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Autism, Chemicals, Probable Cause and Mitigation: A New Examination

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Abstract

This extensive overview has addressed in a scientific manner the probable cause of autism. Although seemingly an impossible task, an important clue has always been autism's triggered growth from the late 90s. This triggering eliminated genetics as a major cause and redirected it to changes in the anthropogenic environment. Global availability for ingestion by women of child-bearing years of all neurotoxic chemicals has been reviewed and potential changes examined. Surprisingly, these simple criteria eliminate almost everything except the neurotoxic metal elements. These are all present in recent blood analyses of pregnant women and also in the fetal cord with some at risk level concentrations. However, the two predominant neurotoxic elements that clearly stand out are Al and Hg. Furthermore, isotopically labeled experiments on animals coupled to fetal autopsies indicate that these in the forms of Al^{3+}, $HgCH_3^+$ and $HgC_2H_5^+$ can penetrate the usually tight blood/brain barrier and enter the brain with now known half-lives. Normally, these elements are controlled and neutralized by brain seleno-cysteine proteins. However, an overloading burden has become plausible in current times and even a temporary failure leaves the fetal brain vulnerable. For the first time, the burden is seen to arise not from a single source, but from the combination of medicine and diet. If these neurological illnesses are to be controlled, the body-burden for these and all the other toxins that the body has to constantly manage has to be reduced. To begin with, this will have to involve modifying currently high inoculation rates and procedures particularly in the US, and minimizing risks from consuming fish especially in a Japanese sushi life-style. This is not only of importance for women of child-bearing ages but for the whole population considering the consequences of such body burdens throughout life.

Keywords: Autism; Triggered growth; Neurotoxins; Body-burden; Blood testing; Selenium importance; Multisource roles

Introduction

Although it is the responsibility of the Environmental Protection Agency in the USA to assess environmental risks for its population, this is a major task, and they are faced with dozens of new chemical products each year. This is in addition to still having to reassess a backlog of hundreds of complex organic molecules that now show evidence of possible toxic natures and require re-examination to new standards [1]. Utilizing the analyses of urine samples from the US population in one large National Health and Nutrition Examination Survey a new methodology is in fact being suggested [2]. This is permitting approximate unknown levels of exposure to be modeled for general types of anthropogenic chemicals utilizing observed distributions of others in the main database. As a result, it is becoming a concern that this potential body-burden of undesired chemicals that have to be purged from the body and brain are possibly playing some role in the spectrum of neurological illnesses now seen in the aged and moreover also in the young. Although a demanding task, it is therefore appropriate to critically review the almost overwhelming number of publications that have appeared in recent years addressing this topic. The growth in analytical ability and its more widespread availability is an important advance, and now has spawned the acquisition of large medical databases of a more reliable nature. Moreover, more refined techniques of animal studies and isotopic labeling experiments have emerged. As a result, it is timely to pause and consider, in a more rigorous scientific manner, whether new insights are present particularly with emphasis on the current undeniable neurological epidemic evident particularly in the young. Although there is a rich literature on this subject and several excellent reviews, none have really examined the topic emphasizing the full chemical nature of the potential environmental species involved and how these have changed in recent decades in our diets.

Questions to be addressed in this environmental and neurotoxic review include:

- Which neurotoxins are most likely to have suddenly triggered an increase in autism cases starting in the 1990s? Can it be one, several or a synergist effect of toxins and neurotoxins? What has changed to have caused this on a globally distributed scale?
- How are these neurotoxins ingested?
- Why are babies and infants most affected?
- Are known toxic thresholds for chemicals adequately assessed and are "safe exposure levels" meaningful and at what degree of risk?
- Can the potential toxins in the body be adequately monitored by simple biomarkers and are these reasonably scaled to the prescribed ingestion rate or "safe exposure levels"?
- Do we have an approximate understanding of a neurotoxin's destructive mechanisms?
- Are genetic susceptibilities involved or do DNA analyses simply reflect the consequence of toxic damage from some breakdown in the natural body defenses?
- Can this situation be changed by modifying the human environment or life-style?
- Does this apply mainly to births and pregnancies or are there neurological implications across the total population?

