graphite furnace atomic absorption spectrometry (GFAAS)

In this technique, the sample introduced into the graphite furnace undergoes the successive steps of matrix dehydration and mineralisation, element atomization, and pyrolysis. The last step serves to clean the furnace to prevent inter-sample contamination.

To improve selectivity and eliminate interference, this technique requires the use of background correctors, Zeeman correction being the preferred method, preventing molecular interference and conferring high specificity. Alternatively, matrix modifiers are used to displace chlorine atoms and prevent the formation of volatile aluminium chloride in the pre-atomization stages. However, matrix modifiers can be a source of contamination, so their use is not advisable.

One of the main sources of contamination with this technique is atmospheric dust, particularly in the sampler cups, a type of contamination that appears to be almost non-existent with ICP.

Advantages of this technique include its simplicity, sensitivity and low cost. In fact, it does not require sample pre-treatment, and only a small sample volume is required. Detection limits in urine and blood samples are around 1-2 $\mu g.L^{-1}$ (0.04-0.07 $\mu mol.L^{-1}$) (ANSES 2003; ATSDR 2008; San Martín, Bauçà, and Martinez-Morillo 2022). The LOQ was reported to be of 2 $\mu g.L^{-1}$ (INRS Biotox).

Inductively coupled plasma atomic emission spectrometry (ICP-AES):

This technique is based on the production of excited atoms within an argon plasma (partially ionized gas with a temperature ranging from 3000 to 8000 K). The plasma is generated by an electromagnetic field produced by an induction coil connected to a high-frequency generator. Element identification and quantification are achieved by measuring the intensity of the light emitted by the elements excited in the neutral or ionised state.
While less sensitive than ETAAS, ICP-AES offers several advantages:

- analysis speed (resulting in a significantly reduced need for re-analysis),
- dynamic range (a larger linear range, requiring fewer dilutions),
- specificity (less sensitive to matrix effects, allowing analysis of diverse samples without modifications of the analytical parameters),
- multi-element capability (ANSES 2003).

The limits of detection of aluminium using ICP-AES are about 1$\mu g.L^{-1}$ for urine and 4$\mu g.L^{-1}$ for blood samples (Allain et Mauras 1979 in ATSDR 2008). The lowest LOQ was reported to be of 1$\mu g.L^{-1}$ (INRS Biotox).

Hence, ICP-AES is used when high sensitivity is not required, for the analysis of major components, or when the matrix is highly charged (soils, ores, alloys, etc.). It is easy to use and is faster.

Possible interferences for aluminium by ICP-AES are with Ti, Mo, Zr, Fe, U and Ce (Meggers and Corliss 1961; Burden et al. 1995; ATSDR 2008).
The most commonly used spectral lines, because they are more sensitive, are 167.020 nm (Fe interference) and 396.152 nm (Zr, Ce interferences). Interferences in urine do not seem to be problematic.

Inductively coupled plasma mass spectrometry (ICP-MS)

This technology combines two principles: ICP, a highly efficient source of ion production and mass spectrometry for ion separation. It offers several advantages:

- very high sensitivity,
- enhanced detection limits: 0.1–1 µg.L^{-1} (0.004–0.04 µmol.L^{-1}) for most of the elements of the periodic table,
- possibility of multi-element and isotopic analysis of trace elements.

Interferences (spectroscopic and non-spectroscopic) must also be controlled (ANSES 2003; ATSDR 2008; San Martín, Bauçà, and Martinez-Morillo 2022). LOQs take into account potential interferences and background noise and the management of interference does not seem problematic.
Generally, LOQ ranged between 0.2 and 10 µg.L^{-1} (INRS Biotox). In a biomonitoring study, the LOQ of aluminium in urine samples using ICP-MS was of 0.156 µg.L^{-1} and the limit of detection (LOD) 0.052 µg.L^{-1} (Bertram et al. 2023).
The advantages and limitations of the analytical methods for aluminium measurement are summarised in Table 18 (ANSES 2003; ATSDR 2008; Wilschefski and Baxter 2019; San Martín, Bauçà, and Martinez-Morillo 2022).

Table 18. Overview of the advantages, limitations and LODs of the main analytical techniques used for aluminium measurement

Analytical method	Advantages	Limitations	Limit of detection	Limit of quantification
ETAAS / GFAAS	• Simplicity of sample preparation • Low sample volume • Few interferences • Sensitivity	• Single element technique • Limited analytical range	1-2 µg.L^{-1} (0.04-0.07 µmol.L^{-1})	2 µg.L^{-1}
ICP-AES	• Simplicity of sample preparation • Low sample volume • Multi-element analysis • High specificity • Large analytical range	• Possible interferences • Low sensitivity	High detection limit: 1-4 µg.L^{-1}	1 µg.L^{-1}
ICP-MS	• Simplicity of sample preparation • Low sample volume • Multi-element analysis • Very high sensitivity • Large analytical range	• Need for high skilled expertise	0.1–1 µg.L^{-1} (0.004–0.04 µmol.L^{-1})	0.2-10 µg.L^{-1}

Whatever the analytical technique used, measurement uncertainties are estimated by analytical repeatability and intermediate precision.

Laboratories must indicate the limit of detection and quantification and the uncertainties of the method used when reporting the results of aluminium analysis in the corresponding matrix.

The use of reference material, if available, is recommended for any type of biological matrix. For this end, the procedures recommended within the framework of the European projects DEMOCOPHES, HBM4EU and PARC, concerning the harmonisation of biomonitoring of

European populations, can be used (Schindler et al. 2014; Vorkamp et al. 2021; Zare Jeddi et al. 2022).

In fact, reference materials should be incorporated into the analysis process, i.e. samples of the same matrix as the specimen with a well-known amount of biomarker concentration (close to the ones of the specimens). This guarantees reliable results. Control samples are generally commercially available certified samples.

External quality assurance schemes provide a way for laboratories to assess their performance by comparing it to that of other participating laboratories through benchmarking. Different relevant programmes including aluminium are available: the OELM External Quality Program (occupational and environmental laboratory medicine), included matrices are serum, whole blood, and urine; the UKNEQAS for Trace Elements (United Kingdom) involving serum, blood, urine, and dialysis water and fluids; and, the QMEQAS of the Centre de Toxicologie du Québec also using several matrices like serum, blood, urine, and hair (ANSES 2003; SOCIETE FRANCAISE DE MEDECINE DU TRAVAIL 2016; San Martín, Bauçà, et Martinez-Morillo 2022; Biotox INRS[16]).

The laboratory participation in external quality control programs, and the systematic implementation of internal quality controls are determining points for obtaining COFRAC-ISO 15189 accreditation, which is a guarantee, for users, of laboratory reliability (Nübler et al. 2021).

6.4.7.2 Factors that may influence the interpretation of aluminium measurements

Certain practices can influence the interpretation of aluminium measurements in workers by increasing aluminium levels and making the occupational exposure not readily interpretable. Table 19 summarises these different factors.

Table 19. Factors that may influence the interpretation of aluminium measurement

Total aluminium in urine or serum	
Medical treatment	Consumption of certain drugs containing aluminium compounds as an active ingredient or as an adjuvant could increase aluminium levels and should be avoided prior to sampling (e.g.: some antacids, buffered aspirins, antidiarrheals, etc.).
Food intake	Food contact with aluminium packaging, kitchen utensils and, aluminium films under acidic conditions can allow aluminium emission and food contamination (Krewski et al. 2007). Furthermore, fruit juices (containing citric acid which increases aluminium absorption, see section 4.1.2) can increase urinary aluminium levels and should be avoided in the 2 days prior to sampling (Biotox)[17].
Smoking	Even though high concentration of aluminium in tobacco are reported, ranging from 0.6 to 3.7 mg $Al.g^{-1}$ product (Exley et al. 2006), smoking did not influence aluminium concentrations in plasma and urine of occupationally non-exposed subjects (Chiba and Masironi 1992; Nisse et al. 2017). Thus, it might not impact the biomonitoring result's interpretation.
Physiological or pathological factors	As aluminium is mainly eliminated in the urine (see section 4.4), patients with reduced renal function, might have higher levels of aluminium in blood due to the lack of normal clearance (implying reduced urinary levels).

[16] Biotox INRS: https://www.inrs.fr/publications/bdd/biotox/dosage.html?refINRS=Dosage_1 (accessed on March 2024)

[17] https://www.inrs.fr/publications/bdd/biotox.html (accessed in April 2024)

	Aluminium-containing prosthetic implants may increase blood and urine aluminium levels (San Martín, Bauçà, and Martinez-Morillo 2022).
Co-exposure to one or more substances (occupationally)	N/A
Route(s) of exposure, task description	N/A
Physical activity, effort, ...	N/A
Frequency and duration of exposure	N/A

N/A: not applicable

6.4.7.3 Choice of the sampling time

The studies making it possible to characterise the association between urine aluminium concentration and the health effects, and to identify a NOAEL and a LOAEL, have used urinary post-shifts samples. These studies reported the results of post-shift and morning samplings after several working days. They showed no difference on urinary aluminium concentrations at these two sampling times (see section 4.7.1).
Aluminium concentrations in urine samples taken at the beginning or end of a shift are determined by body burden and current exposure. The elimination kinetics of aluminium indicate that its concentration in urine samples taken after a few days' cessation of occupational exposure (for example, before the first shift of the working week) would be less influenced by current exposure, and therefore probably a better indicator of body burden. However, the available data do not allow us to characterise the association between urinary aluminium concentration before the first shift of the work week and health effects.

For the general population, generally exposed to aluminium on a chronic and not very variable basis, and apart from specific acute exposure, the time of sampling is indifferent. However, for good reproducibility and to avoid contamination by this ubiquitous compound, samples should be taken in the morning upon waking or after showering.

There are no recommendations as to when urine samples should be taken in the general population.

6.4.7.4 Sampling, collection and storage of biological specimens

Strict precautions must be taken during sampling, sample preservation, preparation, and analysis. As for other ubiquitous chemicals, the risk of external contamination indeed appears as an issue in aluminium determination.

Below are some recommendations to collect and preserve blood and urine samples for aluminium measurement. However, as a general rule, sampling material should ideally be provided by laboratories that have previously checked their suitability for the analysis. Also, in the case of occupational biomonitoring exposure, samples should preferably be taken outside the workplace and after the worker has removed his work clothes and taken a shower. It is also advisable to enquire in advance, with the laboratory carrying out the analysis, about the

pre-analytical conditions required, e.g.: storage and transportation requirements (SFMT 2016).

In general, the working group on biomarker of exposure suggests the following recommendations to minimise contamination and ensure accurate results.

1. In the first instance, vials and consumables labelled “trace metal-free” should be used, and glass vials should be avoided;
2. If this is not the case, the equipment should be cleaned with 10% ultra-pure nitric acid (up to a maximum of 20%) and soaked overnight, then rinsed thoroughly with ultra-pure water;
3. In all cases, all consumables must be tested for aluminium contamination (blank run with concentrations of reagents and acids identical to those used in the samples). This should also be done after the cleaning step.

- **Urine samples**

For aluminium exposed workers, it is generally recommended to carry out urine sampling at the end of the shift and after several shifts (Klotz et al. 2019), as reference health values were produced using such samples, which inform on both aluminium body burden and aluminium exposure during the last days (see chapter 6). Sampling has also been recommended at the beginning of the week, before the start of the first day’s work shift (WHO 1996; Biotox[18]).
In order to avoid the risk of contamination, samples should be collected at home, using the materials provided by the laboratory or otherwise they must be collected outside the workplace, ideally after showering or at least after washing hands.

As indicated above, materials used for sampling should be those recommended by the laboratory in charge of the analysis, which should have previously verified that they were free of aluminium (WHO 1996; Labat 2010; San Martín, Bauçà, and Martinez-Morillo 2022). If not, precautions must be taken to avoid aluminium contamination of the material used (wash and soak overnight with 10% nitric acid, then rinse with ultrapure water and perform a blank test).

The main limitation of urinary aluminium concentration when measured on spot urine sample is its large inter- and intra-individual variability of urine concentration, depending on water intake and loss. The theoretical remedy to this drawback is the adjustment of the urinary aluminium concentration measured on the sample to the concentration of urine (to its water content). The most commonly used adjustment methods are on the osmolality of urine, its relative density (specific gravity) and especially, on the urinary concentration of creatinine. The adjustment on the concentration of creatinine is the one that is, by far, the most used and in particular, in most studies that have sought associations between cumulative exposure to aluminium and health effects. It has been rightly pointed out that adjustment for urinary creatinine concentration is not ideal, because regardless of aluminium exposure and its body burden, the factors of variation in urinary aluminium and creatinine concentrations are not always identical: indeed, urinary creatinine excretion is partly determined by muscle mass, physical effort, consumption of meat-based foods, etc. Even if adjustment on creatinine concentration is not ideal for taking into account variations in urinary flow rate, it is preferable to no adjustment, as the amplitudes of inter- and intra-individual variations are much lower for creatinine excretion than for urine concentration (i.e. water content). This is confirmed by studies showing a stronger association of the urinary excretion of aluminium over a period of 24 hours (as the gold standard) with concentrations in spot samples with: no adjustment of urinary aluminium concentration on the one hand and adjustment for creatinine concentration on the other hand (X. Zhang et al. 2017; Wang et al. 2019).

[18] https://www.inrs.fr/publications/bdd/biotox.html (accessed in April 2024)

- **Blood samples**

For workers, blood sampling is also recommended at the end of a shift after several shifts (WHO 1996; Biotox[19]). Whereas, for the general population, there is no recommendation on blood sampling time.

Most blood sampling tubes and tools are made of rubber containing aluminium silicate. For this reason, the collection of blood in specific vacuum tubes for trace elements is recommended. The use of separating gel vacuum tubes is permitted, but, as mentioned previously, the use of glass tubes is not. As noted above, materials used for sampling should be those recommended by the laboratory in charge of the analysis, which should have previously verified that they were free of aluminium otherwise, strict precautions must be taken (WHO 1996; Labat 2010; San Martín, Bauçà, and Martinez-Morillo 2022).

For serum measurements, after the blood has been collected and coagulated, it is centrifugated in a closed container (to avoid contamination or evaporation) for 10 minutes at 1,000-1,200 g. Serum is kept in suitable sealed polypropylene or polystyrene tubes for less than 14 days at 4°C (refrigerated) or is frozen at -20ºC for prolonged preservation before analysis (WHO 1996; Labat 2010; San Martín, Bauçà, and Martinez-Morillo 2022).

