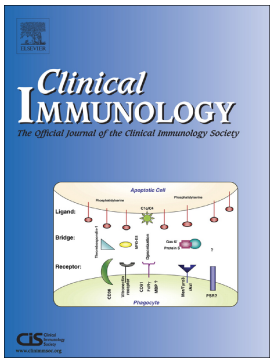

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Mercury-induced autoimmunity: drifting from micro to macro concerns on autoimmune disorders

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Abstract

Mercury (Hg) is widely recognized as a neurotoxic metal, besides it can also act as a proinflammatory agent and immunostimulant, depending on individual exposure and susceptibility. Mercury exposure may arise from internal body pathways, such as via dental amalgams, preservatives in drugs and vaccines, and seafood consumption, or even from external pathways, i.e., occupation, environmental pollution, and handling of metallic items and cosmetics containing Hg. In susceptible individuals, chronic low Hg exposure may trigger local and systemic inflammation, even exacerbating the already existing autoimmune response in patients with autoimmunity. Mercury exposure can trigger dysfunction of the autoimmune responses and aggravate immunotoxic effects associated with elevated serum autoantibodies titers. The purpose of the present report is to provide a critical overview of the many issues associated with Hg exposure and autoimmunity. In addition, the paper also focuses on individual susceptibility and other health effects of Hg.

Keywords: mercury; autoimmunity; lupus; acrodynia; autism; chronic fatigue syndrome; neurodegenerative disease; multiple sclerosis; delayed-type hypersensitivity; allergy

Abbreviations

AD	Alzheimer's disease
ALS	amyotrophic lateral sclerosis
ASD	autism spectrum disorder
ASIA	autoimmune/ inflammatory syndrome induced by adjuvants
BBB	blood-brain barrier
CFS	chronic fatigue syndrome
CNS	Central nervous system
FDA	Food and Drugs Administration
FM	fibromyalgia
Hg	mercury
iHg	inorganic Hg
IgE	immunoglobulin E
KD	Kawasaki disease
MHC	major histocompatibility complex
MN	membranous nephropathy
MCD	minimal change disease
MHC	major histocompatibility complex
MRP	multidrug resistance-associated protein
MS	multiple sclerosis
NHANES	National Health and Nutrition Examination Survey
oHg	organic Hg
PD	Parkinson's disease
VEGF	vascular endothelial growth factor

Introduction

Mercury (Hg), in either its inorganic or its organic forms, is not known to have any positive and essential role in human physiology [1]. Mercury is, in fact, a well-known toxicant, which may affect humans, either modulating immune tolerance and promoting autoimmune responses or affecting biochemical pathways via its chemical toxicity [2]. Elemental Hg (metallic), as well as inorganic and organic Hg, are known to occur frequently in various environmental sources, and Hg is available in different chemical forms [2]. Widely recognized for its extreme toxicity, Hg induces toxic effects even upon exposure at low concentrations [2-5]. Both elemental Hg and methylmercury (MeHg) can reach the brain by passing through the blood-brain barrier (BBB), and it is retained in significant quantities in the brain, damaging nerve cells and acting as a triggering agent of different neurological disorders [5-9]. Research reports indicate that Hg can induce developmental delay and mental retardation [10, 11], Alzheimer's disease (AD), and Parkinson's disease (PD) [12-16], and even multiple sclerosis (MS) [6]. Furthermore, it has been shown that exposure to high Hg levels can also induce the accumulation of Hg in glands, heart, kidneys, liver, and placenta in amalgam treated individuals proportionally to the amount of Hg-burden from dental amalgam fillings (containing about 50% Hg), favoring the occurrence of cytotoxic, neurotoxic, and immunotoxic effects [3, 17-20]. Moreover, Hg may induce metabolic disruption, leading to the generation of toxic metabolites, besides being involved in disorders, such as oral lichen planus, fibromyalgia (FM), lupus, acrodynia, connective tissue disease, and chronic fatigue syndrome (CFS) [21-29]. Thus, based on these crucial aspects, the present report aims to provide a critical overview of the aspects related to Hg exposure, individual susceptibility, and health-related effects, focusing on immune-mediated effects (e.g., autoimmunity, MS, delayed-type hypersensitivity, and allergy), and inflammatory reactions [30, 31].