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- As with smoking and drinking, should we accept a greater personal responsibility with the aid of modern medical testing for the state of our bodies?
- Should youngsters from birth through child-bearing years have their baseline body toxic-level summation be measured periodically?

Environmental Impacts on Humans

At present, society is plagued by various medical epidemics that appear to have a strong environmental basis. The current review examines one such situation in an attempt to see if sufficient information yet exists to pinpoint a potential cause and remedy. From about the year 2000, a new phrase has come into existence in medical diagnostics, namely "on the spectrum". It relates to the now much larger and growing fraction of young children that exhibit neurological problems spanning a wide range of symptoms, but all a reflection of some DNA permanent brain damage. The most obvious and severe cases are termed autistic, which also displays their own spectral range of behavioral difficulties. This human defect now has been labeled for almost a century but generally was always at a very low incidence rate. However, as indicated in Figure 1, this has drastically changed within a very short period of about two decades, being most pronounced in the US. Although psychiatrics quibble about the diagnostic boundaries for autism there is no diminishing the overall magnitude of the problem however approximate the data may be. Teachers in schools can be the best measure of whether there has been change. Moreover, it is also reflected by the current need to establish specific schools, research and care centers in many communities. Such a growth rate that is also evident globally, but at a slightly lower rate in other countries is a very important piece of scientific data as it pinpoints a "triggering effect" that occurred in the later 1990 s and was not present at that rate before. Also, autism appears to show no racial, ethnic or social boundaries and does not relate readily to income, lifestyle or educational level [3].

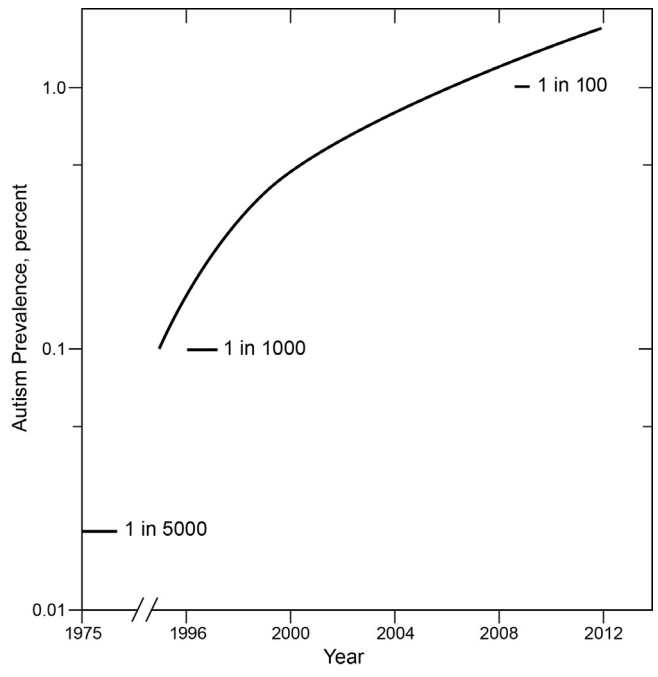

Figure 1: The approximate annual rate of change for the prevalence of autistic babies and young children in the United States.

Moreover, although numerous theories exist implying a genetic basis, this is incompatible with such a sudden triggered change [4,5].

In the 1960 period, mainly in Europe, a new drug under the name of thalidomide was used as a remedy for sickness in pregnant women. Within a short period of its usage, deformed babies were born. This was soon diagnosed correctly as being the result of this drug, which then was immediately removed from the market before the consequences grew to have a global effect. Later, quite extensively studied, it was found that the drug did the most damage in the first trimester of pregnancy (20-36 days after conception) when most of the organs and the critical neural brain and spinal cord tube are completing neurulation [6,7]. An interesting observation was that 5% or more of these babies were also autistic (a rate then estimated to be 50 times higher than normal). This was possibly the first case of drug induced autism that was clearly defined as well as illustrating potential drug induced fetal deformities. Later, it became apparent that viral infections during pregnancy could also induce autism in pregnancy and body immunity factors could be important [4].