[19] https://www.inrs.fr/publications/bdd/biotox.html (accessed in April 2024)

7 Biological values in the general population

7.1 Urine, blood, serum, plasma and hair aluminium in the general population

Several studies report measurements of aluminium concentration in the general population in urine, blood and hair samples. These data are summarised in Table 20.

Valkonen and Aitio measured aluminium levels in the serum and urine of occupationally non-exposed people (laboratory workers, n=44) in three towns of southern Finland using Zeeman Graphite furnace atomic absorption spectrophotometer. For serum, samples from 12 women and 9 men (mean age 39.4 years) were analysed and, for urine, samples were collected from 28 women and 16 men (mean age 39.6 years). The 95th percentile of the urinary aluminium results was of 0.63 µmol.L^{-1} (17 µg.L^{-1}) and for the serum aluminium of 0.09 µmol.L^{-1} (2.4 µg.L^{-1}) (Valkonen and Aitio 1997).

The findings from the German Environmental Survey (GerES) conducted in 1990/1992, which was a large-scale representative population study, indicated that the 95th percentile of the distribution of hair aluminium concentration was 23.1 µg.g^{-1} in the German population aged 6 to 14 years (n= 638). Additionally, the 95th percentile of aluminium concentration in scalp hair among the German adult population, aged 25 to 69 years (n= 3246), was found to be 14.0 µg.g^{-1}. Adult males and boys exhibited higher levels of aluminium in their hair compared to adult females and girls, although specific numerical values were not provided. The analysis of hair samples was carried out using ICP-MS with a LOD of 1.0 µg.g^{-1} (Seifert et al. 2000).

Goullé et al. measured levels of 27-32 elements, including aluminium, in whole blood (n = 100), plasma (n = 100), urine (n = 100) and hair (n=45) samples of healthy volunteers using ICP-MS. The 95th percentile of aluminium levels were of 11.2 µg.L^{-1}, 6.35 µg.L^{-1}, 17.3 µg.L^{-1} and 5.30 µg.g^{-1} respectively, in urine, whole blood, plasma and hair (Goullé et al. 2005).

Hoet et al. conducted a study to determine the reference distribution and the upper reference limit of 26 trace elements, including aluminium, in the urine of the general adult population residing in 10 provinces of Belgium (either in urban, suburban or rural areas). Adults were not occupationally or extra occupationally exposed to the trace elements and were recruited by an occupational health service during their annual medical check-up. Non-fasting spot urine samples were analysed for 460 males and 541 females (age range: 18 – 80 years) by ICP-MS. A 95th percentile value of 9.3 µg.L^{-1} (7.5 µg.g^{-1} creatinine) was identified for aluminium (Hoet et al. 2013).

Morton et al. measured levels of 61 elements, including aluminium, in urine samples collected from 132 (50 females and 82 males) occupationally unexposed UK adults aged from 18 to 66 years old, by ICP-MS. The sample was not representative of the whole UK population (staff at the Health and Safety Laboratory (HSL) and friends/relatives). The 95th percentile of urine aluminium levels was of 25.73 µg.L^{-1} (215.19 µmol/mol creatinine; 51.4 µg.g^{-1} creatinine) (Morton et al. 2014).

A study by Nisse et al. named ‘IMEPOGE’, evaluated the blood and urinary levels of various metals and metalloids in a representative sample of adults aged 20–59 years from the general population of Northern France, a formerly heavily industrialised area that retains some industrial activity. The study was conducted between 2008 and 2010, a total of 982 men and 1018 women participated, allowing the analysis of 1992 blood and 1910 urine samples using ICP-MS. 95th percentile of aluminium concentrations were 11.5 µg.L^{-1} (13.3 µg.g^{-1} creatinine) and 11.2 µg.L^{-1} in urine and blood respectively (Nisse et al. 2017).

The Santé Publique France (SpF) Esteban study, identified 95th percentile values of 27.66 µg.L^{-1} (62.36 µg.g^{-1} creatinine) in adults (18-74 years old) and 26.5 µg.L^{-1} (34.8 µg.g^{-1} creatinine) in children (6-17 years old). The target population for the Esteban study was the general population of mainland France, aged 6 to 74 and living in an ordinary household during the study period. Participants were included between April 2014 and March 2016, in four successive waves of equal duration to balance inclusions according to the seasonality of environmental and dietary exposures. Urinary metals were analysed by ICP-MS. It is important to note that, in this study, aluminium contamination of the samples could not be dismissed. Indeed, after analysing the control samples (water for injections), they were found to contain boron, aluminium and arsenic. Similarly, six pairs of replicates were blindly introduced into the analytical series, with concordant results for all metals except one for aluminium, suggesting environmental contamination issues. The results should therefore be interpreted with caution (SpF 2021).

No biomonitoring data of aluminium is reported by Health Canada, INSPQ, NHANES and HBM4EU.

Table 20. 95th percentiles of aluminium levels in blood, urine or hair, from various studies

Study, Country	Sampling Year	Population	95th percentile value
Urine			
Valkonen and Aitio (1997), Finland	-	Mean age 39.6 years n=44	17.01 µg.L^{-1} (0.63 µmol.L^{-1})
Goullé et al. (2005), France	-	Healthy volunteers n=100	11.2 µg.L^{-1}
Hoët et al. (2013), Belgium	2010-2011	Adults (18 -80 years old) n=1022	9.3 µg.L^{-1} (7.5 µg.g^{-1} creatinine)
Morton et al. (2014), UK	-	Adults (18-66 years old) n=132	25.73 µg.L^{-1} (215.19 µmol/mol creatinine)
Nisse et al. (2017), France	2008-2010	Adults (20–59 years old) n=1910	11.5 µg.L^{-1} (13.3 µg.g^{-1} creatinine)
SPF (2021), France	2014-2016	Adults (18-74 years old) n=2419	27.66 µg.L^{-1} (62.36 µg.g^{-1} creatinine)
SPF (2021), France	2014-2016	Children (6-17 years old) n=1052	26.5 µg.L^{-1} (34.8 µg.g^{-1} creatinine)
Whole Blood			
Goullé et al. (2005), France	-	Healthy volunteers n=100	6.35 µg.L^{-1}
Nisse et al. (2017), France	2008-2010	Adults (20–59 years) n=1992	11.2 µg.L^{-1}
Serum			
Valkonen and Aitio (1997), Finland	-	Mean age 39.4 years n=21	2.43 µg.L^{-1} (0.09 µmol.L^{-1})
Plasma			
Goullé et al. (2005), France	-	Healthy volunteers n=45	17.3 µg.L^{-1}
Hair			
Seifert et al. (2000), Germany	1990-1992	German children (6 to 14 years old) n=638	23.1 µg.g^{-1}
Seifert et al. (2000), Germany	1990-1992	German adult (25 to 69 years old) n= 3246	14.0 µg.g^{-1}
Goullé et al. (2005), France	-	Healthy volunteers n=45	5.30 ng/mg

7.2 Derivation of a populational internal exposure level

In general, when selecting a populational internal exposure level, the 95th percentile of the distribution in the general population of a reference study is used. In the case of aluminium, urinary levels from the 'ESTEBAN' study, which would normally serve as a reference study for the French population, cannot be interpreted due to the probable external contamination of urine samples by aluminium. On the other hand, the 'IMEPOGE' study (2008-2010) by Nisse et al (2017), with a large number of adult participants (n = 1920 aged 20 to 59), representative of the adult population living in the north of France (Hauts-de-France), is retained as a reference study, leading to a reference value for exposure to urinary aluminium of 11.5 µg. L^{-1} (or 13.3 µg.g^{-1} creatinine), corresponding to the 95th percentile of the distribution of urinary aluminium levels in this population.

It should be noted that the population sampled in this study is probably representative not only of the Hauts-de-France region, but also of the French population as a whole. Indeed, as indicated in the study, the median aluminium levels collected from plant mosses in the Nord-Pas-de-Calais were even lower than those at national level, suggesting that the population is not overexposed to aluminium in this region and that the results can be extrapolated to the rest of France. In addition, the 95th percentile urinary aluminium concentration observed in the Nisse et al. study (2017) is consistent with those of the studies conducted in France by Goullé et al. (2005) (11.2 µg.L^{-1}, n = 100) and in Belgium by Hoet et al. (2013) (9.3 µg.L^{-1}, or 7.5 µg.g^{-1} creatinine, n = 1022).

In conclusion, a populational internal exposure level of 13.3 µg.g^{-1} creatinine, corresponding to the 95th percentile of the "IMEPOGE" study (Nisse et al. 2017), is proposed for urinary aluminium.

8 Conclusions of the HRV committee

The HRV committee proposed three TRVs: long-term oral and respiratory TRVs, an internal TRV and a populational internal exposure level. However, it was unable to propose a short-term respiratory TRV due to a lack of data (Table 21).

An internal TRV of 20 µg.g^{-1} of creatinine in morning urine, based on human data from occupational exposure, was derived. In the case of an ubiquitous substance such as aluminium, which has multiple sources and routes of exposure, the use of an internal TRV makes it possible to take into account all the sources of exposure to aluminium and to interpret IBE concentrations in the context of biological monitoring and the quantitative assessment of health risks for the general population.

A populational internal exposure level of 13.3 µg.g^{-1} creatinine was identified in a study considered representative of the general French adult population (“IMEPOGE” study) (Nisse et al. 2017).

The HRV committee derived a long-term oral TRV of 40 µg.kg bw^{-1}.d^{-1}, based on the cognitive effects observed in rats after 3 months' exposure. This TRV has a medium-high level of confidence.

Considering the geometric mean dietary intakes of aluminium are 40.3 µg.kg bw^{-1}.d^{-1} in adults and 62.2 µg.kg bw^{-1}.d^{-1} in children; the corresponding P95s are 69.7 and 118.8 µg.kg bw^{-1}.d^{-1} in the EAT2, the oral TRV appears to be conservative. **The HRV committee considers that the internal TRV is more relevant than the oral TRV.**

On the basis of an extrapolation from the oral route to the respiratory route, the HRV committee has derived a long-term respiratory TRV of 12 µg.m^{-3} with a medium level of confidence. The development of such a long-term respiratory TRV was considered to be of little relevance in view of the sources of exposure of the general population to aluminium. **Although it has proposed a long-term respiratory TRV in response to demand, the HRV committee does not recommend its use, since it only takes into account the respiratory route, which is never isolated and rarely predominant. Even when there are sources of airborne emissions of aluminium compounds into the environment in the form of smoke or dust, they are ultimately deposited on soil, surfaces and plants and accumulate there. The main ways in which people become contaminated are by putting dust-contaminated hands or objects to the mouth and by eating locally-grown plants. As the oral route accounts for the vast majority of exposure, assessment of exposure to aluminium by the respiratory route is inappropriate; compliance with the respiratory TRV cannot guarantee the absence of overexposure of all or part of the population concerned.**

The HRV committee therefore does not recommend its use and stresses the need to use an internal TRV, which it has therefore derived.

Table 21: Long-term oral and respiratory TRV, internal TRV and populational internal exposure level

RV	**Organism**	Anses			
	Year	2024			
	Type	**$TRV_{Long\ term,\ oral}$***	**$TRV_{Long\ term,\ respiratory}$***	**$TRV_{interne}$**	**populational internal exposure level**
	Value	0,036 mg.kg $bw^{-1}.d^{-1}$	0,0125 $mg.m^{-3}$	20 $\mu g.g^{-1}$ créatinine, prélèvement le matin	13,3 $\mu g.g^{-1}$ creatinine
	BME	NC	NC	Urinary aluminium	Urinary aluminium
Critical effect		Cognitive effects			NC
Key study	**Reference**	Cao et al., 2016		Buchta et al. (2003) ; Kiesswetter et al. (2009)	IMEPOGE, 2008 – 2010 (Nisse et al. 2017)
	Study population or species	Rats		Workers	n=1992 (1016 women, 976 men)
	Exposure (duration, route)	3 months (gavage)		4.7 years ± 1,6 Inhalation, ingestion, skin at workplace	NC
Point of departure (PoD)		NOAEL = 10 mg.kg $bw^{-1}.d^{-1}$		NOAEL = 38 $\mu g.g^{-1}$ creatinine	P95 observed
Allometric scaling		$NOAEL_{HED}$ = 2,83 mg.kg $bw^{-1}.d^{-1}$		NA	NC
Route to route extrapolation		NC	$NOAEC_{HEC}$ = 0,99 $mg.m^{-3}$		
Uncertainty factor (UF)		79 (UF_A 2,5 ; UF_H 10 ; UFs √10)		2 (UF_A: 1; UF_H: 2; UF_L: 1; UF_S: 1; FI_D: 1)	NC
Confidence level		**Medium-high**	**Medium**	**NC**	**NC**

NA: not applied; NC: not concerned; NOAEL/C: No Observed Adverse Effect Level/Concentration; HED/C: Human Equivalent Dose/Concentration; UF: uncertainty factor.

* HRV committee does not recommend the use of External TRVs for aluminium, in particular the respiratory TRV since considering i) aluminium exposure of the general population is mainly through the oral route and ii) compliance with the respiratory external TRV does not guarantee the absence of overexposure in the general population.

9 Bibliography

Abu-Taweel, Gasem M., Jamaan S. Ajarem, and Mohammad Ahmad. 2012. 'Neurobehavioral Toxic Effects of Perinatal Oral Exposure to Aluminum on the Developmental Motor Reflexes, Learning, Memory and Brain Neurotransmitters of Mice Offspring'. *Pharmacology, Biochemistry, and Behavior* 101 (1): 49–56. https://doi.org/10.1016/j.pbb.2011.11.003.

Affourtit, F, MI Bakker, and MEJ Pronk. 2020. 'Human Health Risk Assessment of Aluminium'. RIVM. https://doi.org/10.21945/RIVM-2020-0001.

Afssaps. 2004. 'Myofasciite à Macrophages'. Conseil Scientifique (2004-006). Saint-Denis: Agence française de sécurité sanitaire des produits de santé.

Akila, R., B. T. Stollery, and V. Riihimäki. 1999. 'Decrements in Cognitive Performance in Metal Inert Gas Welders Exposed to Aluminium'. *Occupational and Environmental Medicine* 56 (9): 632–39. https://doi.org/10.1136/oem.56.9.632.