Mercury occurrence and exposure

Mercury is the only metal found in the three main environments (i.e., soil, water, and atmosphere). There are several estimates of Hg concentration in the earth's crust, as a native or in a variety of different

minerals. In summary, the average Hg contents in soils can be estimated approximately to be comprised in the range from a few ppb to some hundred ppb [32]. The majority sources of Hg mined is from cinnabar (α-HgS) ores sometimes associated with other minority sources of corderoite ($Hg_3S_2Cl_2$), livingstonite ($HgSb_4S_8$), or metacinnabar (β-HgS). In freshwater Hg is found as inorganic Hg(II), gaseous elemental (Hg0), and organic MeHg(I) forms with the total Hg concentrations of oxidizable forms variable, ranging from $0.3\text{-}8\cdot10^{-3}$ μg/L in an uncontaminated site to more than 450 μg/L in a waters downstream of mine drainages or industrial waste. In seawater, Hg also exists as dimethylmercury ($Me_2Hg(I)$) in addition to the forms of Hg present in freshwater with concentrations normally not exceeding $0.8\cdot10^{-3}$ μg/L, except, for instance, in the sea costs near to estuaries or harbors [33]. These forms of Hg with low water solubility became more soluble when they are complexed with organic (carboxylic acids and thiols) or inorganic (sulfate, chloride, sulfide) ligands depending on the pH and oxic or anoxic redox characteristics of the water. The inorganic Hg form predominates in water, soils, and sediments, while organic Hg dominates in biota [32].

Both natural and anthropogenic sources are responsible for the global distribution of Hg in surface waters and soils. In particular, natural volcanic and hydrothermal activities, forest fires, weathering of soils and rocks, together with human activities such as metal mining and smelting of metal ores, combustion of fossil fuels, coal burning, and waste incineration increased the level of Hg in the atmosphere and the subsequent local and long-range transport and deposition. The high volatility characteristic of elemental Hg and its long atmospheric lifetime results in its global distribution and potential pollution of pristine areas [32, 34].

The risk of Hg exposure for human populations is considerable, occurring thought several routes: occupational exposure, environmental pollution, dietary contamination (especially seafood), handling of metallic items, overuse of therapeutic, cosmetics (skin lighting cream, hair-dyeing agents), and dental amalgams (Figure 1) [2]. In microorganisms in water, inorganic Hg can be methylated. The resulting

neurotoxin MeHg is concentrated in the nutrition chain. Humans are exposed to MeHg through the eating of fish [35, 36].

Mercury is able to disturb the normal health condition essentially through its toxic characteristics and with immunological reactions that determine hypersensitivity or autoimmunity. Other transition metals, such as nickel (Ni), are known to exert a double threat [37, 38]. Nickel, beyond being known as a carcinogen, is the most common contact allergen. Nickel allergic contact hypersensitivity has been recognized as deriving from the binding of Ni(II) with imidazole nitrogen of specific histidine residues of the innate immune toll-like receptor 4 (TLR4) protein, which is thus activated and consequently trigger the pro-inflammatory cytokine gene expression [39, 40]. In addition, beryllium (Be), cobalt (Co), chromium (Cr), gold (Au), together with Ni and Hg, are responsible for clinically relevant hypersensitivity reactions dominated by T cell-mediated allergic contact dermatitis [41]. The main clinical manifestations of Hg exposure include neurological, gastrointestinal, and dermatological symptoms, which might masquerade degenerative neurological, autoimmune, metabolic, and mitochondrial disorders. For example, in a study by Malek and coworkers [42], chronic Hg exposure in a young male artisanal gold miner manifested in multiple organ clinical anomalies as severe neurological disturbances, inflammatory bowel disease-like symptoms, and skin rash. Nonetheless, the authors pointed out that after diagnosed, the mercury intoxication was easily treated with steroids to reduce systemic inflammation without the need for more aggressive/invasive therapeutic strategies [42]. Pamphlett and Jew [43] in a clinical case of a man who injected himself with metallic Hg (o), detected quantities inorganic iHg in all five types of human brain astrocytes, as well as in cortical corticomotoneurons, oligodendrocytes, and neurons of the locus ceruleus. The location of neurotoxin iHg in the central nervous system (CNS) seems connected to the pathogenesis of MS, AD as well as brain tumors [43].

