# ALUMINUM TOXICOKINETICS

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*In this study of the toxicokinetics of aluminum we have examined some of the fundamental issues that currently define our understanding of the toxicology of aluminum in humans. There is a vast literature on this subject, and it was not our aim to review this literature but to use it to develop our understanding of the toxicokinetics of aluminum and to identify critical and unresolved issues related to its toxicity. In undertaking this task we have chosen to define the term toxicokinetics to encompass those factors that influence both the lability of aluminum in a body and the sites at which aluminum is known to accumulate, with or without consequent biological effect. We have approached our objective from the classical pharmacological approach of ADME: the absorption, distribution, metabolism, and excretion of aluminum. This approach was successful in identifying several key deficits in our understanding of aluminum toxicokinetics. For example, we need to determine the mechanisms by which aluminum crosses epithelia, such as those of the gastrointestinal tract and the central nervous system, and how these mechanisms influence both the subsequent transport and fate of the absorbed aluminum and the concomitant nature and severity of the biological response to the accumulation of aluminum. Our hope in highlighting these unresolved issues (summarized in Table 1) is that they will be addressed in future research.*

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In this examination of the toxicokinetics of aluminum we have chosen to follow Al from its environmental sources to its possible points of entry into the body, to its subsequent transport and deposition throughout the body, through the organ and cellular response to the presence of Al and to its removal from both systemic and non-systemic stores. Our findings are discussed under the subheadings of the absorption, distribution, metabolism, and excretion of Al, and a summary of these discussions follows these headings. We should point out that since our work was not intended as a review our choice of references is based solely upon their immediate pertinence and not necessarily upon any intellectual priority.

## ABSORPTION

In humans, Al is absorbed and accumulated systemically via (1) the diet (including water and medications), with absorption occurring across the gastrointestinal tract (Ittel, 1993); (2) the inhalation of particulate Al through the nose (Roberts, 1986), with absorption occurring across the olfactory epithelium; (3) the inhalation of particulate Al through the mouth (Röllin et al., 1993), with absorption occurring via the gastrointestinal tract and, possibly, across the lung epithelia, and, controversially, (4) the skin (Barr et al., 1993). Only absorption via the gastrointestinal (GI) tract has received adequate consideration in scientific research.

Despite a significant research effort we do not know how Al is absorbed across the GI tract. A predominant mechanism, if there is one, is as yet unidentified. For example, it has been suggested that Al in the intestinal mucosa is bound by two Al-specific proteins (Cochran et al., 1993) that might act to increase or decrease its absorption. Confirmation of a role for these proteins in Al absorption has not been provided. The reality of Al absorption in the GI tract may well be one of several mechanisms, both passive and active. The individual contributions of these processes to the net absorption of Al are dependent upon a number of factors including the chemistry of the gut lumen and the health of the individual.

The identification of aluminosilicates in the human brain (Candy et al., 1986) has prompted the suggestion that Al would be absorbed via the olfactory system (Roberts, 1986), by the inhalation of particulate Al through the nose. Research in rabbits (Perl & Good, 1987) and in fish (Rouleau et al., 1995) supports a role for the olfactory epithelia in the accumulation of Al in the brain. For example, rabbits exposed to intranasal Al chloride were found to have accumulated Al in the olfactory bulb and the pyriform cortex. A similar pattern of accumulation of manganese was found in the brains of brown trout exposed to this metal in their water. The route of entry of manganese into the

brain was via the olfactory rosette, and this important finding may implicate this same route in the accumulation of Al in the telencephalon (phylogenetically equivalent to the hippocampus and cortex of the human brain) of rainbow trout chronically exposed to the metal (Exley, 1996).

A significant body of evidence that describes the systemic accumulation of Al in aluminum welders (Gitelman et al., 1995) has suggested that inhaled Al will enter the bloodstream in humans. The inhalation of Al via the mouth may result in absorption across the lung epithelia or the deposition of Al in the lung and its subsequent passage to the gut. This mucociliary pathway may be the principal mechanism by which Al in the lung becomes systemic. However, the possibility of direct uptake of Al across the lung epithelia and into the bloodstream remains unresolved.