Albina, M. L., M. Bellés, D. J. Sanchez, and J. L. Domingo. 2000. 'Evaluation of the Protective Activity of Deferiprone, an Aluminum Chelator, on Aluminum-Induced Developmental Toxicity in Mice'. *Teratology* 62 (2): 86–92. https://doi.org/10.1002/1096-9926(200008)62:2<86::AID-TERA4>3.0.CO;2-P.

Allain, P., and Y. Mauras. 1979. 'Determination of Aluminum in Blood, Urine, and Water by Inductively Coupled Plasma Emission Spectrometry'. *Analytical Chemistry* 51 (13): 2089–91. https://doi.org/10.1021/ac50049a008.

Anane, R., M. Bonini, J. M. Grafeille, and E. E. Creppy. 1995. 'Bioaccumulation of Water Soluble Aluminium Chloride in the Hippocampus after Transdermal Uptake in Mice'. *Archives of Toxicology* 69 (8): 568–71. https://doi.org/10.1007/s002040050214.

ANSES. 2003. 'Evaluation des risques sanitaires liés à l'exposition de la population française à l'aluminium'. AGENCE FRANCAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE. https://www.anses.fr/fr/content/evaluation-des-risques-sanitaires-li%C3%A9s-%C3%A0-l%E2%80%99exposition-de-la-population-fran%C3%A7aise-%C3%A0-l-2.

Aslam, null, K. Davis, A. Pejović-Milić, and D. R. Chettle. 2009. 'Noninvasive Measurement of Aluminium in Human Bone: Preliminary Human Study and Improved System Performance'. *Journal of Inorganic Biochemistry* 103 (11): 1585–90. https://doi.org/10.1016/j.jinorgbio.2009.07.021.

ATSDR. 2008. 'Toxicological Profile of Aluminum'. Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/toxprofiles/tp22.pdf.

Bagepally, Bhavani Shankara, Rakesh Balachandar, Ravibabu Kalahasthi, Ravikesh Tripathi, and Madhumita Haridoss. 2021. 'Association between Aluminium Exposure and Cognitive Functions: A Systematic Review and Meta-Analysis'. *Chemosphere* 268 (April):128831. https://doi.org/10.1016/j.chemosphere.2020.128831.

Bast-Pettersen, R., P. A. Drabløs, L. O. Goffeng, Y. Thomassen, and C. G. Torres. 1994. 'Neuropsychological Deficit among Elderly Workers in Aluminum Production'. *American Journal of Industrial Medicine* 25 (5): 649–62. https://doi.org/10.1002/ajim.4700250505.

Bast-Pettersen, R., V. Skaug, D. Ellingsen, and Y. Thomassen. 2000. 'Neurobehavioral Performance in Aluminum Welders'. *American Journal of Industrial Medicine* 37 (2): 184–92. https://doi.org/10.1002/(sici)1097-0274(200002)37:2<184::aid-ajim4>3.0.co;2-o.

Bernuzzi, V., D. Desor, and P. R. Lehr. 1986. 'Effects of Prenatal Aluminum Exposure on Neuromotor Maturation in the Rat'. *Neurobehavioral Toxicology and Teratology* 8 (2): 115–19.

———. 1989b. 'Effects of Postnatal Aluminum Lactate Exposure on Neuromotor Maturation in the Rat'. *Bulletin of Environmental Contamination and Toxicology* 42 (3): 451–55. https://doi.org/10.1007/BF01699975.

Bernuzzi, Viviane, Didier Desor, and Paul R. Lehr. 1989a. 'Developmental Alterations in Offspring of Female Rats Orally Intoxicated by Aluminum Chloride or Lactate during Gestation'. *Teratology* 40 (1): 21–27. https://doi.org/10.1002/tera.1420400104.

Berthon, Guy. 2002. 'Aluminium Speciation in Relation to Aluminium Bioavailability, Metabolism and Toxicity'. *Coordination Chemistry Reviews* 228 (2): 319–41. https://doi.org/10.1016/S0010-8545(02)00021-8.

Bertram, Jens, Peter Brand, Laura Hartmann, Thomas Schettgen, Veronika Kossack, Klaus Lenz, Ellwyn Purrio, Uwe Reisgen, and Thomas Kraus. 2015. 'Human Biomonitoring of Aluminium after a Single, Controlled Manual Metal Arc Inert Gas Welding Process of an Aluminium-Containing Worksheet in Nonwelders'. *International Archives of Occupational and Environmental Health* 88 (7): 913–23. https://doi.org/10.1007/s00420-015-1020-7.

Bertram, Jens, André Esser, Sven Thoröe-Boveleth, Nina Fohn, Thomas Schettgen, and Thomas Kraus. 2023. 'Quantification of 26 Metals in Human Urine Samples Using ICP-MSMS in a Random Sample Collective of an Occupational and Environmental Health Care Center in Aachen, Germany'. *Journal of Trace Elements in Medicine and Biology* 78 (July):127161. https://doi.org/10.1016/j.jtemb.2023.127161.

Bittencourt, Leonardo Oliveira, Rakhel Dayanne Damasceno-Silva, Walessa Alana Bragança Aragão, Luciana Eiró-Quirino, Ana Carolina Alves Oliveira, Rafael Monteiro Fernandes, Marco Aurelio M. Freire, et al. 2022. 'Global Proteomic Profile of Aluminum-Induced Hippocampal Impairments in Rats: Are Low Doses of Aluminum Really Safe?' *International Journal of Molecular Sciences* 23 (20): 12523. https://doi.org/10.3390/ijms232012523.

Bryliński, Ł, K. Kostelecka, F. Woliński, P. Duda, J. Góra, M. Granat, J. Flieger, et al. 2023. 'Aluminium in the Human Brain: Routes of Penetration, Toxicity, and Resulting Complications'. *International Journal of Molecular Sciences* 24 (8). https://doi.org/10.3390/ijms24087228.

Buchta, M., E. Kiesswetter, A. Otto, K. H. Schaller, A. Seeber, W. Hilla, K. Windorfer, et al. 2003. 'Longitudinal Study Examining the Neurotoxicity of Occupational Exposure to Aluminium-Containing Welding Fumes'. *International Archives of Occupational and Environmental Health* 76 (7): 539–48. https://doi.org/10.1007/s00420-003-0450-9.

Buchta, Mark, E. Kiesswetter, M. Schäper, W. Zschiesche, K. H. Schaller, A. Kuhlmann, and S. Letzel. 2005. 'Neurotoxicity of Exposures to Aluminium Welding Fumes in the Truck Trailer Construction Industry'. *Environmental Toxicology and Pharmacology* 19 (3): 677–85. https://doi.org/10.1016/j.etap.2004.12.036.

Burden, Trevor J., J. J. Powell, R. P. H. Thompson, and P. D. Taylor. 1995. 'Optimal Accuracy, Precision and Sensitivity of Inductively Coupled Plasma Optical Emission Spectrometry: Bioanalysis of Aluminium'. *Journal of Analytical Atomic Spectrometry* 10 (3): 259–66. https://doi.org/10.1039/JA9951000259.

Cao, Zheng, Xu Yang, Haiyang Zhang, Haoran Wang, Wanyue Huang, Feibo Xu, Cuicui Zhuang, Xiaoguang Wang, and Yanfei Li. 2016. 'Aluminum Chloride Induces Neuroinflammation, Loss of Neuronal Dendritic Spine and Cognition Impairment in Developing Rat'. *Chemosphere* 151:289–95. https://doi.org/10.1016/j.chemosphere.2016.02.092.

Chalansonnet, Monique, Nathalie Carabin, Stéphane Boucard, Lise Merlen, Mathieu Melczer, Guillaume Antoine, Jérôme Devoy, Aurélie Remy, and François Gagnaire. 2018. 'Study of

Potential Transfer of Aluminum to the Brain via the Olfactory Pathway'. *Toxicology Letters* 283 (February):77–85. https://doi.org/10.1016/j.toxlet.2017.11.027.

Cherroret, G., V. Bernuzzi, D. Desor, M. F. Hutin, D. Burnel, and P. R. Lehr. 1992. 'Effects of Postnatal Aluminum Exposure on Choline Acetyltransferase Activity and Learning Abilities in the Rat'. *Neurotoxicology and Teratology* 14 (4): 259–64. https://doi.org/10.1016/0892-0362(92)90005-u.

Chiba, M., and R. Masironi. 1992. 'Toxic and Trace Elements in Tobacco and Tobacco Smoke'. *Bulletin of the World Health Organization* 70 (2): 269–75.

Colomina, M. T., M. Gómez, J. L. Domingo, and J. Corbella. 1994. 'Lack of Maternal and Developmental Toxicity in Mice given High Doses of Aluminium Hydroxide and Ascorbic Acid during Gestation'. *Pharmacology & Toxicology* 74 (4–5): 236–39. https://doi.org/10.1111/j.1600-0773.1994.tb01104.x.

Colomina, M. T., M. Gómez, J. L. Domingo, J. M. Llobet, and J. Corbella. 1992. 'Concurrent Ingestion of Lactate and Aluminum Can Result in Developmental Toxicity in Mice'. *Research Communications in Chemical Pathology and Pharmacology* 77 (1): 95–106.

Colomina, M. Teresa, José L. Roig, Domènec J. Sánchez, and José L. Domingo. 2002. 'Influence of Age on Aluminum-Induced Neurobehavioral Effects and Morphological Changes in Rat Brain'. *Neurotoxicology* 23 (6): 775–81. https://doi.org/10.1016/S0161-813X(02)00008-6.

Colomina, M. Teresa, Jose L. Roig, Margarita Torrente, Paloma Vicens, and Jose L. Domingo. 2005. 'Concurrent Exposure to Aluminum and Stress during Pregnancy in Rats: Effects on Postnatal Development and Behavior of the Offspring'. *Neurotoxicology and Teratology* 27 (4): 565–74. https://doi.org/10.1016/j.ntt.2005.06.014.

Cranmer, J. M., J. D. Wilkins, D. J. Cannon, and L. Smith. 1986. 'Fetal-Placental-Maternal Uptake of Aluminum in Mice Following Gestational Exposure: Effect of Dose and Route of Administration'. *Neurotoxicology* 7 (2): 601–8.

Crépeaux, Guillemette, Housam Eidi, Marie-Odile David, Eleni Tzavara, Bruno Giros, Christopher Exley, Patrick A. Curmi, Christopher A. Shaw, Romain K. Gherardi, and Josette Cadusseau. 2015. 'Highly Delayed Systemic Translocation of Aluminum-Based Adjuvant in CD1 Mice Following Intramuscular Injections'. *Journal of Inorganic Biochemistry* 152 (November):199–205. https://doi.org/10.1016/j.jinorgbio.2015.07.004.

Cunat, L., M. C. Lanhers, M. Joyeux, and D. Burnel. 2000. 'Bioavailability and Intestinal Absorption of Aluminum in Rats: Effects of Aluminum Compounds and Some Dietary Constituents'. *Biological Trace Element Research* 76 (1): 31–55. https://doi.org/10.1385/BTER:76:1:31.

Da Silva Lima, Danilo, Liana Da Silva Gomes, Esther De Sousa Figueredo, Murion Monteiro De Godoi, Edvaldo Mendes Silva, Hiasmin Franciely Da Silva Neri, Sebastião Roberto Taboga, Manoel Francisco Biancardi, Paulo César Ghedini, and Fernanda Cristina Alcantara Dos Santos. 2020. 'Aluminum Exposure Promotes Histopathological and Pro-Oxidant Damage to the Prostate and Gonads of Male and Female Adult Gerbils'. *Experimental and Molecular Pathology* 116 (October):104486. https://doi.org/10.1016/j.yexmp.2020.104486.

Da Silva Lima, Danilo, Liana Da Silva Gomes, Esther De Sousa Figueredo, Yasmin Inocêncio Fernandes E Silva, Edvaldo Mendes Silva, Thais De Souza Bovi, Sebastião Roberto Taboga, Mara Rúbia Marques, Manoel Francisco Biancardi, and Fernanda Cristina Alcantara Dos Santos. 2022. 'Subacute Exposure to Aluminum Chloride Causes Prolonged Morphological Insults in the Ventral Male Prostate and in the Female Prostate of Adult Gerbils'. *Environmental Toxicology* 37 (2): 299–309. https://doi.org/10.1002/tox.23398.

Daley, Matthew F., Liza M. Reifler, Jason M. Glanz, Simon J. Hambidge, Darios Getahun, Stephanie A. Irving, James D. Nordin, et al. 2023. 'Association Between Aluminum Exposure From Vaccines Before Age 24 Months and Persistent Asthma at Age 24 to 59 Months'. *Academic Pediatrics* 23 (1): 37–46. https://doi.org/10.1016/j.acap.2022.08.006.

Darbre, P. D. 2005. 'Aluminium, Antiperspirants and Breast Cancer'. *Journal of Inorganic Biochemistry* 99 (9): 1912–19. https://doi.org/10.1016/j.jinorgbio.2005.06.001.

Daydé, Sandrine, Véronique Brumas, Delphine Champmartin, Patrice Rubini, and Guy Berthon. 2003. 'Aluminum Speciation Studies in Biological Fluids. Part 9. A Quantitative Investigation of Aluminum(III)-Glutamate Complex Equilibria and Their Potential Implications for Aluminum Metabolism and Toxicity'. *Journal of Inorganic Biochemistry* 97 (1): 104–17. https://doi.org/10.1016/s0162-0134(03)00244-7.

Desroches, S., S. Daydé, and G. Berthon. 2000. 'Aluminum Speciation Studies in Biological Fluids. Part 6. Quantitative Investigation of Aluminum(III)-Tartrate Complex Equilibria and Their Potential Implications for Aluminum Metabolism and Toxicity'. *Journal of Inorganic Biochemistry* 81 (4): 301–12. https://doi.org/10.1016/s0162-0134(00)00072-6.

DeVoto, E., and R. A. Yokel. 1994. 'The Biological Speciation and Toxicokinetics of Aluminum'. *Environmental Health Perspectives* 102 (11): 940–51. https://doi.org/10.1289/ehp.94102940.

Di Ciaula, Agostino, Patrizia Gentilini, Giusy Diella, Marco Lopuzzo, and Ruggero Ridolfi. 2020. 'Biomonitoring of Metals in Children Living in an Urban Area and Close to Waste Incinerators'. *International Journal of Environmental Research and Public Health* 17 (6): 1919. https://doi.org/10.3390/ijerph17061919.

Dixon, R. L., R. J. Sherins, and I. P. Lee. 1979. 'Assessment of Environmental Factors Affecting Male Fertility'. *Environmental Health Perspectives* 30 (June):53–68. https://doi.org/10.1289/ehp.793053.