The placenta rapidly develops with the embryo and separates the fetal blood from that of the mother. However, it is far from perfect and many drugs and chemicals in the mother become shared. As will be seen, this further extends to, but is of a much reduced concern with breast milk [8]. Toxins are measured in units of dosage per body weight, such as milligrams/kilogram body mass. Consequently, the fact that a fetus starts with a very minimal mass and weighs only 1 g at 8 weeks makes one wonder how any healthy baby ever gets born [9]. Consequently, this fact alone indicates that of the very many chemicals that have a potential for affecting a fetus, it would seem fortunate that few do. Medical lists of drugs now known to be potentially dangerous during pregnancy have been established by the medical profession and are listed in their handbooks. However, it should be noted that the adult body and that of babies are very different. Adults are not only larger in weight but are fully formed. Toxins to an adult are better characterized as poisons. They can do damage but generally display clinical symptoms that can be reversed in many cases. Babies not only have small body mass but are still in a growing formative period when their brain in particular is still completing its task of creation and DNA can become damaged. Even at birth a baby's brain is only one-quarter full size, but by its first birthday this has grown to three-quarter size followed by slow growth to full maturity by about age eighteen. As a result, children are at most risk for neurological damage particularly during pregnancy and the first year after birth. Even so, in this period of rapid development, the brain does have certain plasticity and can invoke mechanisms for repair and adjustments if at risk [10]. As a result, these considerations would seem to raise the possibility of a limitless number of chemicals as potential suspects with no hope of ever resolving the cause of any such neurological defects. There is some truth to this, but the thalidomide example suggests possibly not. Every environmental problem in the past that has impacted adults and births generally has become apparent sooner or later before becoming fully global. Smoking and alcohol consumption may be two exceptions of course and although recognized as hazards by doctors for pregnancies do not correlate to an outcome of autism. Nevertheless, there have been many examples, mainly connected to industry, where a manufacturing process and its wastes have caused concern due to its toxic nature and become evidenced by malformed births. Well known cases that did so affect the general public might be, for example, the Love Canal chemical dumping and leaching near Niagara, the Minamata mercury pollution and poisoning in Japan, the chromium (VI) drinking water pollution case in Hinckley, California, and the consequences of coal ash pond spills. One important

point that the Japanese mercury/fish poisoning case did illustrate was that a mother could appear perfectly normal yet have a deformed baby [11]. The important point in all such cases is that these were all realized sooner or later due to the obvious impacts on babies and adults and clearly could be identified as regional. In other words, after getting a stamp of approval from the EPA or the National Institute of Health, if a product is having a major adverse effect on the general public this will generally become apparent in some geographic distribution depending on its usage; it rarely will have time to become a global occurrence. The current surge of neurological illnesses is not local but apparent in such culturally diverse countries as the USA, China, India, Thailand and Mexico. The true extent is difficult to assess in many countries due to a political culture of concern over potential consequences of such data release. However, it is now too apparent globally that some change has occurred concerning a neurological toxin that in the US, as seen in Figure 1, has moved onto a percentage scale in affecting new births. A high rate of neural tube defective births (one in a thousand) also has been reported in some heavily industrialized cities in China and most recently has been loosely correlated to high molecular weight polycyclic aromatic hydrocarbons (PAHs) [7,12]. Current rates for autism in the UK are quoted as moving towards a fractional percentage stage as well as in Japan, Mexico and India. Although not clearly documented there are suggestions that the level of autism in African more isolated cultures is very minimal, as it appears also to be in the US Amish people, who have a simpler natural life style, facts that would seem to support an acceptance of an anthropogenic trigger as a cause.