The transdermal uptake of Al is beginning to generate research interest. This interest should be further stimulated by the recent suggestion that the transdermal uptake of Al in shaved mice resulted in its preferential accumulation in the hippocampus of the brain (Anane et al., 1995). Whether the action of shaving prior to the application of Al chloride made the skin more permeable to Al was not determined. However, the findings should be of interest to manufacturers of deodorants, several of which have for some time been supporting research into the effects of the topical administration of Al-containing preparations upon, for example, the activity and efficacy of sweat glands. Whether this current research will determine the mechanism through which topically applied Al gains entry to the systemic circulation remains to be seen. Certainly, what is known is that the intradermal penetration of soil aluminosilicates is linked to conditions like elephantiasis (Blundell et al., 1989), and recently it was demonstrated that the topical application of Al compounds used in the treatment of hyperhidrosis resulted in a specific histiocytic reaction. Aluminum accumulated in a number of histiocytic cells (Barr et al., 1993), and if this internalized Al is transported away from the local inflammation, this route of uptake of Al may have implications for the use of Al compounds in cosmetic and health-care products.

In light of the consensus opinion (for example, Jouhanneau et al., 1995) that the gastrointestinal absorption of Al generally constitutes less than 1% of the total ingested Al (though this may be a significant underestimation; see Xu et al., 1992), the contributions of the olfactory system, the lung, and the skin to the systemic absorption of Al and the total body burden of Al warrant further investigation.

In each of these possible routes of absorption Al must cross an epithelium. Often this epithelium has a lining of mucus and the interactions of Al with this mucus layer, or glycocalyx, will be the first stages in the absorption of Al. The importance of mucosa in the gas-

trointestinal absorption of Al has received some attention (Powell et al., 1994) and, as alluded to earlier, it has been suggested that mucosal proteins bind Al to reduce entry of the metal into the portal blood (Cochran et al., 1993). Whether the gut mucosa might also act as a sink for Al from which Al is available for systemic absorption is not clear (Van der Voet & De Wolff, 1984). It is interesting to consider that Al, under specific physicochemical conditions, can interact with epithelial mucins to alter their rheological properties (Exley et al., 1996). Where the viscosity or diffusional properties of the mucus are changed the integrity of the underlying epithelium may be altered, and this may significantly influence the barrier properties of the epithelium. The contribution of epithelial mucins to the absorption of Al across the olfactory, lung, and dermal epithelia remains largely unknown.

Similar ambiguity surrounds the actual mechanisms by which Al becomes systemic. They are likely to involve both the cellular internalization (transcellular transport) and the paracellular transport of Al. The cellular internalization of Al is almost certainly a passive process. Possible mechanisms include cell-mediated endocytosis, the simple diffusion of electrically neutral, and possibly lipophilic, Al complexes, and facilitative diffusion via cation-specific ion channels (Exley & Birchall, 1992). The paracellular transport of Al is likely to be not only a consequence of the presence of Al in extracellular media, but also the result of the toxicity of Al. For example, an Al-induced disruption in intracellular calcium homeostasis is suggested to reduce the efficacy of the intercellular tight junctions in the fish gill epithelium (Exley et al., 1991). The result is a significant increase in the permeability of this epithelium. The citrate-enhanced absorption of Al across the GI tract has similarly been attributed to an effect of citrate upon the permeability of intercellular tight junctions (Froment et al., 1989). Recent research in which the general permeability of Caco-2 cells in the presence of citrate was investigated now questions this thesis (Alvarez-Hernandez et al., 1994), and further research is required to understand the citrate-enhanced absorption of Al. What now seems certain is that Al is not absorbed across the GI epithelium as a citrate complex (Jouhanneau et al., 1995) but that citrate expedites the absorption of Al by maintaining the Al in a form that can be readily incorporated into one or more mechanisms of GI absorption. The association of Al with membranes and the subsequent disruption of their barrier properties has been suggested as a common theme in Al toxicity in biota (Exley, 1996).