Methylmercury compounds induce chromosomal abnormalities and affect nerve cells in the brain resulting in serious damages, such as blindness, nerve coordination, mental deficit, and even death (Figure 1). The chemical pathways underlying these processes appear to be related to the high affinity of Hg for

sulfur donors present in proteins (methionine and cysteine), which hence may have an effect on altering the protein structure, making them foreign and susceptible to autoimmune defense [44, 45]. Moreover, the Hg-protein complex can enhance ion transit through membranes, damaging enzymatic and mitochondrial activity, and induce autoimmune disturbances [21, 46, 47].

Mercury-induced autoimmunity

In humans, Hg exposure is considered to be an autoimmunity-inducing pollutant, which triggers the production of pro-inflammatory factors, e.g., interferon-gamma (IFN-γ), interleukin 1β (IL-1β), tumor necrosis factor (TNF)-α, and autoantibodies [48-50]. Furthermore, studies involving murine models under Hg-stimulated autoimmunity have substantially increased the insight about systemic Hg-dependent autoimmunity [51, 52]. Actually, in these studies, numerous hallmarks regarding humoral autoimmunity, hyper-gammaglobulinemia, immune-complex disease and lymphadenopathy have been reported as having a close relationship with systemic autoimmunity [49, 53]. Several clinical studies have shown the underlying mechanisms through which different Hg forms, such as elemental (Hg0), inorganic (iHg), and organic Hg (oHg), participate in triggering a variety of chronic conditions, including autoimmune diseases [21, 22, 27, 46, 47, 54]. Table 1 briefly describes the mechanisms by which Hg exposure induces autoimmunity, including the clinical impact and related consequences.

Mercury can accumulate in significant quantities in the brain, leading to nerve cell damages, besides possibly being involved in raising the risk to develop MS [9, 55]. In turn, some *in vivo* reports using animal models have already shown that Hg-induced autoimmunity can reveal a specific loss of tolerance to self-antigens [46, 47, 56-58]. Indeed, after exposure to subtoxic Hg doses, susceptible mouse quickly produced highly specific antibodies to nucleolar antigens, besides presenting an overall activation of the immune system, a particular glomerulonephritis with immunoglobulin deposits [57, 59], and overexpression of susceptible major histocompatibility complex (MHC) class II genes, mimicking the scenario seen in many autoimmune disorders [37]. Furthermore, Nielsen and Hultman (2002) stated that Hg-induced autoantigen fibrillarin alteration led to T-cell-dependent immune activation through altered

fibrillarin [22]. Studies on Hg-exposed mice revealed a common stimulation of the immune system, such as transient glomerulonephritis with immunoglobulin deposits and also a marked activation of the T-helper cells of type 2 (Th2) subset [22, 60]. T helper cells and T cells from Hg(II) chloride ($HgCl_2$)-injected rats are capable of actively inducing autoimmunity in normal mice [61, 62]. Apparently, autoreactive T cells are involved in Hg-induced autoimmunity pathogenesis, because they induce suppressor/cytotoxic T cells to proliferate in normal syngeneic recipients, which suggest that $HgCl_2$ also affects T suppressor cells. Further, the emerging effects of autoreactive T cells and the defects at the T suppressor level may induce accumulation of a notable blood Hg content although total Hg alone did not relates with the presence of specific autoantibodies or anti-nuclear antibodies [63, 64]. On the other hand, some animal models with existing autoimmunity revealed no correlation with the level of Hg exposure. In humans, there is currently no evidence to explore the critical role of Hg^0 exposure from dental amalgams in the development of autoimmune syndrome, apart from case reports suggesting individual sensitivity [49, 65].