Domingo, J. L., M. Gómez, M. A. Bosque, and J. Corbella. 1989. 'Lack of Teratogenicity of Aluminum Hydroxide in Mice'. *Life Sciences* 45 (3): 243–47. https://doi.org/10.1016/0024-3205(89)90256-7.

Domingo, J. L., J. M. Llobet, M. Gómez, J. M. Tomás, and J. Corbella. 1987b. 'Nutritional and Toxicological Effects of Short-Term Ingestion of Aluminum by the Rat'. *Research Communications in Chemical Pathology and Pharmacology* 56 (3): 409–19.

Domingo, J. L., J. L. Paternain, J. M. Llobet, and J. Corbella. 1987c. 'Effects of Oral Aluminum Administration on Perinatal and Postnatal Development in Rats'. *Research Communications in Chemical Pathology and Pharmacology* 57 (1): 129–32.

———. 1987a. 'The Effects of Aluminium Ingestion on Reproduction and Postnatal Survival in Rats'. *Life Sciences* 41 (9): 1127–31. https://doi.org/10.1016/0024-3205(87)90631-x.

Donald, J. M., M. S. Golub, M. E. Gershwin, and C. L. Keen. 1989. 'Neurobehavioral Effects in Offspring of Mice given Excess Aluminum in Diet during Gestation and Lactation'. *Neurotoxicology and Teratology* 11 (4): 345–51. https://doi.org/10.1016/0892-0362(89)90005-6.

Drew, R. T., B. N. Gupta, J. R. Bend, and G. E. Hook. 1974. 'Inhalation Studies with a Glycol Complex of Aluminum-Chloride-Hydroxide'. *Archives of Environmental Health* 28 (6): 321–26. https://doi.org/10.1080/00039896.1974.10666500.

EFSA. 2008. 'Safety of Aluminium from Dietary Intake - Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (AFC) | EFSA'. European Food Safety Authority. https://www.efsa.europa.eu/en/efsajournal/pub/754.

———. 2011. 'Statement of EFSA on the Evaluation of a New Study Related to the Bioavailability of Aluminium in Food'. *EFSA Journal* 9 (5): 2157. https://doi.org/10.2903/j.efsa.2011.2157.

Eickhoff, Theodore C., and Martin Myers. 2002. 'Workshop Summary. Aluminum in Vaccines'. *Vaccine* 20 Suppl 3 (May):S1-4. https://doi.org/10.1016/s0264-410x(02)00163-9.

Eidi, Housam, Marie-Odile David, Guillemette Crépeaux, Laetitia Henry, Vandana Joshi, Marie-Hélène Berger, Mohamed Sennour, Josette Cadusseau, Romain K. Gherardi, and Patrick A. Curmi. 2015. 'Fluorescent Nanodiamonds as a Relevant Tag for the Assessment of Alum Adjuvant Particle Biodisposition'. *BMC Medicine* 13 (June):144. https://doi.org/10.1186/s12916-015-0388-2.

Ellis, H., and J. H. Scurr. 1979. 'Axillary Hyperhidrosis - Topical Treatment with Aluminium Chloride Hexahydrate'. *Postgraduate Medical Journal* 55 (654): 868–69. https://doi.org/10.1136/pgmj.55.650.868.

Erazi, Hasna, Wafa Sansar, Samir Ahboucha, and Halima Gamrani. 2010. 'Aluminum Affects Glial System and Behavior of Rats'. *Comptes Rendus Biologies* 333 (1): 23–27. https://doi.org/10.1016/j.crvi.2009.09.016.

Exley, Christopher, Amina Begum, Mark P. Woolley, and Roger N. Bloor. 2006. 'Aluminum in Tobacco and Cannabis and Smoking-Related Disease'. *The American Journal of Medicine* 119 (3): 276.e9-276.e11. https://doi.org/10.1016/j.amjmed.2005.08.004.

Exley, Christopher, Lisa M. Charles, Lester Barr, Claire Martin, Anthony Polwart, and Philippa D. Darbre. 2007. 'Aluminium in Human Breast Tissue'. *Journal of Inorganic Biochemistry* 101 (9): 1344–46. https://doi.org/10.1016/j.jinorgbio.2007.06.005.

Fernandes, Rafael Monteiro, Márcio Gonçalves Corrêa, Walessa Alana Bragança Aragão, Priscila Cunha Nascimento, Sabrina C. Cartágenes, Caroline Azulay Rodrigues, Luis Felipe Sarmiento, et al. 2020. 'Preclinical Evidences of Aluminum-Induced Neurotoxicity in Hippocampus and Pre-Frontal Cortex of Rats Exposed to Low Doses'. *Ecotoxicology and Environmental Safety* 206 (December):111139. https://doi.org/10.1016/j.ecoenv.2020.111139.

Flarend, Richard E., Stanley L. Hem, Joe L. White, David Elmore, Mark A. Suckow, Anita C. Rudy, and Euphemie A. Dandashli. 1997. '*In Vivo* Absorption of Aluminium-Containing Vaccine Adjuvants Using 26Al'. *Vaccine* 15 (12): 1314–18. https://doi.org/10.1016/S0264-410X(97)00041-8.

Froment, D. P., B. A. Molitoris, B. Buddington, N. Miller, and A. C. Alfrey. 1989. 'Site and Mechanism of Enhanced Gastrointestinal Absorption of Aluminum by Citrate'. *Kidney International* 36 (6): 978–84. https://doi.org/10.1038/ki.1989.290.

Fu, Y., F. B. Jia, J. Wang, M. Song, S. M. Liu, Y. F. Li, S. Z. Liu, and Q. W. Bu. 2014. 'Effects of Sub-Chronic Aluminum Chloride Exposure on Rat Ovaries'. *Life Sciences* 100 (1): 61–66. https://doi.org/10.1016/j.lfs.2014.01.081.

GACVS. 2012. 'Global Advisory Committee on Vaccine Safety'. Meeting report. Geneva, Switzerland. https://www.who.int/publications/i/item/WER8730.

Gallego, H., E. J. Lewis, and C. E. Crutchfield. 1999. 'Crystal Deodorant Dermatitis: Irritant Dermatitis to Alum-Containing Deodorant'. *Cutis* 64 (1): 65–66.

Ganrot, P. O. 1986. 'Metabolism and Possible Health Effects of Aluminum'. *Environmental Health Perspectives* 65 (March):363–441. https://doi.org/10.1289/ehp.8665363.

García-Alegría, Alejandro Monserrat, Agustín Gómez-Álvarez, Iván Anduro-Corona, Armando Burgos-Hernández, Eduardo Ruíz-Bustos, Rafael Canett-Romero, Humberto González-Ríos, José Guillermo López-Cervantes, Karen Lillian Rodríguez-Martínez, and Humberto Astiazaran-Garcia. 2020. 'Genotoxic Effects of Aluminum Chloride and Their Relationship with N-Nitroso-N-Methylurea (NMU)-Induced Breast Cancer in Sprague Dawley Rats'. *Toxics* 8 (2): 31. https://doi.org/10.3390/toxics8020031.

Gherardi, R. K., M. Coquet, P. Chérin, F. J. Authier, P. Laforêt, L. Bélec, D. Figarella-Branger, J. M. Mussini, J. F. Pellissier, and M. Fardeau. 1998. 'Macrophagic Myofasciitis: An Emerging Entity. Groupe d'Etudes et Recherche Sur Les Maladies Musculaires Acquises et Dysimmunitaires (GERMMAD) de l'Association Française Contre Les Myopathies (AFM)'. *Lancet (London, England)* 352 (9125): 347–52. https://doi.org/10.1016/s0140-6736(98)02326-5.

Ghosh, Buddhadeb, Ravi Kant Sharma, and Suman Yadav. 2021a. 'Toxic Effects of Aluminium on Testis in Presence of Ethanol Coexposure'. https://eurjanat.com/articles/toxic-effects-of-aluminium-on-testis-in-presence-of-ethanol-coexposure/.

Ghosh, Buddhadeb, Ravi Kant Sharma, Suman Yadav, and Ankita Randev. 2021b. 'Toxic Effects of Aluminium on Female Reproductive System in Presence of Ethanol Coexposure'. *Research Journal of Pharmacy and Technology*, 3809–15. https://doi.org/10.52711/0974-360X.2021.00660.

Giorgianni, Concetto Mario, Graziella D'Arrigo, Renato Brecciaroli, Adriana Abbate, Giovanna Spatari, Maria Antonietta Tringali, Silvia Gangemi, and Annamaria De Luca. 2014. 'Neurocognitive Effects in Welders Exposed to Aluminium'. *Toxicology and Industrial Health* 30 (4): 347–56. https://doi.org/10.1177/0748233712456062.

Gitelman, H. J., F. R. Alderman, M. Kurs-Lasky, and H. E. Rockette. 1995. 'Serum and Urinary Aluminium Levels of Workers in the Aluminium Industry'. *The Annals of Occupational Hygiene* 39 (2): 181–91. https://doi.org/10.1016/0003-4878(94)00113-f.

Goh, C. L. 1990. 'Aluminum Chloride Hexahydrate versus Palmar Hyperhidrosis. Evaporimeter Assessment'. *International Journal of Dermatology* 29 (5): 368–70. https://doi.org/10.1111/j.1365-4362.1990.tb04766.x.

Golub, M. S., J. M. Donald, M. E. Gershwin, and C. L. Keen. 1989. 'Effects of Aluminum Ingestion on Spontaneous Motor Activity of Mice'. *Neurotoxicology and Teratology* 11 (3): 231–35. https://doi.org/10.1016/0892-0362(89)90064-0.

Golub, M. S., and S. L. Germann. 1998. 'Aluminum Effects on Operant Performance and Food Motivation of Mice'. *Neurotoxicology and Teratology* 20 (4): 421–27. https://doi.org/10.1016/s0892-0362(97)00133-5.

———. 2001. 'Long-Term Consequences of Developmental Exposure to Aluminum in a Suboptimal Diet for Growth and Behavior of Swiss Webster Mice'. *Neurotoxicology and Teratology* 23 (4): 365–72. https://doi.org/10.1016/s0892-0362(01)00144-1.

Golub, M. S., S. L. Germann, B. Han, and C. L. Keen. 2000. 'Lifelong Feeding of a High Aluminum Diet to Mice'. *Toxicology* 150 (1–3): 107–17. https://doi.org/10.1016/s0300-483x(00)00251-1.

Golub, M. S., B. Han, C. L. Keen, and M. E. Gershwin. 1992b. 'Effects of Dietary Aluminum Excess and Manganese Deficiency on Neurobehavioral Endpoints in Adult Mice'. *Toxicology and Applied Pharmacology* 112 (1): 154–60. https://doi.org/10.1016/0041-008x(92)90291-y.

Golub, M. S., B. Han, C. L. Keen, M. E. Gershwin, and R. P. Tarara. 1995. 'Behavioral Performance of Swiss Webster Mice Exposed to Excess Dietary Aluminum during Development or during Development and as Adults'. *Toxicology and Applied Pharmacology* 133 (1): 64–72. https://doi.org/10.1006/taap.1995.1127.

Golub, M. S., C. L. Keen, and M. E. Gershwin. 1992a. 'Neurodevelopmental Effect of Aluminum in Mice: Fostering Studies'. *Neurotoxicology and Teratology* 14 (3): 177–82. https://doi.org/10.1016/0892-0362(92)90013-z.

Golub, M. S., P. T. Takeuchi, M. E. Gershwin, and S. H. Yoshida. 1993. 'Influence of Dietary Aluminum on Cytokine Production by Mitogen-Stimulated Spleen Cells from Swiss Webster

Mice'. *Immunopharmacology and Immunotoxicology* 15 (5): 605–19. https://doi.org/10.3109/08923979309019733.

Gomes, Liana Da Silva, Danilo Da Silva Lima, Janaína Ribeiro Costa, Cinthia Rio Branco Da Silva, Mara Rúbia Marques, Pedro Vale De Azevedo Brito, Manoel Francisco Biancardi, Sebastião Roberto Taboga, Paulo César Ghedini, and Fernanda Cristina Alcantara Dos Santos. 2020. 'Neonatal Exposure to Aluminum Chloride Disrupts Branching Morphogenesis and Hormonal Signaling of the Ventral Male Prostate and Female Prostate of Gerbils'. *Journal of Trace Elements in Medicine and Biology* 61 (September):126559. https://doi.org/10.1016/j.jtemb.2020.126559.

Gomes, Liana S., Janaína R. Costa, Mônica S. Campos, Mara R. Marques, Manoel F. Biancardi, Sebastião R. Taboga, Paulo C. Ghedini, and Fernanda C.A. Santos. 2019. 'Aluminum Disrupts the Prenatal Development of the Male and Female Gerbil Prostate (Meriones Unguiculatus)'. *Experimental and Molecular Pathology* 107 (April):32–42. https://doi.org/10.1016/j.yexmp.2019.01.005.

Gomez, M., M. A. Bosque, J. L. Domingo, J. M. Llobet, and J. Corbella. 1990. 'Evaluation of the Maternal and Developmental Toxicity of Aluminum from High Doses of Aluminum Hydroxide in Rats'. *Veterinary and Human Toxicology* 32 (6): 545–48.

Gómez, M., J. L. Domingo, J. M. Llobet, J. M. Tomás, and J. Corbella. 1986. 'Short-Term Oral Toxicity Study of Aluminium in Rats'. *Archivos De Farmacologia Y Toxicologia* 12 (2–3): 145–51.

Gorsky, J. E., A. A. Dietz, H. Spencer, and D. Osis. 1979. 'Metabolic Balance of Aluminum Studied in Six Men'. *Clinical Chemistry* 25 (10): 1739–43.

Goullé, Jean-Pierre, Loïc Mahieu, Julien Castermant, Nicolas Neveu, Laurent Bonneau, Gilbert Lainé, Daniel Bouige, and Christian Lacroix. 2005. 'Metal and Metalloid Multi-Elementary ICP-MS Validation in Whole Blood, Plasma, Urine and Hair. Reference Values'. *Forensic Science International* 153 (1): 39–44. https://doi.org/10.1016/j.forsciint.2005.04.020.

Goullé, J.-P., and L. Grangeot-Keros. 2020. 'Aluminum and Vaccines: Current State of Knowledge'. *Medecine Et Maladies Infectieuses* 50 (1): 16–21. https://doi.org/10.1016/j.medmal.2019.09.012.