The rate of absorption of Al, for example, via the gut, will depend upon the route of uptake, with paracellular transport expected to proceed at a much faster rate than cellular internalization. A clear example of how these two absorption mechanisms contribute toward toxicity is found in acute Al toxicity in the fish. In this condition an

interaction of Al with the gill epithelium increases the rate of the cellular internalization of Al (by an as yet unidentified mechanism) and, as a direct consequence of the increased cellular burden, the paracellular permeability of the membrane is also dramatically increased (Exley et al., 1991). The result is an accelerated cell death, primarily necrotic as opposed to apoptotic, in the gill epithelium. This bipartite mechanism of cell death in the fish gill has been suggested as a general mechanism of Al-induced cell death (Exley et al., 1991) and would likely result in a significant increase in the systemic absorption of Al across any affected epithelia. However, the relationship between the cellular internalization of Al and cell death is not straightforward. For example, the form in which the Al is taken up by the cell will have a critical influence upon any subsequent toxicity. Whether Al is internalized as an Al–transferrin complex or absorbed as a neutral lipophilic molecule will determine the intracellular fate and effect of the internalized Al. Thus, the importance of any particular uptake route to the toxicity of Al will depend upon not only the amount of Al coming into contact with that route but also the rate at which Al can be taken up by any particular route and, importantly, the form in which the Al is internalized or, in paracellular transport, enters the bloodstream and interstitial fluids.

The issues that remain unresolved in the systemic absorption of Al are the key uptake mechanisms and the critical role of Al speciation in making Al available to be taken up by these mechanisms. This latter point is addressed in detail by the preceding article (Harris et al., 1996). For the purposes of the present discussion the chemical speciation of Al could be conveniently divided into those mechanisms that promote the binding of $Al^{3+}$ by target groups at the surface of epithelia (including those associated with mucus) and those mechanisms that enhance either the passive diffusion or dissolution of neutral and/or lipophilic Al complexes across or into mucus matrices and lipid membranes. More research needs to be conducted to identify the mechanism by which Al is absorbed in vivo. As alluded to earlier, we have a significant amount of literature describing those factors that influence absorption, for example, citrate (Slanina et al., 1986), silicic acid (Edwardson et al., 1993), and fluoride (Ahn et al., 1995), but the mechanisms of these effects remain largely unknown.

## DISTRIBUTION

The route and the mechanism of the absorption of Al and the form in which the Al will become systemic will be critical influences upon the subsequent systemic distribution of the metal. The term "distribution" has been interpreted to encompass both the transport of Al and its accumulation in the various body compartments. There are

only a few body (or cellular) compartments in which a trace of Al is not found. For example, in fish chronically exposed to Al over a 2-yr period Al was found in significant accumulations in various tissues (Exley, 1996) but was absent from the lens of the eye (Exley, unpublished observation). The identification of these compartments, as well as those in which Al is known to accumulate, will present important information on how Al redistributes within the body (the lability of Al). When this information is combined with the metabolic lifetimes of these compartments then the relative affinities of these compartments for Al could be estimated. For example, in a tissue that is rapidly turned over, such as many epithelia, an accumulation of Al probably implies a high affinity (combined with a high exposure) of this tissue for Al. There is a considerable amount of literature pertaining to the accumulation of Al while the reasons why Al is not found at certain sites have not been fully explored. The distribution and accumulation of Al have been documented in whole blood (Moxon & Jeffery, 1991) and at both the organ and tissue level (Walker et al., 1994) and the cellular level (King et al., 1994).