Mercury-induced inflammation

Several studies have also reported that inflammatory pathways might be useful biomarkers of Hg-stimulated autoimmunity, related to the observed up-regulation of proinflammatory cytokines in humans following Hg intake [25]. Observations in rodents indicate that this response is dependent on IFN-γ-associated genes [48]. Similarly, Nyland et al. (2011) stated that MeHg exposure could increase proinflammatory (IFN-γ and IL-6), anti-inflammatory (IL-4), and IL-17 cytokine contents in plasma. The authors stated that changes in serum cytokine profiles were different according to an antinuclear autoantibody response. In the MeHg-exposure subset, high antinuclear autoantibody levels were associated with low pro-inflammatory (TNF-α, IL-6, IL-1β, and IFN-γ) and anti-inflammatory (IL-4) cytokine levels [66, 67]. In the same way, previous studies assessing the *in vitro* human immune cell response to low Hg exposures reported that iHg could increase pro-inflammatory cytokine response [68,

69], is also similar outcomes reached by authors when investigating the *in vitro* pro-inflammatory cytokine responses to MeHg and ethyl-Hg (EtHg) [25, 70].

Moreover, different responses in Hg-induced autoimmunity in resistant DBA/2J and sensitive B10.S mice, regarding pro-inflammatory biomarkers, indicated that proinflammatory cytokines expression could not be evoked in resistant DBA/2J mice [53]. The authors observed that CD4+ T-cell activation, autoantibodies production, and splenomegaly did not occur in resistant DBA/2J mice, whereas the inflammatory response described in sensitive B10.S mice could be attributed to an increase of cathepsin B activity [53]. Interestingly, in human peripheral blood mononuclear cells exposed to low $HgCl_2$ levels, it was observed a decreased secretion of anti-inflammatory cytokines such as IL-10 and IL-1-receptor antagonist (IL-1Ra) and increased production of pro-inflammatory cytokines including TNF-α and IL-1β. [68]. Recent studies have shown that autoimmunity and macrophage activation can be precipitated by the C1q deficit and deficient function of the complement cascade [71, 72]. All of the 12 cysteine units in the human C1q-protein [73] are supposed to interact with Hg, leading to a C1q deficit and thereby to lupus (SLE) and autoimmune nephritis [74, 75]. Secondarily, $HgCl_2$ also induces the release of vascular endothelial growth factor (VEGF) and IL-6 from human mast cells. These reactions might also stimulate brain inflammation (Table 1) because of the disruption of the BBB barrier [76].

Genetic susceptibility to mercury

Genetic predisposition is considered as co-responsible for autoimmune diseases. Several reports showed a relation between genetic susceptibility to Hg exposition (for instance, via dental amalgam, via therapeutic treatment, after vaccination, etc..) with a number of neurobehavioral consequences, including acrodynia (pink disease), CFS, myalgia, rheumatoid arthritis, and ALS [77]. In this contest, the individual genotype plays a significant role, as proven by the symbolic report of 0.2 % incidence rate for neurologic disease, acrodynia, and hypersensitivity, observed in children treated with calomel (Hg_2Cl_2) [78, 79]. Another study reported a case of a family of seven living in Hg polluted area in which only one kid developed neurobehavioral defects and anorexia, despite the level of Hg in the blood for all family members were

found to be comparable [80]. In addition, low-level but continuous releases of Hg from dental amalgams have been showed to induce long-term risks of neurological damage for persons with specific genetic polymorphism [81, 82]. The consequent dental amalgam removal, also combined with medical treatment (as chelation therapy with DMSA), resulted in a significant reduction of neurological symptoms [82]. Interestingly also the removal of dental amalgams in CFS patients improved their health condition, suggesting that the causes of CFS onset may also be dependent on immune disorders triggered by Hg [83]. Moreover, there are several evidence supporting a causal relationship between Hg exposure from dental amalgams and CFS, FM, depression, anxiety, tremor, and even suicide [84]. It seems that adult dental amalgam (ADA) syndrome comprise a series of illness that share common mechanisms exacerbated by a genetic predisposition to autoimmune response. In a study, including 13,906 dentists who attended the American Dental Association, indicated that the occupational exposure to Hg0 from amalgam might increase the risk of tremor in practicing dentists if compared with average incidence data reported in the US population [85]. Investigations of the type of tremor are needed since it can be a sign of multiple neurologic diseases, including MS and PD, that can be, in this contest, induced by occupational Hg exposure. A synergistic interaction has been postulated between thimerosal, together with protein malnutrition, as a significant factor in the altered immune response in FM [86]. Mercury sensitivity appears to be a heritable risk factor also for autism spectrum disorder (ASD). In a family history, 7 % of the incidence of ASD in the grandchildren was linked to infantile acrodynia survivors [87]. Genetic transporters seem to be associated in the toxicokinetics of Hg also in the mucocutaneous lymph node syndrome, better known as Kawasaki disease (KD), that has clinical symptoms similar to acrodynia. Genetic depletion of glutathione S-transferase (GST), a susceptibility marker for KD, is known to be also a risk factor for acrodynia and may also increase susceptibility to Hg [88]. The cumulative Hg exposure, such as from dietary seafood intake, was clearly evidenced in KD patients [89]. Major histocompatibility complex (MHC)-related genes are known as the main genetic factors of human autoimmune disorders [51]. So, according to MHC haplotype, animal models could be effectively selected to investigate Hg-induced autoimmunity, although other genes also act as contributors to Hg-

