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## The role of aluminum adjuvants in vaccines raises issues that deserve independent, rigorous and honest science

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Comments on the review « Aluminum and vaccines: Current state of knowledge, Aluminium et vaccins, ce que l'on sait aujourd'hui » by J.-P. Goullé & L. Grangeot-Keros, Médecine et maladies infectieuses, 2019.

In their recent review on aluminum and vaccines [1], JP Goullé & L Grangeot-Keros described general knowledge on aluminum (Al) exposure, kinetics and toxicity but made very little effort to delineate the scientific questions specifically related to Al adjuvants in vaccines. Instead of representing the bulk of their review, the subject of Al adjuvants covered no more than one third of the 3 page-text. Numerous important papers on the topic were omitted, *i.e.* 20 years of scientific publications in clinical, post-mortem, *in vitro* and *in vivo* experimental studies published by independent research teams, worldwide experts in this topic were simply omitted.

For instance, in 2018, a critical analysis of reference studies on Al adjuvant toxicokinetics revealed their extreme paucity, several major methodological weaknesses, and profound misconception of the fate of injected Al adjuvants [2]. The Goullé and Grangeot-Keros review suffers from the same fundamental misunderstanding of the question. Specialized Al toxicologists have now recognized that comparing toxicological properties of different forms of Al (soluble vs particulate) administered by different routes (oral vs intramuscular (im) or intravenous) is incorrect [3]. In the case of Al adjuvants such comparisons are misleading and therefore inadmissible [2]. Goullé and Grangeot-Keros stated that, similarly to lead for instance, “only biologically measurable excessive levels of aluminium in the organism can be potentially toxic”. Such a sweeping statement of classical toxicology may be in line with the “dose makes the poison” paradigm but does not correspond to the true situation when, for example, i) particulate forms of metals are considered; ii) specific intracellular capture is involved. Moreover Al in vaccines do not represent low doses, [especially for babies](#) [4,5]. Let us ironically state that a man shot dead by a lead bullet does not die from saturnism (lead

toxicity!). In contrast to soluble [dietary](#) Al reaching the blood across the intestinal barrier and excreted in urine, Al hydroxide adjuvant particles are nearly insoluble at pH 7.35 [2]. They are rapidly phagocytosed after injection, and selectively concentrate with very long residence time in immune cells which represent a very small but highly reactogenic cell compartment (for review see [6]). Isotopic  $^{26}\text{Al}$  hydroxide adjuvant studies indicate that a single vaccine dose administered through im injections to an adult rabbit will induce a small increase of 0.8% in plasma concentration, masked by the Al background, with cumulative Al excretion becoming quasi-flat a few days after injection [7]. This is due to the insolubility of Al hydroxide and explains why increased Al is not found in blood and hair of vaccine recipients [8]. This represents a legitimate reason of concern since instead of being efficiently eliminated the insoluble crystalline particulate adjuvant persists intra-cellularly. In contrast to the opposite contention made by Goullé and Grangeot-Keros, it has been repeatedly shown, in both mouse and sheep, that Al particles exit the injection site to reach the draining lymph nodes and spleen and more distant organs like the central nervous system [9-14]. There is no reason to believe that the adjuvant particles translocated beyond the vaccine injection site lose their immunogenic properties and are non-toxic.

Goullé and Grangeot-Keros focused on the lack of detectable increase of Al plasma levels following Al adjuvant injections and so apparently ignored that increased Al tissue levels have been indeed repeatedly reported following Al adjuvant or adjuvanted vaccines injections, in rabbit brains [7], in mouse brains [11], in rat bones and brains [15], and in sheep draining lymph nodes and spinal cord [13,14]. This was observed despite a marked dilution effect linked to the selective distribution of Al particles to a limited microglial cell compartment.

Other “reassuring” claims of Goullé and Grangeot-Keros were related to clinical studies. They dismissed the fact that Al-containing vaccines may be associated with myalgia, chronic fatigue syndrome and cognitive impairment typically observed in patients with Al hydroxide induced macrophagic myofasciitis [16,17], on the grounds of an ANSM study on HPV-vaccine that excluded these symptoms from the survey [18]. Moreover, they ignored that these symptoms have been significantly and uniquely associated with immunization in US military personnel undeployed during the Gulf War II [19], and an array of cognitive and behavioral changes have been naturally observed and experimentally reproduced in sheep repetitively inoculated with Al-containing vaccines [20,21]. [Furthermore, growing evidence offers clues as a putative role of Al early exposure in the marked increase of neurodevelopmental disorders in humans \[22-30\].](#)

[In the light of these elements](#), we thus agree with the conclusion of Goullé and Grangeot-Keros that health authorities should design specific multidisciplinary experimental protocols to clarify Al adjuvants toxicokinetics and hazards, [instead of accept the use of Al-adjuvants as placebos in clinical trials \[31\].](#) It will be of particular importance to map the fate and effect of particles of Al adjuvant beyond the vaccine injection site. A similar effort by relevant health agencies should be made epidemiologically, considering the complete lack of population-based studies specifically evaluating associations between clinical outcomes and Al adjuvants. According to the CDC, though feasible, such studies have not been conducted until now [32].

Finally, in this inherently incomplete review on Al adjuvants, several dozens of papers from the first signal of alert concerning Al adjuvants biopersistence and toxicity are purely and simply excluded! [Altogether, these rigorous and complementary available published studies](#) show biopersistence and toxic effects of Al salts, both in human and in various animal models, and allow a better understanding of the behavior of these molecules after injection due to *in vitro* approaches. [Such scientific data should be used by public health policies to assess the risk of Al-adjuvants, instead of relying on this widespread misinformation about the presumed safety of these molecules.](#)

[Furthermore, on the Goullé & Grangeot-Keros paper](#), apparent refusal to debate on this issue citing rationales such as “irrational polemics” and “one cannot question the safety of Al salts contained in vaccines” is not acceptable from scientists. Scientific debate should always be encouraged, especially in a topic where long-term safety studies are notoriously lacking in both adults and children. We believe that an issue as crucial to public health as the safety of vaccines, on which optimal vaccine coverage depends, deserves more than a subjective publication of badly documented personal opinion and should be addressed in the light of all available scientific studies, in an honest, rigorous and objective manner.

[While reaffirming our position in favor of vaccination, we claim that the safety of aluminum-based vaccine adjuvants, like that of any environmental factor presenting a risk of neurotoxicity and to which the young child is exposed, must be seriously evaluated without further delay, particularly at a time when the CDC is announcing a still increasing prevalence of autism spectrum disorders, of 1 child in 54 in the USA \(2020 figure for 2016\) \[33\].](#)

#### Authors contribution

RKG & GC wrote the first draft of the letter. FJA, CE & LL corrected and improved the letter.

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