The sites of the subcellular distribution of Al remain extremely controversial with very little strong evidence for any single dominant sink. Aluminum has been ascribed to cytosolic, mitochondrial, lysosomal, and nuclear compartments. However, chemical compartments such as those defined by intracellular ligands such as citrate, ATP, and the various calcium-binding proteins have not been adequately considered in this respect. The accumulation of Al at the organ and tissue level has received considerably more research interest. Bone appears to be a significant sink for absorbed Al. This has prompted a considerable research effort into the role of Al in bone disorders such as osteomalacia and osteoporosis (Romanski et al., 1993; Chary-Valckenaere et al., 1994). The observation of Al in the brain (Crapper et al., 1973) was similarly responsible for the first suggestion of a link between the metal and Alzheimer's disease. Aluminum is also found to accumulate in the kidney (Spencer et al., 1995) and in the liver (Lote et al., 1993) as well as in several other hematopoetic tissues. Generally Al is identified as associated with many epi- and endothelia, including the blood–brain barrier (Wen & Wisniewski, 1985; Exley, 1996), and may be responsible for compromising the barrier properties of these membranes (Banks & Kastin, 1983).

The blood–brain barrier has received a research effort commensurate with its probable involvement in Al-induced neurodegenerative dysfunction. For example, we know that the peptide transport system of this membrane is compromised by Al (Banks et al., 1993). Whether this can be explained by the observed effects of Al upon the surface chemistry of this membrane (Vorbrodt & Trowbridge, 1993) or is related to the transport of Al across the blood–brain barrier via the iron

transport system (Roskams & Connor, 1990) or any other mechanism (Jagarlamudi & Melethil, 1995) remains unresolved. Indeed, in the research to date it has been demonstrated that Al under one set of exposure conditions will cross the blood–brain barrier without altering the functional characteristics of the membrane, while under different conditions the Al will interact with the blood–brain barrier with subsequent effects upon its barrier function (see, for example, Banks et al., 1993; Vorbrodt et al., 1994). These possibly conflicting observations are probably easily explained in terms of the concentration and predominant form of Al in the immediate vicinity of the membrane. Related to these observations of the interaction of Al with the blood–brain barrier is the recent suggestion that Al in the extracellular fluid of the brain is actively excreted either into the blood or into neurons (Allen et al., 1995). Recent kinetic modeling experiments suggest that the excretion of Al from the extracellular fluid into the blood is the more probable of these possibilities (R. A. Yokel, personal communication). This apparently homeostatic mechanism may be related to another recent observation in which it was suggested that an opioid agonist was controlling the levels of Al in the brain (Gulya et al., 1995).

In discussing the distribution of Al in the body it is important to recognize that the transport and fate of systemic Al are under both thermodynamic and kinetic control. Thermodynamic control defines the biological availability of Al from the perspective of chemical equilibrium, whereas kinetic control, through the influence of rate-determining processes, defines the route that Al might take in approaching any equilibrium position. The latter is by far the more important influence upon the biological availability of Al (Exley et al., 1996), and it is also an area of research in which many issues remain unresolved. The body is a truly dynamic system that is far from chemical equilibrium. The total body burden of Al is in a continuous state of flux, both between different systemic compartments and involving those mechanisms that influence the absorption and excretion of Al. The transport and accumulation of Al might be considered in terms of competition between many Al equilibria. The predominance of any one equilibrium system, perhaps leading to the redistribution and accumulation of Al in a specific compartment (for example, the brain), will depend upon many different factors. For example, in various forms of trauma, such as postrenal transplantation, Al is rapidly mobilized from body stores (as evidenced by transient increases in the plasma Al concentration) and redistributed within the body (Davenport et al., 1988). Such events can transform a benign body burden of Al into an immediate or developing health risk. It is tempting to speculate that the relationship between head injury and dementing illnesses might be explained in part by the redistribution of the body burden