induced autoimmunity pathogenesis. Several studies, using animal models with Hg-induced autoimmunity, tried to evaluate the genetic differences between susceptible and resistant mouse models. The association of detoxification protein peroxisome proliferative activated receptor, gamma, coactivator-related 1 (PPRC1) on Hg-related autoimmunity has been ascribed to its effect on Hg metabolism and elimination in the body, through inducing Nrf-1 and Nrf-2 function, which regulates, respectively, multidrug resistance-associated protein (MRP) genes related to Hg elimination and control glutathione genes involved in Hg conjugation [90].

Mercury and multiple sclerosis

Nowadays, both environmental and genetic factors have been recognized as triggering factors towards autoimmune diseases. Among environmental factors, Hg exposure, organic solvents, ultraviolet radiation, infection, and even dietary lifestyle, have received pivotal attention. In fact, the incidence of autoimmune diseases, including MS, is alarmingly increasing, which might reflect raised levels of triggering pollutants. MS is a complex autoimmune inflammatory disease that is presumed to arise from complex molecular interactions, with different pathological and clinical phenotypes. The cellular accumulation of Hg has been closely associated with the development of autoantibodies against cytoskeletal proteins and myelin basic proteins [91]. In a study performed by Prochazkova et al. (2004), the authors reported that dental amalgams appeared to be a critical etiological risk factor for MS since amalgam replacement could induce a high improvement rate in MS patients [92]. Furthermore, even low-to-moderate Hg exposure levels can cause functional alterations in T-lymphocytes and macrophages, which may trigger hypersensitivity and cytokine production and increase inflammation-associated tissue damage risk [91]. In a study of 217 prevalent MS patients and 496 race-, gender-, age-, and geographically-matched controls, Napier et al. reported possible interaction between SNPs and Hg in the TNF-β MBP, VDR, TNF-α, and APOE genes [91]. However, recent advances in genetics and immunology research have demonstrated that immunomodulatory treatment can alleviate disease effects [93]. Thus, provided that MS is an inflammatory T-cell–regulated autoimmune disease, it was suggested a Th1-type mediated response (IL-

12, IL-18, IFN-γ, and osteopontin), associated with a Th2-type (IL-4 and IL-10) response [94]. On the other hand, different susceptibility patterns have been evidenced by individuals, explained by both external and genetic variables influences.

Mercury-specific biomarkers in autoimmune disease

Mercury-induced autoimmune disease in rodent models can be described by elevated levels of circulating auto-antibodies, immunoglobulin (IgE and IgG) overproduction, and lymphoproliferation [25, 49]. These proteins are involved in both pro- and anti-inflammatory cytokine regulation, antioxidant responses, oxidative reactions, and stress signaling [24, 95]. Increasing evidence has shown that dysregulations of these proteins may act as a triggering factor to autoimmune disorders, including lupus and MS [96-98]. In a study performed by Somers et al. (2015), which enrolled females aged 16–49 years from the National Health and Nutrition Examination Survey (NHANES) in 1999–2004, the authors observed that among females in reproductive-age, Hg was significantly related with antinuclear antibody contents and that MeHg levels were associated with subclinical autoimmunity [99]. In another study carried out by Gallagher and Meliker (2012), multiple logistic regression was used to infer the positive relevance between total thyroglobulin autoantibody and blood Hg contents. The authors found that Hg levels >1.81 µg/L were linked to the thyroglobulin antibody in women [100]. Previous investigations had reported a significant relationship between high anti-nuclear/anti-nucleolar autoantibodies levels and Hg exposure, i.a., among Brazilian fish consumers, and other reports showed a relation between serum autoantibody concentrations and iHg exposure in gold miners [25, 90, 95, 101, 102].