Greger, J. L., and M. J. Baier. 1983. 'Excretion and Retention of Low or Moderate Levels of Aluminium by Human Subjects'. *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 21 (4): 473–77. https://doi.org/10.1016/0278-6915(83)90105-9.

Guo, Guiwen, Huirong Ma, Xinshi Wang, and Youxin Liang. 1999. 'Age-Dependent Differences of Neurobehavioural Function among Workers Exposed to Aluminium'. *Journal of Environmental Medicine* 1 (2): 81–85. https://doi.org/10.1002/(SICI)1099-1301(199904/06)1:2<81::AID-JEM17>3.0.CO;2-W.

Hänninen, H., E. Matikainen, T. Kovala, S. Valkonen, and V. Riihimäki. 1994. 'Internal Load of Aluminum and the Central Nervous System Function of Aluminum Welders'. *Scandinavian Journal of Work, Environment & Health* 20 (4): 279–85. https://doi.org/10.5271/sjweh.1397.

Hantson, P., P. Mahieu, M. Gersdorff, C. Sindic, and R. Lauwerys. 1995. 'Fatal Encephalopathy after Otoneurosurgery Procedure with an Aluminum-Containing Biomaterial'. *Journal of Toxicology. Clinical Toxicology* 33 (6): 645–48. https://doi.org/10.3109/15563659509010622.

HCSP. 2013. 'Aluminium et vaccins'. *Rapport de l'HCSP*. Paris: Haut Conseil de la Santé Publique. https://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=369.

He, S.C., N. Qiao, and W. Sheng. 2003. 'Neurobehavioral, Autonomic Nervous Function and Lymphocyte Subsets among Aluminum Electrolytic Workers'. *International Journal of*

Immunopathology and Pharmacology 16 (2): 139–44. https://doi.org/10.1177/039463200301600207.

Health Council of the Netherlands. 2010. 'Aluminium and Aluminium Compounds'. https://www.healthcouncil.nl/documents/advisory-reports/2010/07/15/aluminium-and-aluminium-compounds-health-based-recommended-occupational-exposure-limit.

Hethey, Christoph, Niklas Hartung, Gaby Wangorsch, Karin Weisser, and Wilhelm Huisinga. 2021. 'Physiology-Based Toxicokinetic Modelling of Aluminium in Rat and Man'. *Archives of Toxicology* 95 (9): 2977–3000. https://doi.org/10.1007/s00204-021-03107-y.

Hichem, Nadia, Michèle El May, Nizar Ladhari, Ali Mrabet, and Rafik Gharbi. 2014. 'Aluminum Chloride Impacts Dentate Gyrus Structure in Male Adult Albino Wistar Rats'. *Tissue & Cell* 46 (6): 409–14. https://doi.org/10.1016/j.tice.2014.05.006.

Hirata-Koizumi, Mutsuko, Sakiko Fujii, Atsushi Ono, Akihiko Hirose, Toshio Imai, Kumiko Ogawa, Makoto Ema, and Akiyoshi Nishikawa. 2011a. 'Evaluation of the Reproductive and Developmental Toxicity of Aluminium Ammonium Sulfate in a Two-Generation Study in Rats'. *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 49 (9): 1948–59. https://doi.org/10.1016/j.fct.2011.04.035.

———. 2011b. 'Two-Generation Reproductive Toxicity Study of Aluminium Sulfate in Rats'. *Reproductive Toxicology* 31 (2): 219–30. https://doi.org/10.1016/j.reprotox.2010.11.004.

Hoet, Perrine, Chantal Jacquerye, Gladys Deumer, Dominique Lison, and Vincent Haufroid. 2013. 'Reference Values and Upper Reference Limits for 26 Trace Elements in the Urine of Adults Living in Belgium'. *Clinical Chemistry and Laboratory Medicine* 51 (4): 839–49. https://doi.org/10.1515/cclm-2012-0688.

Hosovski, E., Z. Mastelica, D. Sunderić, and D. Radulović. 1990. 'Mental Abilities of Workers Exposed to Aluminium'. *La Medicina Del Lavoro* 81 (2): 119–23.

Hull, Mindy J., and Jerrold L. Abraham. 2002. 'Aluminum Welding Fume-Induced Pneumoconiosis'. *Human Pathology* 33 (8): 819–25. https://doi.org/10.1053/hupa.2002.125382.

IARC. 1984. 'IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS Polynuclear Aromatic Compounds, Part 3, Industrial Exposures in Aluminium Production, Co al Gasification, Coke Production, and Iron and Steel Founding'. Volume 34. INTERNATIONAL AGENCY FOR RESEARCH ON CANCER.

———. 2012. 'OCCUPATIONAL EXPOSURES DURING ALUMINIUM PRODUCTION'. In *Chemical Agents and Related Occupations*. International Agency for Research on Cancer. https://www.ncbi.nlm.nih.gov/books/NBK304404/.

INERIS. 2005. 'Aluminium et dérivés'. Institut national de l'environnement industriel et des risques.

———. 2015. 'Aluminium'. Institut national de l'environnement industriel et des risques.

INRS. 2021. 'Aluminium et Ses Composés Minéraux'. Institut national de recherche et de sécurité.

Iregren, A., B. Sjögren, K. Gustafsson, M. Hagman, L. Nylén, W. Frech, M. Andersson, K. G. Ljunggren, and A. Wennberg. 2001. 'Effects on the Nervous System in Different Groups of Workers Exposed to Aluminium'. *Occupational and Environmental Medicine* 58 (7): 453–60. https://doi.org/10.1136/oem.58.7.453.

Ittel, T. H., B. Buddington, N. L. Miller, and A. C. Alfrey. 1987. 'Enhanced Gastrointestinal Absorption of Aluminum in Uremic Rats'. *Kidney International* 32 (6): 821–26. https://doi.org/10.1038/ki.1987.282.

Jalili, Pégah, Sylvie Huet, Rachelle Lanceleur, Gérard Jarry, Ludovic Le Hegarat, Fabrice Nesslany, Kevin Hogeveen, and Valérie Fessard. 2020. 'Genotoxicity of Aluminum and Aluminum Oxide Nanomaterials in Rats Following Oral Exposure'. *Nanomaterials (Basel, Switzerland)* 10 (2): 305. https://doi.org/10.3390/nano10020305.

JECFA. 2012. 'Safety Evaluation of Certain Food Additives: Prepared by the Seventy-Sixth Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)'. SERIES: 65. Geneva: Joint FAO/WHO Expert Committee on Food Additives. https://www.who.int/publications-detail-redirect/9789241660679.

Jouhanneau, P., G. M. Raisbeck, F. Yiou, B. Lacour, H. Banide, and T. B. Drüeke. 1997. 'Gastrointestinal Absorption, Tissue Retention, and Urinary Excretion of Dietary Aluminum in Rats Determined by Using 26Al'. *Clinical Chemistry* 43 (6 Pt 1): 1023–28.

Katz, A. C., D. W. Frank, M. W. Sauerhoff, G. M. Zwicker, and R. I. Freudenthal. 1984. 'A 6-Month Dietary Toxicity Study of Acidic Sodium Aluminium Phosphate in Beagle Dogs'. *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 22 (1): 7–9. https://doi.org/10.1016/0278-6915(84)90045-0.

Khan, Zakir, Christophe Combadière, François-Jérôme Authier, Valérie Itier, François Lux, Christopher Exley, Meriem Mahrouf-Yorgov, et al. 2013. 'Slow CCL2-Dependent Translocation of Biopersistent Particles from Muscle to Brain'. *BMC Medicine* 11 (April):99. https://doi.org/10.1186/1741-7015-11-99.

Kierulf, Alastair, Cameron Ollson, Caroline Whitehead, Diane Beauchemin, and Iris Koch. 2022. 'Literature Review and Meta-Analysis of Gastric and Intestinal Bioaccessibility for Nine Inorganic Elements in Soils and Soil-like Media for Use in Human Health Risk Assessment'. *International Journal of Hygiene and Environmental Health* 240 (March):113929. https://doi.org/10.1016/j.ijheh.2022.113929.

Kiesswetter, E., M. Schäper, M. Buchta, K. H. Schaller, B. Rossbach, H. Scherhag, W. Zschiesche, and S. Letzel. 2007. 'Longitudinal Study on Potential Neurotoxic Effects of Aluminium: I. Assessment of Exposure and Neurobehavioural Performance of Al Welders in the Train and Truck Construction Industry over 4 Years'. *International Archives of Occupational and Environmental Health* 81 (1): 41–67. https://doi.org/10.1007/s00420-007-0191-2.

Kiesswetter, Ernst, M. Schäper, M. Buchta, K. H. Schaller, B. Rossbach, T. Kraus, and S. Letzel. 2009. 'Longitudinal Study on Potential Neurotoxic Effects of Aluminium: II. Assessment of Exposure and Neurobehavioral Performance of Al Welders in the Automobile Industry over 4 Years'. *International Archives of Occupational and Environmental Health* 82 (10): 1191–1210. https://doi.org/10.1007/s00420-009-0414-9.

Klotz, Katrin, Hans Drexler, Andrea Hartwig, and MAK Commission. 2020. 'Aluminium – Addendum for Evaluation of a BAR. Assessment Values in Biological Material – Translation of the German Version from 2019'. https://doi.org/10.34865/BB742990E5_1.

Klotz, Katrin, M. Meyer-Baron, Christoph Thriel, D. Pallapies, M. Nasterlack, s Letzel, Bernd Rossbach, et al. 2019. 'Addendum to Aluminium [BAT Value Documentation, 2019]'. https://doi.org/10.1002/3527600418.bb742990vere2419.

Konishi, Y., K. Yagyu, H. Kinebuchi, N. Saito, T. Yamaguchi, and Y. Ohtsuki. 1996. 'Chronic Effect of Aluminium Ingestion on Bone in Calcium-Deficient Rats'. *Pharmacology & Toxicology* 78 (6): 429–34. https://doi.org/10.1111/j.1600-0773.1996.tb00231.x.

Korogiannos, C, F Babatsikou, and S Tzimas. 1998. 'Aluminum Compounds and Occupational Lung Disease'. *Eur Respir J 12(Suppl 28):139S*.

Kraus, T., K. H. Schaller, J. Angerer, and S. Letzel. 2000. 'Aluminium Dust-Induced Lung Disease in the Pyro-Powder-Producing Industry: Detection by High-Resolution Computed

Tomography'. *International Archives of Occupational and Environmental Health* 73 (1): 61–64. https://doi.org/10.1007/pl00007939.

Krause, Benjamin C., Fabian L. Kriegel, Daniel Rosenkranz, Nadine Dreiack, Jutta Tentschert, Harald Jungnickel, Pegah Jalili, Valerie Fessard, Peter Laux, and Andreas Luch. 2020. 'Aluminum and Aluminum Oxide Nanomaterials Uptake after Oral Exposure - a Comparative Study'. *Scientific Reports* 10 (1): 2698. https://doi.org/10.1038/s41598-020-59710-z.

Krewski, Daniel, Robert A. Yokel, Evert Nieboer, David Borchelt, Joshua Cohen, Jean Harry, Sam Kacew, Joan Lindsay, Amal M. Mahfouz, and Virginie Rondeau. 2007. 'Human Health Risk Assessment for Aluminium, Aluminium Oxide, and Aluminium Hydroxide'. *Journal of Toxicology and Environmental Health. Part B, Critical Reviews* 10 Suppl 1 (Suppl 1): 1–269. https://doi.org/10.1080/10937400701597766.

Kwon, Jung-Taek, Gyun-Baek Seo, null Jo, Mimi Lee, Hyun-Mi Kim, Ilseob Shim, Byung-Woo Lee, Byung-Il Yoon, Pilje Kim, and Kyunghee Choi. 2013. 'Aluminum Nanoparticles Induce ERK and p38MAPK Activation in Rat Brain'. *Toxicological Research* 29 (3): 181–85. https://doi.org/10.5487/TR.2013.29.3.181.

Labat, Laurence. 2010. 'La préparation des matrices biologiques pour l'analyse des métaux'. *Annales de Toxicologie Analytique* 22 (2): 81–88. https://doi.org/10.1051/ata/2010011.

Lankoff, Anna, Anna Banasik, Anna Duma, Edyta Ochniak, Halina Lisowska, Tomasz Kuszewski, Stanisław Góźdź, and Andrzej Wojcik. 2006. 'A Comet Assay Study Reveals That Aluminium Induces DNA Damage and Inhibits the Repair of Radiation-Induced Lesions in Human Peripheral Blood Lymphocytes'. *Toxicology Letters* 161 (1): 27–36. https://doi.org/10.1016/j.toxlet.2005.07.012.

Lauwerys, RR, and P Hoët. 2001. *Industrial Chemical Exposure : Guidelines for Biological Monitoring*. Vol. 3rd edition.

Letzel, Maximilian, Hans Drexler, Thomas Göen, and Julia Hiller. 2020. 'Impact of Daily Antiperspirant Use on the Systemic Aluminum Exposure: An Experimental Intervention Study'. *Skin Pharmacology and Physiology* 33 (1): 1–8. https://doi.org/10.1159/000502239.

Letzel, S., C. J. Lang, K. H. Schaller, J. Angerer, S. Fuchs, B. Neundörfer, and G. Lehnert. 2000. 'Longitudinal Study of Neurotoxicity with Occupational Exposure to Aluminum Dust'. *Neurology* 54 (4): 997–1000. https://doi.org/10.1212/wnl.54.4.997.

Lévêque, C., D. Soulié, J. L. Sarrazin, F. Hor, M. Desgeorges, and Y. S. Cordoliani. 1996. '[Toxic aluminum encephalopathy. Predominant involvement of the limbic system on MRI]'. *Journal of Neuroradiology = Journal De Neuroradiologie* 23 (3): 168–72.

Li, Xinwei, Chongwei Hu, Yanzhu Zhu, Hao Sun, Yanfei Li, and Zhigang Zhang. 2011. 'Effects of Aluminum Exposure on Bone Mineral Density, Mineral, and Trace Elements in Rats'. *Biological Trace Element Research* 143 (1): 378–85. https://doi.org/10.1007/s12011-010-8861-4.

Ligt, Rianne de, Esther van Duijn, Dimitri Grossouw, Sieto Bosgra, Jacobus Burggraaf, Albert Windhorst, Pierre A. M. Peeters, Gerrit A. van der Luijt, Camilla Alexander-White, and Wouter H. J. Vaes. 2018. 'Assessment of Dermal Absorption of Aluminum from a Representative Antiperspirant Formulation Using a 26 Al Microtracer Approach'. *Clinical and Translational Science* 11 (6): 573–81. https://doi.org/10.1111/cts.12579.