of Al. The rate of reaction of Al with ligands, either mobile (as in the blood) or compartmentalized (as in membranes), will play a critical role in the eventual fate of the Al. For example, whether plasma Al is bound by high- or low-molecular-weight ligands determines whether the fate of the bulk of the Al will be the liver or the urine, respectively (Maitani et al., 1994). The fate, and therefore the potential for toxicity, cannot be predicted upon the basis of stability constants alone, which only describe the reactions of Al at chemical equilibrium. In biology, where reaction times are characteristically short (a small change in the reaction rate of an enzyme can produce a profound biological response), the ease with which Al will form labile complexes is much more important than the hierarchy of stability constants of any such complexes. We must begin to consider the body burden of Al as much more than the sum of several disparate Al sinks. For example, Al that is found in bone may not necessarily be contributing, by its presence, to bone disease. However, bone Al may be the principal factor controlling the biological availability of Al in the brain. We need to determine which are the principal sinks for Al in the body, what the lability of the Al is in these sinks, what the mechanisms are by which Al is released and, once released, what will be the consequence of any redistribution of the metal. These are critical considerations in our understanding of the systemic toxicity of Al.

## METABOLISM

The metabolism of Al might otherwise be defined as the systemic and cellular response to the body burden of Al. When metabolism is considered in the context of an essential metal we would be looking to identify the way the body handles the metal. This would include the form in which the metal is stored, the treatment of the metal once it had fulfilled its function, and the packaging of the metal either for excretion or later use. These are areas of Al research that have received only minor attention. Most of the work that has been carried out has been related to the substitution of Al in cellular iron homeostasis. However, any cotransport and metabolism of iron and Al must simply be the consequence of a similar solution chemistry and cannot be interpreted as evidence that the iron metabolic pathway evolved to, additionally, cope with systemic Al. Similarly, there is no known adaptative response to the cellular internalization of Al. The metabolism of other nonessential, potentially toxic, metals is achieved through specific cellular responses such as the metal-induced metallothionein system. This detoxification system has not evolved to cope with Al. Its sulfur-based ligands cannot bind Al with any avidity, and while some research has demonstrated the induction of metallothionein as a

response to environmental Al (Jeffery et al., 1987) this cellular response can be explained either in terms of an Al-induced imbalance of a metal that is actively bound by this ligand or as a generalized stress response. The fact that biology appears to have no inherent defense against an Al challenge is an interesting enigma and one that requires further study. There is a suggestion that Al has, until very recently, been excluded from the majority of biological systems by silicon, a geochemical control of the biological availability of Al (Exley & Birchall, 1992). The lack of a specific cellular response to Al does not, of course, preclude its metabolism in some form or another. Aluminum does accumulate in most cell types, and in those cells that are lysed through necrosis or die due to apoptosis the cellular Al burden is metabolized. The redistribution of this Al is a cause for concern. Certainly, a portion of this Al is bound in lysosomes and will probably be excreted. However, the action of cellular metabolism could conceivably convert an inert Al store into a freely biologically available Al fraction with the potential for extreme toxicity. Very little is currently known of this possibility, and the biological equivalent of a life-cycle analysis for systemic Al is urgently required.

Several studies have used a $^{26}Al$ tracer to study the fate and metabolism of Al in humans (Priest, 1993; Priest et al., 1995). A criticism of these studies is that the intravenous injection of Al citrate is not representative of an everyday exposure to Al. A single pulse of an Al salt or complex will result in an Al speciation in the plasma that is specific to that pulse and will concomitantly produce a systemic distribution that will also be characteristic of that pulse (see, for example, Xu et al., 1991). Thus, any calculations of half-lives based upon intravenous injection are only appropriate to the exposure conditions created upon injection. This failure to appreciate the role of exposure in the toxicity of Al is currently exemplified in the argument that uses the lack of an Alzheimer's-like brain pathology in dialysis encephalopathy to discount a role for Al in the etiology of Alzheimer's disease (Wisniewski & Wen, 1992). In making such judgments it is critical to consider that the Al burden in any one compartment will dictate the transport, fate, and effect of that Al. We should not expect similar cellular pathologies to result from vastly different exposures (Exley & Birchall, 1993). We have not yet begun to fully understand the mechanics of systemic Al exposure, and until we do we can neither discard nor accept a role for Al in progressive diseases such as Alzheimer's disease, Parkinson's disease, and motor neuron disease.