The relationship between Hg exposure level and increased cytokine expression is not yet well understood and requires further studies [49]. While the biomarkers present in urine are indicative of nephrotoxicity, the development of biomarkers that are predictive of neurotoxic effect mediate by Hg toxicity is a challenging task. In the perspective to discover new specific biomarkers for Hg-induced outcomes, the identification of Hg protein targets with critical function is essential, together with the characterization of

epigenetic markers that will help to highlight individual predispositions for Hg-induced toxic responses [103].

Concluding remarks

It is tricky to provide a general risk assessment of the health effects of Hg since its toxicity varies considerably among exposed subjects. Further research is needed to elucidate the role of Hg in human autoimmune diseases, and especially in MS, including the hazardous exposure levels in large populations. But, until then, it is recommended to follow the Food and Drug Administration (FDA) rules in connection with iHg and MeHg. Although experimental animal studies have shown that high Hg concentrations may increase the risk to develop autoimmune diseases, such as MS, based on findings highlighted here, it is tempting to hypothesize that low Hg levels may cause autoimmune disorders through interaction with triggering events, such as genetic predisposition, antigenic exposure, or infection. Further research is also recommended on the role of defective function of C1q and the complement cascade in the pathogenesis of autoimmunity, in particular, the role of Hg-binding to thiol groups of C1q. On the other hand, the role of Hg in developing autoimmunity is still ambiguous, without any robust scientific evidence. In fact, *in vitro* investigations have revealed that both MeHg and EtHg possess active suppressive effects on lymphocytes compared with iHg, while iHg as immunostimulant seems to be cell-density and dose-dependent. Further, some studies using murine models genetically sensitive to Hg-induced autoimmunity have reported that biologically relevant $HgCl_2$ doses induce an enhancement in autoantibodies production. Also, MeHg-exposed murine models evidence an immunosuppressive response, although it shows to be a less severe form of autoimmunity responses when compared to $HgCl_2$ induction. Moreover, elemental Hg exposure can induce systemic autoimmunity in an animal model (rats) with susceptible haplotype. In fact, the effect of Hg on MS severity needs further human observational studies, specifically assessing elemental and inorganic Hg exposure, as also their relevance with genetic components and autoimmune disorders that confer susceptibility to Hg stimulated autoimmunity.

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Table 1. Mercury (Hg)-induced autoimmunity and inflammation, and related mechanisms of action and clinical impact

Clinical features	Mechanism of action	Consequences	References
Proteinuria, glomerulonephritis with immunoglobulin deposits, minimal change disease, and membranous nephropathy	Loss of tolerance to self-antigens	Production of antibodies to nucleolar antigens, immune system activation, and overexpression of susceptible MHC II genes	[90, 104]
Scleroderma	Autoantigen fibrillarin changes	T-cell immune dependent activation	[22, 60]
Lymph node hypertrophy, and notable accumulation of blood Hg contents	Activation of Th2 subset	Suppressor/cytotoxic T cells stimulation	[22, 63]
Membranous nephropathy, changes in microglial polarization, lupus, and multiple sclerosis	Proinflammatory cytokines production	Expression of IFN-γ, IL-1β, 1L-4, IL-6, IL-10, IL-12, IL-17, IL-18, TNF-α, antibodies IgE, IgG, thyroglobulin, and osteopontin	[49, 70, 94, 105, 106]
Splenomegaly and production of autoantibodies	Cathepsin B activity stimulation	Lysosomal membrane destabilization, CD4+ T-cell activation	[53, 107]
Brain inflammation and neuronal damage	VEGF and IL-6 release induction	Blood-brain-barrier disruption	[60, 76]