Ligt, Rianne de, Joost Westerhout, Dimitri Grossouw, Thomas P. Buters, Robert Rissmann, Jacobus Burggraaf, Albert D. Windhorst, et al. 2022. 'Assessment of Dermal Absorption of Aluminium from a Representative Antiperspirant Formulation Using a (26Al)Al Microtracer Approach: A Follow-up Study in Humans'. *Toxicology Research* 11 (3): 511–19. https://doi.org/10.1093/toxres/tfac029.

Linhart, Caroline, Heribert Talasz, Evi M. Morandi, Christopher Exley, Herbert H. Lindner, Susanne Taucher, Daniel Egle, Michael Hubalek, Nicole Concin, and Hanno Ulmer. 2017. 'Use of Underarm Cosmetic Products in Relation to Risk of Breast Cancer: A Case-Control Study'. *EBioMedicine* 21 (July):79–85. https://doi.org/10.1016/j.ebiom.2017.06.005.

Liu, Jianyu, Qin Wang, Xudong Sun, Xu Yang, Cuicui Zhuang, Feibo Xu, Zheng Cao, and Yanfei Li. 2016. 'The Toxicity of Aluminum Chloride on Kidney of Rats'. *Biological Trace Element Research* 173 (2): 339–44. https://doi.org/10.1007/s12011-016-0648-9.

Llobet, J. M., J. L. Domingo, M. Gómez, J. M. Tomás, and J. Corbella. 1987. 'Acute Toxicity Studies of Aluminium Compounds: Antidotal Efficacy of Several Chelating Agents'. *Pharmacology & Toxicology* 60 (4): 280–83. https://doi.org/10.1111/j.1600-0773.1987.tb01752.x.

Lu, Xiao-Ting, Shi-Meng Xu, Yun-Wei Zhang, Dan Gao, Hui Yang, Jing Song, Lin-Ping Wang, Qin-Li Zhang, Nan Shang, and Qiao Niu. 2021. 'Longitudinal Study of the Effects of Occupational Aluminium Exposure on Workers' Cognition'. *Chemosphere* 271 (May):129569. https://doi.org/10.1016/j.chemosphere.2021.129569.

Mameli, O., M. A. Caria, P. Melis, P. Zambenedetti, M. Ramila, and P. Zatta. 2006. 'Effect of Aluminum Consumption on the Vestibulo-Ocular Reflex'. *Metabolic Brain Disease* 21 (2–3): 89–107. https://doi.org/10.1007/s11011-006-9010-9.

Martinez, Caroline S., Caroline D. C. Alterman, Franck M. Peçanha, Dalton V. Vassallo, Pâmela B. Mello-Carpes, Marta Miguel, and Giulia A. Wiggers. 2017c. 'Aluminum Exposure at Human Dietary Levels for 60 Days Reaches a Threshold Sufficient to Promote Memory Impairment in Rats'. *Neurotoxicity Research* 31 (1): 20–30. https://doi.org/10.1007/s12640-016-9656-y.

Martinez, Caroline Silveira, Alyne Gourlart Escobar, José Antonio Uranga-Ocio, Franck Maciel Peçanha, Dalton Valentim Vassallo, Christopher Exley, Marta Miguel, and Giulia Alessandra Wiggers. 2017b. 'Aluminum Exposure for 60days at Human Dietary Levels Impairs Spermatogenesis and Sperm Quality in Rats'. *Reproductive Toxicology (Elmsford, N.Y.)* 73:128–41. https://doi.org/10.1016/j.reprotox.2017.08.008.

Martinez, Caroline Silveira, Janaina Trindade Piagette, Alyne Gourlart Escobar, Ángela Martín, Roberto Palacios, Franck Maciel Peçanha, Dalton Valentim Vassallo, et al. 2017a. 'Aluminum Exposure at Human Dietary Levels Promotes Vascular Dysfunction and Increases Blood Pressure in Rats: A Concerted Action of NAD(P)H Oxidase and COX-2'. *Toxicology* 390:10–21. https://doi.org/10.1016/j.tox.2017.08.004.

Martinez, Caroline Silveira, Gema Vera, José Antonio Uranga Ocio, Franck Maciel Peçanha, Dalton Valentim Vassallo, Marta Miguel, and Giulia Alessandra Wiggers. 2018. 'Aluminum Exposure for 60days at an Equivalent Human Dietary Level Promotes Peripheral Dysfunction in Rats'. *Journal of Inorganic Biochemistry* 181 (April):169–76. https://doi.org/10.1016/j.jinorgbio.2017.08.011.

Massand, Amit, Mallika Basera, Sonal Grace, Reshma Kumarachandra, K Sudha, Rajalakshmi Rai, Bv Murlimanju, and K Sowndarya. 2022. 'Effect of Different Doses of Aluminum Chloride on Neurodegeneration in Hippocampus Region of the Rat Brain'. *Journal of the Anatomical Society of India* 71 (4): 307. https://doi.org/10.4103/jasi.jasi_39_22.

Mazzoli-Rocha, Flavia, Aline Nogueira Dos Santos, Silviane Fernandes, Valeria Marques Ferreira Normando, Olaf Malm, Paulo Hilário Nascimento Saldiva, Domingos Luiz Wanderley Picanço-Diniz, Débora Souza Faffe, and Walter Araujo Zin. 2010. 'Pulmonary Function and Histological Impairment in Mice after Acute Exposure to Aluminum Dust'. *Inhalation Toxicology* 22 (10): 861–67. https://doi.org/10.3109/08958378.2010.489074.

Meggers, William Frederick, and Charles H. Corliss. 1961. *Tables of Spectral-Line Intensities*. National Bureau of Standards.

Meng, Huaxing, Shanshan Wang, Junhong Guo, Yarong Zhao, Shuhui Zhang, Yuqing Zhao, and Qiao Niu. 2019. 'Cognitive Impairment of Workers in a Large-Scale Aluminium Factory in China: A Cross-Sectional Study'. *BMJ Open* 9 (6): e027154. https://doi.org/10.1136/bmjopen-2018-027154.

Meyer-Baron, Monika, Michael Schäper, Guido Knapp, and Christoph van Thriel. 2007. 'Occupational Aluminum Exposure: Evidence in Support of Its Neurobehavioral Impact'. *Neurotoxicology* 28 (6): 1068–78. https://doi.org/10.1016/j.neuro.2007.07.001.

Migliore, L., L. Cocchi, C. Nesti, and E. Sabbioni. 1999. 'Micronuclei Assay and FISH Analysis in Human Lymphocytes Treated with Six Metal Salts'. *Environmental and Molecular Mutagenesis* 34 (4): 279–84. https://doi.org/10.1002/(sici)1098-2280(1999)34:4<279::aid-em8>3.0.co;2-7.

Mitkus, Robert J., David B. King, Maureen A. Hess, Richard A. Forshee, and Mark O. Walderhaug. 2011. 'Updated Aluminum Pharmacokinetics Following Infant Exposures through Diet and Vaccination'. *Vaccine* 29 (51): 9538–43. https://doi.org/10.1016/j.vaccine.2011.09.124.

Mohammed, Rateba S., Walaa Ibrahim, Dina Sabry, and Shaimaa Ibrahim El-Jaafary. 2020. 'Occupational Metals Exposure and Cognitive Performance among Foundry Workers Using Tau Protein as a Biomarker'. *Neurotoxicology* 76 (January):10–16. https://doi.org/10.1016/j.neuro.2019.09.017.

Morton, Jackie, Emma Tan, Elizabeth Leese, and John Cocker. 2014. 'Determination of 61 Elements in Urine Samples Collected from a Non-Occupationally Exposed UK Adult Population'. *Toxicology Letters* 231 (2): 179–93. https://doi.org/10.1016/j.toxlet.2014.08.019.

Mouro, Viviane G. S., Tatiana P. Menezes, Graziela D. A. Lima, Rafael R. Domingues, Ana Cláudia F. Souza, Juraci A. Oliveira, Sérgio L. P. Matta, and Mariana Machado-Neves. 2018. 'How Bad Is Aluminum Exposure to Reproductive Parameters in Rats?' *Biological Trace Element Research* 183 (2): 314–24. https://doi.org/10.1007/s12011-017-1139-3.

Movsas, Paneth, Rumbeiha, Zyskowski, and Gewolb. 2013. 'Effect of Routine Vaccination on Aluminum and Essential Element Levels in Preterm Infants'. https://pubmed.ncbi.nlm.nih.gov/23856981/.

Mrak, R. E. 1982. 'Muscle Granulomas Following Intramuscular Injection'. *Muscle & Nerve* 5 (8): 637–39. https://doi.org/10.1002/mus.880050808.

Muller, Guy, Viviane Bernuzzi, Didier Desor, Marie-France Hutin, Daniel Burnel, and Paul R. Lehr. 1990. 'Developmental Alterations in Offspring of Female Rats Orally Intoxicated by Aluminum Lactate at Different Gestation Periods'. *Teratology* 42 (3): 253–61. https://doi.org/10.1002/tera.1420420309.

Mussi, I., G. Calzaferri, M. Buratti, and L. Alessio. 1984. 'Behaviour of Plasma and Urinary Aluminium Levels in Occupationally Exposed Subjects'. *International Archives of Occupational and Environmental Health* 54 (2): 155–61. https://doi.org/10.1007/BF00378518.

Nisse, Catherine, Romuald Tagne-Fotso, Mike Howsam, Camille Richeval, Laurence Labat, and Ariane Leroyer. 2017. 'Blood and Urinary Levels of Metals and Metalloids in the General Adult Population of Northern France: The IMEPOGE Study, 2008–2010'. *International Journal of Hygiene and Environmental Health* 220 (2): 341–63. https://doi.org/10.1016/j.ijheh.2016.09.020.

Nolte, E, E Beck, C Winklhofer, and C Steinhausen. 2001. 'Compartmental Model for Aluminium Biokinetics'. *Human & Experimental Toxicology* 20 (2): 111–17. https://doi.org/10.1191/096032701673730925.

Nübler, Stefanie, Marta Esteban López, Argelia Castaño, Hans Mol, Moritz Schäfer, Karin Haji-Abbas-Zarrabi, Daniel Bury, et al. 2021. 'Interlaboratory Comparison Investigations (ICI) and

External Quality Assurance Schemes (EQUAS) for Cadmium in Urine and Blood: Results from the HBM4EU Project'. *International Journal of Hygiene and Environmental Health* 234 (May):113711. https://doi.org/10.1016/j.ijheh.2021.113711.

Oneda, S., T. Takasaki, K. Kuriwaki, Y. Ohi, Y. Umekita, S. Hatanaka, T. Fujiyoshi, A. Yoshida, and H. Yoshida. 1994. 'Chronic Toxicity and Tumorigenicity Study of Aluminum Potassium Sulfate in B6C3F1 Mice'. *In Vivo (Athens, Greece)* 8 (3): 271–78.

Oteiza, P. I., C. L. Keen, B. Han, and M. S. Golub. 1993. 'Aluminum Accumulation and Neurotoxicity in Swiss-Webster Mice after Long-Term Dietary Exposure to Aluminum and Citrate'. *Metabolism: Clinical and Experimental* 42 (10): 1296–1300. https://doi.org/10.1016/0026-0495(93)90128-b.

Paternain, J. L., J. L. Domingo, J. M. Llobet, and J. Corbella. 1988. 'Embryotoxic and Teratogenic Effects of Aluminum Nitrate in Rats upon Oral Administration'. *Teratology* 38 (3): 253–57. https://doi.org/10.1002/tera.1420380309.

Paz, Letícia Nazareth Fernandes, Laís Mesquita Moura, Danielle Cristinne A. Feio, Mirella de Souza Gonçalves Cardoso, Wagner Luiz O. Ximenes, Raquel C. Montenegro, Ana Paula N. Alves, Rommel R. Burbano, and Patrícia Danielle L. Lima. 2017. 'Evaluation of in Vivo and in Vitro Toxicological and Genotoxic Potential of Aluminum Chloride'. *Chemosphere* 175 (May):130–37. https://doi.org/10.1016/j.chemosphere.2017.02.011.

Peña-Fernández A, González-Muñoz Mj, and Lobo-Bedmar Mc. 2014. '"Reference Values" of Trace Elements in the Hair of a Sample Group of Spanish Children (Aged 6-9 Years) - Are Urban Topsoils a Source of Contamination?' *Environmental Toxicology and Pharmacology* 38 (1). https://doi.org/10.1016/j.etap.2014.05.011.

Pettersen, J. C., D. S. Hackett, G. M. Zwicker, and G. L. Sprague. 1990. 'Twenty-Six Week Toxicity Study with KASAL® (Basic Sodium Aluminum Phosphate) in Beagle Dogs'. *Environmental Geochemistry and Health* 12 (1–2): 121–23. https://doi.org/10.1007/BF01734061.

Phelps, K. R., K. Naylor, T. P. Brien, H. Wilbur, and S. S. Haqqie. 1999. 'Encephalopathy after Bladder Irrigation with Alum: Case Report and Literature Review'. *The American Journal of the Medical Sciences* 318 (3): 181–85. https://doi.org/10.1097/00000441-199909000-00013.

Pigott, G. H., B. A. Gaskell, and J. Ishmael. 1981. 'Effects of Long Term Inhalation of Alumina Fibres in Rats'. *British Journal of Experimental Pathology* 62 (3): 323–31.

Poddalgoda, Devika, Sean M. Hays, Chris Kirman, Natasha Chander, and Andy Nong. 2021. 'Derivation of Biomonitoring Equivalents for Aluminium for the Interpretation of Population-Level Biomonitoring Data'. *Regulatory Toxicology and Pharmacology: RTP* 122 (June):104913. https://doi.org/10.1016/j.yrtph.2021.104913.

Poirier, J., H. Semple, J. Davies, R. Lapointe, M. Dziwenka, M. Hiltz, and D. Mujibi. 2011. 'Double-Blind, Vehicle-Controlled Randomized Twelve-Month Neurodevelopmental Toxicity Study of Common Aluminum Salts in the Rat'. *Neuroscience* 193 (October):338–62. https://doi.org/10.1016/j.neuroscience.2011.05.008.