## EXCRETION

The low solubility of Al, particularly the phosphate salts, ensures that the great majority of ingested Al is excreted in the feces.

However, absorption of Al in the gut can easily vary by a factor of 10 or more (Edwardson et al., 1993), and this is a reflection of both dietary and physiological differences among individuals. Gastrointestinal mucus was suggested to contribute toward the effective excretion of Al (Powell et al., 1994). The mucus acted as a sink for Al, with mucus sloughing ensuring the removal of the Al in the feces. However, if the mucus became saturated before it was sloughed the mucus layer might be expected to facilitate, rather than slow, the absorption of Al, from the gut. The analogy is that of a gravel or carbon filter, which upon becoming saturated begins to let through a concentrated slurry of the substances that had previously been adsorbed to its surfaces. It is interesting to postulate that the excretion of Al in the feces is the body's natural defense against Al. Certainly changes in the human diet over the last 60 years have been considerable, and these changes, including a possible increase in ingested Al, could be a factor in reducing the effectiveness of excretion in protecting the body against Al.

Excretion of Al from the body continues in the kidney and to a lesser extent in the bile. Evidence of the importance of excretion of Al in bile can be considered as equivocal (Xu et al., 1991; Wilhelm et al., 1992; Klein, et al., 1993; D'Haese et al., 1994). The most recent evidence has suggested that biliary excretion of Al was most important in the rapid clearance of Al following single doses of Al citrate by gavage (Sutherland et al., 1995). This finding may also represent further evidence of the liver as an early sink for absorbed Al. The mechanisms that influence the excretion of Al in the kidney are largely unresolved. For any particular steady-state condition the majority of Al in the blood is bound in transferrin (Martin, 1986). However, is this the fraction of the total Al burden that is excreted in the kidney? We have no mechanism to describe the removal of Al from transferrin to allow for its excretion via the kidney. It is much more plausible that the fraction of Al bound in transferrin is not excreted in the kidney, and the fact that Al is excreted in the kidney is evidence that other much smaller ligands for Al that are ultrafilterable in the kidney play a key role in the removal of systemic Al via the kidney. This low-molecular-mass fraction (<65,000 Da) may contain transitory forms of Al, for example, hydroxyaluminosilicates (Bellia et al., 1994), and is almost certainly in equilibrium with the most predominant, labile form of Al in the body. The location of this source of Al is unknown, but we might speculate that the extracellular surfaces of membranes will be important. Certainly the role of small intermediate carriers in influencing the excretion of Al deserves further attention (see Yokel et al., 1996). For example, excretion by the kidney is dependent upon how Al gets into the blood, that is, via the gut or through intravenous administration, as well as the form that the Al is

in upon its entry into the blood. Excretion via the kidney is very much dependent upon Al speciation and the kinetics that describe the many competing Al equilibria. One recent suggestion is that the silicon-enhanced excretion of systemic Al was through a reduction in the reabsorption of ultrafilterable Al (Birchall et al., 1995). This suggestion is supported by the most recent evidence on Al excretion in the kidney (Lote et al., 1995).

The occurrence and possible mechanisms of the cellular and tissue excretion of Al are almost completely unresolved. It would be important to know, for example, whether Al is actively exocytosed from cells, and if it were, in what form is it removed and where does it go upon its removal? Research has indicated that the body is a net accumulator of Al. There is no Al homeostasis and the body has no specific strategy for dealing with Al. A better understanding of the mechanisms underlying the removal of Al from the body would benefit therapeutic strategies for Al overload.