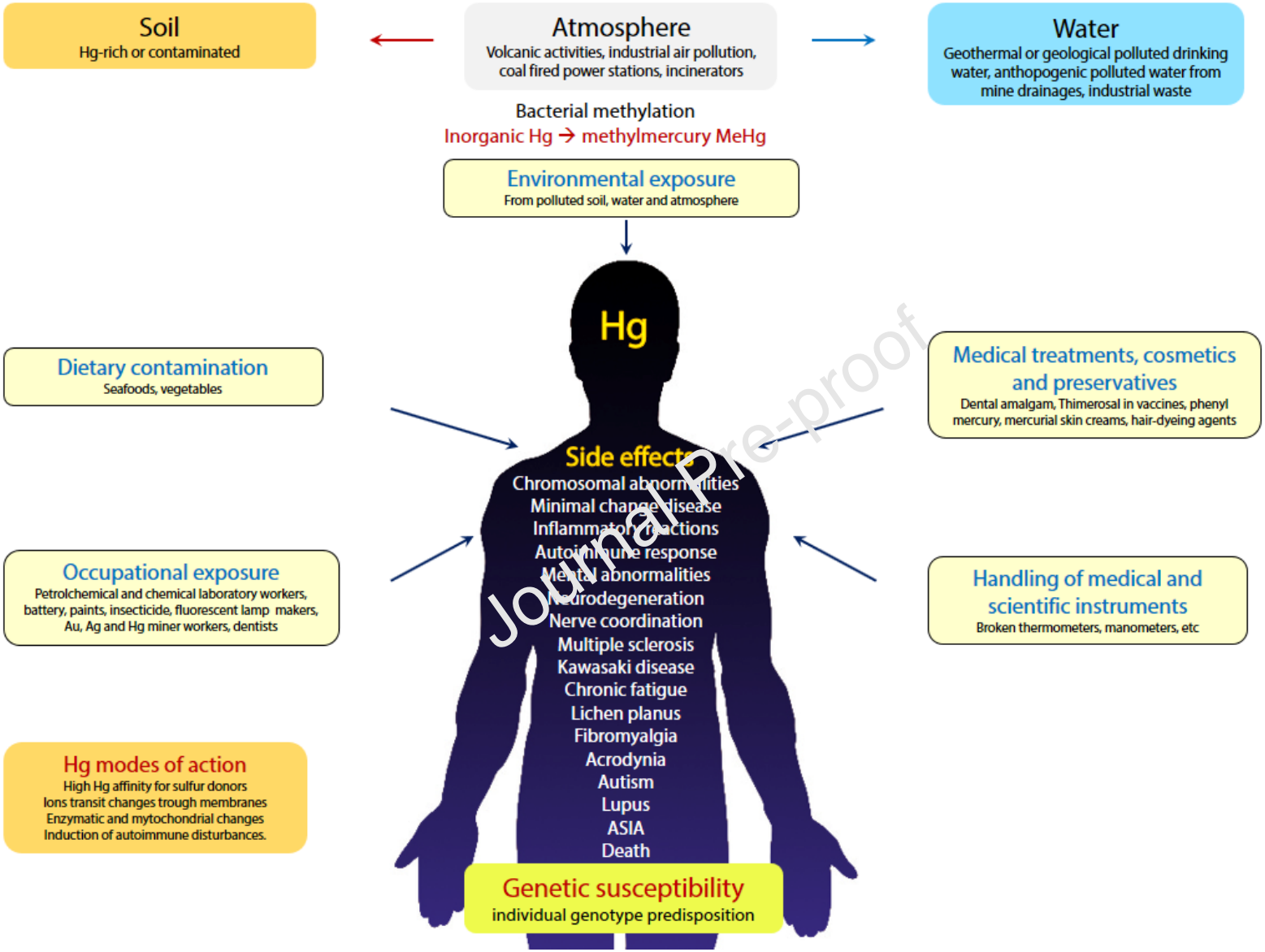

Fig. 1. Anthropogenic and environmental mercury (Hg) sources, main ways of uptake and absorption into the human body (trough inhalation, ingestion, injection, and permeation), modes of action, and potential risks

Highlights

- Mercury (Hg) is a proinflammatory agent and immunostimulant
- Exposure to Hg can trigger immunotoxic effects, inflammation, and autoimmune dysfunction
- In susceptible individuals, Hg may play a role in autoimmune diseases, including MS
- Characterization of epigenetic markers is needed to highlight individual predispositions to Hg-induced toxic outcomes