Polak, T. B., R. Milacic, B. Mitrovic, and M. Benedik. 2001. 'Speciation of Low Molecular Weight Al Complexes in Serum of CAPD Patients'. *Journal of Pharmaceutical and Biomedical Analysis* 26 (2): 189–201. https://doi.org/10.1016/s0731-7085(01)00397-1.

Polizzi, Salvatore, Enrico Pira, Mauro Ferrara, Massimiliano Bugiani, Andrea Papaleo, Roberto Albera, and Silvana Palmi. 2002. 'Neurotoxic Effects of Aluminium among Foundry Workers and Alzheimer's Disease'. *Neurotoxicology* 23 (6): 761–74. https://doi.org/10.1016/S0161-813X(02)00097-9.

Priest, N. D. 2004. 'The Biological Behaviour and Bioavailability of Aluminium in Man, with Special Reference to Studies Employing Aluminium-26 as a Tracer: Review and Study

Update'. *Journal of Environmental Monitoring: JEM* 6 (5): 375–403. https://doi.org/10.1039/b314329p.

Priest, N. D., D. Newton, J. P. Day, R. J. Talbot, and A. J. Warner. 1995. 'Human Metabolism of Aluminium-26 and Gallium-67 Injected as Citrates'. *Human & Experimental Toxicology* 14 (3): 287–93. https://doi.org/10.1177/096032719501400309.

Priest, N. D., E. Skybakmoen, and G. Jackson. 2021. 'The Bioavailability of Ingested 26Al-Labelled Aluminium and Aluminium Compounds in the Rat'. *Neurotoxicology* 83 (March):179–85. https://doi.org/10.1016/j.neuro.2020.06.010.

Recker, R. R., A. J. Blotcky, J. A. Leffler, and E. P. Rack. 1977. 'Evidence of Aluminum Absorption from the Gastrointestinal Tract and Bone Deposition by Aluminum Carbonate Ingestion with Normal Renal Function'. *The Journal of Laboratory and Clinical Medicine* 90 (5): 810–15.

Reisfeld, Rafael, and Karen I. Berliner. 2008. 'Evidence-Based Review of the Nonsurgical Management of Hyperhidrosis'. *Thoracic Surgery Clinics* 18 (2): 157–66. https://doi.org/10.1016/j.thorsurg.2008.01.004.

Reusche, E., P. Pilz, G. Oberascher, B. Lindner, R. Egensperger, K. Gloeckner, E. Trinka, and B. Iglseder. 2001. 'Subacute Fatal Aluminum Encephalopathy after Reconstructive Otoneurosurgery: A Case Report'. *Human Pathology* 32 (10): 1136–40. https://doi.org/10.1053/hupa.2001.28251.

Riihimäki, V., H. Hänninen, R. Akila, T. Kovala, E. Kuosma, H. Paakkulainen, S. Valkonen, and B. Engström. 2000. 'Body Burden of Aluminum in Relation to Central Nervous System Function among Metal Inert-Gas Welders'. *Scandinavian Journal of Work, Environment & Health* 26 (2): 118–30. https://doi.org/10.5271/sjweh.521.

Riihimäki, Vesa, and Antero Aitio. 2012. 'Occupational Exposure to Aluminum and Its Biomonitoring in Perspective'. *Critical Reviews in Toxicology* 42 (10): 827–53. https://doi.org/10.3109/10408444.2012.725027.

Roig, José L., Silvia Fuentes, M. Teresa Colomina, Paloma Vicens, and José L. Domingo. 2006. 'Aluminum, Restraint Stress and Aging: Behavioral Effects in Rats after 1 and 2 Years of Aluminum Exposure'. *Toxicology* 218 (2–3): 112–24. https://doi.org/10.1016/j.tox.2005.10.006.

Rossbach, Bernd, Mark Buchta, György A. Csanády, Johannes G. Filser, Wolfgang Hilla, Klaus Windorfer, Joachim Stork, et al. 2006. 'Biological Monitoring of Welders Exposed to Aluminium'. *Toxicology Letters* 162 (2–3): 239–45. https://doi.org/10.1016/j.toxlet.2005.09.018.

San Martín, Sonia Pérez, Josep Miquel Bauçà, and Eduardo Martinez-Morillo. 2022. 'Determination of Aluminum Concentrations in Biological Specimens: Application in the Clinical Laboratory'. *Advances in Laboratory Medicine* 3 (2): 153–66. https://doi.org/10.1515/almed-2022-0056.

SCCS. 2014. 'Opinion on the Safety of Aluminium in Cosmetic Products'. Scientific Committee on Consumer Safety.

———. 2020. 'Opinion on the Safety of Aluminium in Cosmetic Products: Submission II'. Scientific Committee on Consumer Safety. https://data.europa.eu/doi/10.2875/887898.

———. 2023. 'Opinion on the Safety of Aluminium in Cosmetic Products - Submission III'. Scientific Committee on Consumer Safety. https://health.ec.europa.eu/publications/sccs-safety-aluminium-cosmetic-products-submission-iii_en.

Schindler, Birgit Karin, Marta Esteban, Holger Martin Koch, Argelia Castano, Stephan Koslitz, Ana Cañas, Ludwine Casteleyn, et al. 2014. 'The European COPHES/DEMOCOPHES Project: Towards Transnational Comparability and Reliability of Human Biomonitoring Results'.

International Journal of Hygiene and Environmental Health 217 (6): 653–61. https://doi.org/10.1016/j.ijheh.2013.12.002.

Schroeder, H. A., and M. Mitchener. 1975b. 'Life-Term Effects of Mercury, Methyl Mercury, and Nine Other Trace Metals on Mice'. *The Journal of Nutrition* 105 (4): 452–58. https://doi.org/10.1093/jn/105.4.452.

———. 1975a. 'Life-Term Studies in Rats: Effects of Aluminum, Barium, Beryllium, and Tungsten'. *The Journal of Nutrition* 105 (4): 421–27. https://doi.org/10.1093/jn/105.4.421.

Seifert, Bernd, Kerstin Becker, Dieter Helm, Christian Krause, Christine Schulz, and Margarete Seiwert. 2000. 'The German Environmental Survey 1990/1992 (GerES II): Reference Concentrations of Selected Environmental Pollutants in Blood, Urine, Hair, House Dust, Drinking Water and Indoor Air'. *Journal of Exposure Science & Environmental Epidemiology* 10 (6): 552–65. https://doi.org/10.1038/sj.jea.7500111.

SFMT. 2016. 'RECOMMANDATIONS DE BONNE PRATIQUE SURVEILLANCE BIOLOGIQUE DES EXPOSITIONS PROFESSIONNELLES AUX AGENTS CHIMIQUES'. SOCIETE FRANCAISE DE MEDECINE DU TRAVAIL.

Shang, Nan, Lan Zhang, Shuo Wang, Tao Huang, Yanhong Wang, Xiaocheng Gao, Shimeng Xu, et al. 2021. 'Increased Aluminum and Lithium and Decreased Zinc Levels in Plasma Is Related to Cognitive Impairment in Workers at an Aluminum Factory in China: A Cross-Sectional Study'. *Ecotoxicology and Environmental Safety* 214 (May):112110. https://doi.org/10.1016/j.ecoenv.2021.112110.

Shoji, Hirotaka, Yasuhiro Irino, Masaru Yoshida, and Tsuyoshi Miyakawa. 2018. 'Behavioral Effects of Long-term Oral Administration of Aluminum Ammonium Sulfate in Male and Female C57 BL /6J Mice'. *Neuropsychopharmacology Reports* 38 (1): 18–36. https://doi.org/10.1002/npr2.12002.

Sjögren, B., A. Iregren, W. Frech, M. Hagman, L. Johansson, M. Tesarz, and A. Wennberg. 1996. 'Effects on the Nervous System among Welders Exposed to Aluminium and Manganese'. *Occupational and Environmental Medicine* 53 (1): 32–40. https://doi.org/10.1136/oem.53.1.32.

Sjögren, B., V. Lidums, M. Håkansson, and L. Hedström. 1985. 'Exposure and Urinary Excretion of Aluminum during Welding'. *Scandinavian Journal of Work, Environment & Health* 11 (1): 39–43. https://doi.org/10.5271/sjweh.2255.

Souza-Monteiro, Deiweson, Railson De Oliveira Ferreira, Luciana Guimarães Eiró, Leidiane Alencar De Oliveira Lima, Gabriela Souza Balbinot, Simone Patricia Aranha Da Paz, Alan Rodrigo Leal Albuquerque, et al. 2021. 'Long-Term Exposure to Low Doses of Aluminum Affects Mineral Content and Microarchitecture of Rats Alveolar Bone'. *Environmental Science and Pollution Research* 28 (33): 45879–90. https://doi.org/10.1007/s11356-021-13937-z.

SPF. 2021. 'Imprégnation de la population française par les métaux et métalloïdes. Programme national de biosurveillance. Esteban 2014-2016.' Synthèse. Saint-Maurice: Santé publique France. http://www.santepubliquefrance.fr et http://portaildocumentaire.santepubliquefrance.fr/exl-php/vue-consult/spf___internet_recherche/SPF00003139.

Stauber, Jennifer L., T. Mark Florence, Cheryl M. Davies, Merrin S. Adams, and S. John Buchanan. 1999. 'Bioavailability of Al in Alum-treated Drinking Water'. *Journal AWWA - Wiley Online Library*, 1999. https://awwa.onlinelibrary.wiley.com/doi/full/10.1002/j.1551-8833.1999.tb08736.x.

Steinhagen, W. H., F. L. Cavender, and B. Y. Cockrell. 1978. 'Six Month Inhalation Exposures of Rats and Guinea Pigs to Aluminum Chlorhydrate'. *Journal of Environmental Pathology and Toxicology* 1 (3): 267–77.

Steinhausen, C., G. Kislinger, C. Winklhofer, E. Beck, C. Hohl, E. Nolte, Thomas H. Ittel, and Michael J. L. Alvarez-Brückmann. 2004. 'Investigation of the Aluminium Biokinetics in Humans: A 26Al Tracer Study'. *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 42 (3): 363–71. https://doi.org/10.1016/j.fct.2003.09.010.

Stone, C. J., D. A. McLaurin, W. H. Steinhagen, F. L. Cavender, and J. K. Haseman. 1979. 'Tissue Deposition Patterns after Chronic Inhalation Exposures of Rats and Guinea Pigs to Aluminum Chlorhydrate'. *Toxicology and Applied Pharmacology* 49 (1): 71–76. https://doi.org/10.1016/0041-008x(79)90278-3.

Sulaiman, R., M. Wang, and X. Ren. 2020. 'Exposure to Aluminum, Cadmium, and Mercury and Autism Spectrum Disorder in Children: A Systematic Review and Meta-Analysis'. *Chemical Research in Toxicology* 33 (11): 2699–2718. https://doi.org/10.1021/acs.chemrestox.0c00167.

Sun, Hao, Chongwei Hu, Linlin Jia, Yanzhu Zhu, Hansong Zhao, Bing Shao, Nan Wang, Zhigang Zhang, and Yanfei Li. 2011. 'Effects of Aluminum Exposure on Serum Sex Hormones and Androgen Receptor Expression in Male Rats'. *Biological Trace Element Research* 144 (1–3): 1050–58. https://doi.org/10.1007/s12011-011-9098-6.

Sun, Xudong, Zheng Cao, Qiuyue Zhang, Shimin Liu, Feibo Xu, Jianfang Che, Yanzhu Zhu, Yanfei Li, Chuanyi Pan, and Wannan Liang. 2015. 'Aluminum Trichloride Impairs Bone and Downregulates Wnt/β-Catenin Signaling Pathway in Young Growing Rats'. *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 86 (December):154–62. https://doi.org/10.1016/j.fct.2015.10.005.

Sutherland, J. E., and J. L. Greger. 1998. 'Effect of the Size of an Oral Dose of Aluminium on the Relative Importance of Biliary v. Urinary Aluminium Excretion in Conscious Rats'. *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 36 (6): 505–12. https://doi.org/10.1016/s0278-6915(98)00005-2.

Talbot, R. J., D. Newton, N. D. Priest, J. G. Austin, and J. P. Day. 1995. 'Inter-Subject Variability in the Metabolism of Aluminium Following Intravenous Injection as Citrate'. *Human & Experimental Toxicology* 14 (7): 595–99. https://doi.org/10.1177/096032719501400707.

Thomson, S. M., D. C. Burnett, J. D. Bergmann, and C. J. Hixson. 1986. 'Comparative Inhalation Hazards of Aluminum and Brass Powders Using Bronchopulmonary Lavage as an Indicator of Lung Damage'. *Journal of Applied Toxicology: JAT* 6 (3): 197–209. https://doi.org/10.1002/jat.2550060311.

U.S. EPA. 2006. 'Provisional Peer Reviewed Toxicity Values for Aluminum (CASRN 7429-90-5)'. U.S. Environmental Protection Agency. https://cfpub.epa.gov/ncea/pprtv/documents/Aluminum.pdf.

———. 2023. 'Provisional Peer-Reviewed Toxicity Values for Aluminum Phosphate Salts.' EPA/690/R-23/004F. Washington, DC: U.S. Environmental Protection Agency. https://assessments.epa.gov/risk/document/&deid%3D360196.

Valkonen, S., and A. Aitio. 1997. 'Analysis of Aluminium in Serum and Urine for the Biomonitoring of Occupational Exposure'. *The Science of the Total Environment* 199 (1–2): 103–10. https://doi.org/10.1016/s0048-9697(97)05485-5.

Virk, Sohaib A., and Guy D. Eslick. 2015. 'Occupational Exposure to Aluminum and Alzheimer Disease: A Meta-Analysis'. *Journal of Occupational and Environmental Medicine* 57 (8): 893–96. https://doi.org/10.1097/JOM.0000000000000487.

Vittori, D., A. Nesse, G. Pérez, and G. Garbossa. 1999. 'Morphologic and Functional Alterations of Erythroid Cells Induced by Long-Term Ingestion of Aluminium'. *Journal of Inorganic Biochemistry* 76 (2): 113–20. https://doi.org/10.1016/s0162-0134(99)00122-1.

Vlasak, Thomas, Tanja Dujlovic, and Alfred Barth. 2024. 'Aluminum Exposure and Cognitive Performance: A Meta-Analysis'. *The Science of the Total Environment* 906 (January):167453. https://doi.org/10.1016/j.scitotenv.2023.167453.