## GENERAL

All of the unresolved issues of the toxicokinetics of Al share a single commonality that might be defined as the biological reactivity or availability of Al. It is this property of Al that will ultimately determine the uptake, transport, fate, and effect of an environmental exposure to aluminum. Biological availability is a dynamic process and reflects the natural heterogeneity of the majority of biological systems. It should be considered in the context of a large number of competing equilibria within which the labile environmental Al burden is the common thread. It is probable that as this burden is increased—for example, by the joint action of acid deposition in accelerating environmental silicon deficiency and mobilizing edaphic Al and the burgeoning use of Al compounds in everyday life—an increasing number of Al equilibria are recruited and the biological availability of Al is increased. We have some idea of what happens when the exposure to Al becomes acute (i.e., an exposure that results in overt toxicity). In fish in acid waters death is the result of an accelerated cell death in the gill epithelium, while in humans there is an accelerated neuronal loss that leads to dialysis encephalopathy and subsequently death. We know very little about the biological response to chronic Al intoxication. This might be defined as everyday exposure to the metal, an exposure that, in its early days, is not associated with any overt signs of toxicity. How many of the diseases recognized today, particularly perhaps those of a nutritional nature, might be explained by a gradual increase in our body Al burden? The little we do know about the potential effects of chronic Al intoxication include (1) effects upon many essential metals, including iron (Abreo et al., 1994; Fulton & Jeffery, 1994), copper and

zinc (Röllin et al., 1993; Birchall et al., 1995), silicon (Seaborn & Nielsen, 1994) and manganese (Golub et al., 1993); (2) effects upon the immune status of individuals (Nordal et al., 1988; McGregor et al., 1991); and (3) effects upon the composition and subsequent functioning of membranes (Exley, 1996). These are the unresolved issues of the toxicokinetics of Al that will impact upon all of our lives while our exposure to environmental Al continues (increases) and the population ages.

## UNRESOLVED ISSUES

1. What are the individual contributions of the absorption of Al across the gastrointestinal tract, the lung, the olfactory epithelia, and the skin to the net systemic Al burden? How does each of these possible uptake routes influence the overall distribution of Al in the body?
2. What are the principal mechanisms by which Al crosses membranes? We need to compare the transcellular and paracellular routes and consider the role of mucus in mediating transport.
3. In what form does Al cross membranes and what will be the intracellular/systemic consequences of this form?
4. What is the systemic fate of absorbed Al? How might the identification of systemic Al burdens be used to indicate both the relative affinities of compartments for Al and the relative exposures to the metal?
5. The cellular compartmentalization of Al is almost completely unresolved. What are the main compartments of Al storage, are they different among cell types, and what determines these differences?
6. There is evidence of metal homeostasis in the brain. Is this specific for Al and if so, what are the evolutionary consequences of such a mechanism?
7. We need to appreciate, and if possible quantify, the relative contributions of kinetics and equilibrium thermodynamics to the systemic distribution of Al.
8. Which are the body stores of Al from which the metal is most and least labile? Under what conditions is the metal labile? What role do these stores play in the biological availability of systemic Al?
9. What is the significance of iron homeostasis to the metabolism and potential toxicity of Al? Does a disruption in either iron or Al homeostasis necessarily result in toxicity due to the other metal?
10. Is there a specific systemic response to Al, that is, Al homeostasis?
11. If Al is actively endocytosed, what is the cellular fate of internalized Al and, upon the death of the cell, the systemic fate of this intracellular store?

12. Can the low absorption of Al across the gut be interpreted as a biological mechanism of Al exclusion from the body? Does mucus have a key role in this process?
13. How is Al excreted via the kidney? What is the form of Al in the ultrafilterable fraction and how is the reabsorption of aluminum in the kidney prevented and/or reduced?
14. What are and will be the consequences for human health of a chronic Al accumulation of the type being suffered by most people living today?

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