Vorkamp, Katrin, Argelia Castaño, Jean-Philippe Antignac, Luis D. Boada, Enrique Cequier, Adrian Covaci, Marta Esteban López, et al. 2021. 'Biomarkers, Matrices and Analytical Methods Targeting Human Exposure to Chemicals Selected for a European Human Biomonitoring Initiative'. *Environment International* 146 (January):106082. https://doi.org/10.1016/j.envint.2020.106082.

Walton, J. R. 2009. 'Functional Impairment in Aged Rats Chronically Exposed to Human Range Dietary Aluminum Equivalents'. *Neurotoxicology* 30 (2): 182–93. https://doi.org/10.1016/j.neuro.2008.11.012.

Wang, Nan, Yue She, Yanzhu Zhu, Hansong Zhao, Bing Shao, Hao Sun, Chongwei Hu, and Yanfei Li. 2012. 'Effects of Subchronic Aluminum Exposure on the Reproductive Function in Female Rats'. *Biological Trace Element Research* 145 (3): 382–87. https://doi.org/10.1007/s12011-011-9200-0.

Wang, Shanshan, Huaxing Meng, Nan Shang, Junhong Guo, Ting Zhang, Shuhui Zhang, Yuqing Zhao, Huifang Zhang, Qinli Zhang, and Qiao Niu. 2020. 'The Relationship between Plasma Al Levels and Multi-Domain Cognitive Performance among In-Service Aluminum-Exposed Workers at the SH Aluminum Factory in China: A Cross-Sectional Study'. *Neurotoxicology* 76 (January):144–52. https://doi.org/10.1016/j.neuro.2019.10.011.

Wang, Yi-Xin, An Pan, Wei Feng, Chong Liu, Li-Li Huang, Song-Hua Ai, Qiang Zeng, and Wen-Qing Lu. 2019. 'Variability and Exposure Classification of Urinary Levels of Non-Essential Metals Aluminum, Antimony, Barium, Thallium, Tungsten and Uranium in Healthy Adult Men'. *Journal of Exposure Science & Environmental Epidemiology* 29 (3): 424–34. https://doi.org/10.1038/s41370-017-0002-0.

Wang, Zengjin, Xiaomin Wei, Junlin Yang, Jinning Suo, Jingyi Chen, Xianchen Liu, and Xiulan Zhao. 2016. 'Chronic Exposure to Aluminum and Risk of Alzheimer's Disease: A Meta-Analysis'. *Neuroscience Letters* 610 (January):200–206. https://doi.org/10.1016/j.neulet.2015.11.014.

Weberg, R., and A. Berstad. 1986. 'Gastrointestinal Absorption of Aluminium from Single Doses of Aluminium Containing Antacids in Man'. *European Journal of Clinical Investigation* 16 (5): 428–32. https://doi.org/10.1111/j.1365-2362.1986.tb01018.x.

Weisser, Karin, Thomas Göen, Jennifer D. Oduro, Gaby Wangorsch, Kay-Martin O. Hanschmann, and Brigitte Keller-Stanislawski. 2019. 'Aluminium in Plasma and Tissues after Intramuscular Injection of Adjuvanted Human Vaccines in Rats'. *Archives of Toxicology* 93 (10): 2787–96. https://doi.org/10.1007/s00204-019-02561-z.

WHO. 1996. *Biological Monitoring of Chemical Exposure in the Workplace: Guidelines*. Volume 2. Geneva: WHO.

Willhite, Calvin C., Nataliya A. Karyakina, Eirik Nordheim, Ian Arnold, Vic Armstrong, Franco Momoli, Natalia S. Shilnikova, Nagarajkumar Yenugadhati, and Daniel Krewski. 2021. 'The REACH Registration Process: A Case Study of Metallic Aluminium, Aluminium Oxide and Aluminium Hydroxide'. *Neurotoxicology* 83 (March):166–78. https://doi.org/10.1016/j.neuro.2020.12.004.

Willhite, Calvin C., Nataliya A. Karyakina, Robert A. Yokel, Nagarajkumar Yenugadhati, Thomas M. Wisniewski, Ian M.F. Arnold, Franco Momoli, and Daniel Krewski. 2014.

‘Systematic Review of Potential Health Risks Posed by Pharmaceutical, Occupational and Consumer Exposures to Metallic and Nanoscale Aluminum, Aluminum Oxides, Aluminum Hydroxide and Its Soluble Salts’. *Critical Reviews in Toxicology* 44 (sup4): 1–80. https://doi.org/10.3109/10408444.2014.934439.

Wilschefski, Scott C., and Matthew R. Baxter. 2019. ‘Inductively Coupled Plasma Mass Spectrometry: Introduction to Analytical Aspects’. *The Clinical Biochemist. Reviews* 40 (3): 115–33. https://doi.org/10.33176/AACB-19-00024.

Xu, Feibo, Yanfen Liu, Hansong Zhao, Kaiyuan Yu, Miao Song, Yanzhu Zhu, and Yanfei Li. 2017. ‘Aluminum Chloride Caused Liver Dysfunction and Mitochondrial Energy Metabolism Disorder in Rat’. *Journal of Inorganic Biochemistry* 174 (September):55–62. https://doi.org/10.1016/j.jinorgbio.2017.04.016.

Xu, Shi-Meng, Yun-Wei Zhang, Xiao-Fen Ju, Dan Gao, Hui Yang, Lin-Ping Wang, Jing Song, et al. 2021. ‘Cross-Sectional Study Based on Occupational Aluminium Exposure Population’. *Environmental Toxicology and Pharmacology* 83 (April):103581. https://doi.org/10.1016/j.etap.2020.103581.

Yan, Dongying, Cuihong Jin, Yang Cao, Lulu Wang, Xiaobo Lu, Jinghua Yang, Shengwen Wu, and Yuan Cai. 2017. ‘Effects of Aluminium on Long-Term Memory in Rats and on SIRT 1 Mediating the Transcription of CREB -Dependent Gene in Hippocampus’. *Basic & Clinical Pharmacology & Toxicology* 121 (4): 342–52. https://doi.org/10.1111/bcpt.12798.

Yang, Xiaojuan, Yuzhou Yuan, Xiaoting Lu, Jin Yang, Linping Wang, Jing Song, Jisheng Nie, Qinli Zhang, and Qiao Niu. 2015. ‘The Relationship Between Cognitive Impairment and Global DNA Methylation Decrease Among Aluminum Potroom Workers’. *Journal of Occupational and Environmental Medicine* 57 (7): 713–17. https://doi.org/10.1097/JOM.0000000000000474.

Yokel, R. A. 1994. ‘Aluminum Chelation: Chemistry, Clinical, and Experimental Studies and the Search for Alternatives to Desferrioxamine - PubMed’. https://doi.org/10.1080/15287399409531834.

Yokel, R. A., and P. J. McNamara. 1985. ‘Aluminum Bioavailability and Disposition in Adult and Immature Rabbits’. *Toxicology and Applied Pharmacology* 77 (2): 344–52. https://doi.org/10.1016/0041-008x(85)90334-5.

———. 2001. ‘Aluminium Toxicokinetics: An Updated Minireview’. *Pharmacology & Toxicology* 88 (4): 159–67. https://doi.org/10.1034/j.1600-0773.2001.d01-98.x.

Yokel, Robert A., and Rebecca L. Florence. 2006. ‘Aluminum Bioavailability from the Approved Food Additive Leavening Agent Acidic Sodium Aluminum Phosphate, Incorporated into a Baked Good, Is Lower than from Water’. *Toxicology* 227 (1–2): 86–93. https://doi.org/10.1016/j.tox.2006.07.014.

———. 2008. ‘Aluminum Bioavailability from Tea Infusion’. *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 46 (12): 3659–63. https://doi.org/10.1016/j.fct.2008.09.041.

Yokel, Robert A., Marieangela Wilson, Wesley R. Harris, and Andrew P. Halestrap. 2002. ‘Aluminum Citrate Uptake by Immortalized Brain Endothelial Cells: Implications for Its Blood-Brain Barrier Transport’. *Brain Research* 930 (1–2): 101–10. https://doi.org/10.1016/s0006-8993(02)02234-5.

Yoshida, S., M. E. Gershwin, C. L. Keen, J. M. Donald, and M. S. Golub. 1989. ‘The Influence of Aluminum on Resistance to Listeria Monocytogenes in Swiss-Webster Mice’. *International Archives of Allergy and Applied Immunology* 89 (4): 404–9. https://doi.org/10.1159/000234983.

Yousef, Mokhtar I., Ahmed M.A. El-Morsy, and Mervat S. Hassan. 2005. ‘Aluminium-Induced Deterioration in Reproductive Performance and Seminal Plasma Biochemistry of Male Rabbits:

Protective Role of Ascorbic Acid'. *Toxicology* 215 (1–2): 97–107. https://doi.org/10.1016/j.tox.2005.06.025.

Zare Jeddi, Maryam, Nancy B. Hopf, Henriqueta Louro, Susana Viegas, Karen S. Galea, Robert Pasanen-Kase, Tiina Santonen, et al. 2022. 'Developing Human Biomonitoring as a 21st Century Toolbox within the European Exposure Science Strategy 2020-2030'. *Environment International* 168 (October):107476. https://doi.org/10.1016/j.envint.2022.107476.

Zhang, C., J. Wen, Z. Li, and J. Fan. 2013. 'Efficacy and Safety of Lanthanum Carbonate on Chronic Kidney Disease-Mineral and Bone Disorder in Dialysis Patients: A Systematic Review'. *BMC Nephrology* 14 (1). https://doi.org/10.1186/1471-2369-14-226.

Zhang, Fan, Xudong Sun, Hongyan Yu, Xu Yang, Miao Song, Yanfei Han, Yanfei Li, and Yanzhu Zhu. 2017. 'Effects of Aluminum Trichloride on the Cartilage Stimulatory Growth Factors in Rats'. *BioMetals* 30 (1): 143–50. https://doi.org/10.1007/s10534-016-9982-9.

Zhang, Feifei, Bo Liu, Yinbo Shao, Yan Tan, Qiao Niu, Xiaochun Wang, and Hui Zhang. 2023. 'Evaluation of the Default Mode Network Using Nonnegative Matrix Factorization in Patients with Cognitive Impairment Induced by Occupational Aluminum Exposure'. *Cerebral Cortex* 33 (17): 9815–21. https://doi.org/10.1093/cercor/bhad246.

Zhang, Lichao, Xinwei Li, Qingyun Gu, Yanzhu Zhu, Hansong Zhao, Yanfei Li, and Zhigang Zhang. 2011. 'Effects of Subchronic Aluminum Exposure on Serum Concentrations of Iron and Iron-Associated Proteins in Rats'. *Biological Trace Element Research* 141 (1–3): 246–53. https://doi.org/10.1007/s12011-010-8725-y.

Zhang, Qiuyue, Zheng Cao, Xudong Sun, Cuicui Zuang, Wanyue Huang, and Yanfei Li. 2016. 'Aluminum Trichloride Induces Hypertension and Disturbs the Function of Erythrocyte Membrane in Male Rats'. *Biological Trace Element Research* 171 (1): 116–23. https://doi.org/10.1007/s12011-015-0504-3.

Zhang, Tao, Fan He, Shangtong Lin, Xinyi Wang, Fudong Li, Yujia Zhai, Xue Gu, Mengna Wu, and Junfen Lin. 2021. 'Does Aluminum Exposure Affect Cognitive Function? A Comparative Cross-Sectional Study'. *PloS One* 16 (2): e0246560. https://doi.org/10.1371/journal.pone.0246560.

Zhang, Xuan, Xiaoyong Cui, Chunye Lin, Jin Ma, Xitao Liu, and Yuxiang Zhu. 2017. 'Reference Levels and Relationships of Nine Elements in First-Spot Morning Urine and 24-h Urine from 210 Chinese Children'. *International Journal of Hygiene and Environmental Health* 220 (2): 227–34. https://doi.org/10.1016/j.ijheh.2016.10.013.

Zhang, Yunwei, Jiaping Huan, Dan Gao, Shimeng Xu, Xiao Han, Jing Song, Linping Wang, Huifang Zhang, Qiao Niu, and Xiaoting Lu. 2022. 'Blood Pressure Mediated the Effects of Cognitive Function Impairment Related to Aluminum Exposure in Chinese Aluminum Smelting Workers'. *Neurotoxicology* 91 (July):269–81. https://doi.org/10.1016/j.neuro.2022.05.017.

Zhang, Z. Y., H. R. Jiang, X. R. Sun, X. C. Wang, Q. Niu, H. X. Meng, J. F. Du, G. Q. Yang, H. Zhang, and Y. Tan. 2022. 'Monitoring Mild Cognitive Impairment of Workers Exposed to Occupational Aluminium Based on Quantitative Susceptibility Mapping'. *Clinical Radiology* 77 (11): 840–47. https://doi.org/10.1016/j.crad.2022.06.007.

Zhao, Dan, Xiao Han, Jiaping Huan, Dan Gao, Tianshu Wang, Jing Song, Linping Wang, et al. 2023. 'Forecasting and Analysis of the Effect of Lifestyle on Cognitive Dysfunction Induced by Occupational Aluminum Exposure Based on Bayesian Networks'. *Environmental Toxicology and Pharmacology* 97 (January):104035. https://doi.org/10.1016/j.etap.2022.104035.

Zhao, Xiaoyan, Chanting He, Shanshan Wang, Yang Lei, and Qiao Niu. 2022. 'The Association between Blood Lymphocyte NMDAR, Group I mGluRs and Cognitive Function Changes in Occupationally Aluminum-Exposed Workers and Verification in Rats'. *Journal of Trace*

Elements in Medicine and Biology: Organ of the Society for Minerals and Trace Elements (GMS) 69 (January):126875. https://doi.org/10.1016/j.jtemb.2021.126875.

Zhu, Y. Z., H. Sun, Yang Fu, J. Wang, M. Song, M. Li, Y. F. Li, and L. G. Miao. 2014. 'Effects of Sub-Chronic Aluminum Chloride on Spermatogenesis and Testicular Enzymatic Activity in Male Rats'. *Life Sciences* 102 (1): 36–40. https://doi.org/10.1016/j.lfs.2014.02.035.

AGENCE NATIONALE DE SÉCURITÉ SANITAIRE
de l'alimentation, de l'environnement et du travail

14 rue Pierre et Marie Curie 94701 Maisons-Alfort Cedex
Tél : 01 42 76 40 40
www.anses.fr

ISBN 979-10-286-0547-6 - Dépôt légal : juin 2025