Neurotoxic organic chemicals

One report has listed that there are 440 known organic structures that are neurotoxins. I cannot vouch for this but being a chemist can believe it. As to which other pharmaceutical drugs, herbicides, pesticides, fertilizers, cosmetics or organic molecules might be added for completion remains uncertain. Autopsies of the elderly tend to show the presence of organics and inorganics both in the body and the brain. In one study of mothers in the Faroe Islands, 87 environmental chemicals were detected in maternal and fetal tissues [13]. In a more recent Japanese study, testing of 322 pregnant women for a similar range of anthropogenic organic chemicals also indicated their presence, all alien to the body [14]. As mentioned above, the human body has such a mass that it can absorb significant chemical abuse and still show only minor symptoms such as headaches, shaking, nausea, diarrhea or memory and some brain loss functions. However, this is constantly posing an unnecessary burden on the body. Moreover, babies and young children have a greater sensitivity and are more vulnerable to DNA damage. Such studies illustrate the current magnitude of this modern interface between chemicals in the environment and mankind. Also the almost impossible task facing the medical profession to rank the associated risks of each of these. As a result, studies such as that indicated in Figure 2 are quite informative in outlining an overview that can at least approximate these risks and examine for guidance. This lists the incidence of autism in 8 year old school children per capita in the 50 US States in the 2009-2010 periods. The full accuracy of the data is uncertain but it appears unlikely that it can be manipulated to convey any pronounced correlations. Its significance is simply to show immediately that every State is exhibiting a similar problem. Moreover, an agricultural state such as Iowa with its fertilizers, herbicides and insecticides is not statistically worse than Maine or Alaska or New Jersey with its industrial base is not exceptional in any manner. Like most medical data the random distributions can arise from the many variables involved but really show nothing clearly significant in this case. However, for specific organic chemicals to be a national medical

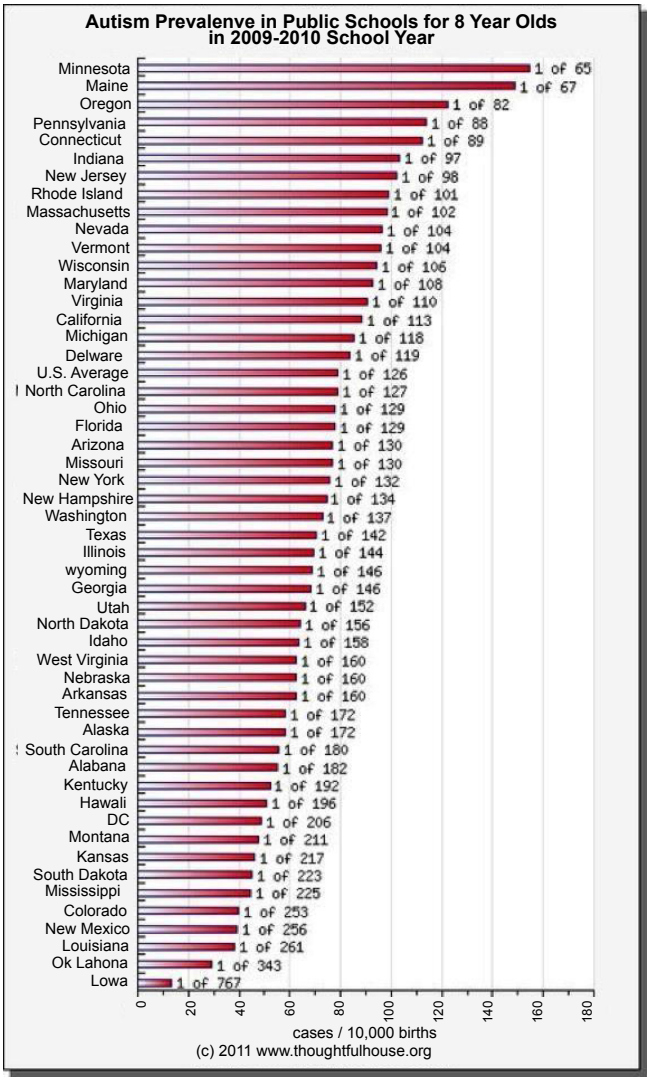

Figure 2: Approximate prevalence of autism as a function of the U.S. State for 8 year old children in public schools (Reproduced acknowledging its copyright source).

cause appears difficult to accept in spite of their potential toxicity. The triggering effect also is required to be initiated in the 1990s, which adds a severe time constraint into this discussion and is a major further limitation on most organic candidates. Moreover, ingestion by the mother or child is also needed in a global discussion. As a result, for babies around the world to similarly experience the same affect demands a certain uniformity and common use of an organo-chemical, and also be newly introduced in the late 90s. There are many hundreds of papers published every month on the Earth's environmental quality from a chemical perspective. However, none of these hints at a triggering change in the 90s that correlates to any known organic structure. Furthermore, analyses of the volatile organics in the air that we breathe do vary geographically but generally are at very low levels and raise little meaningful concern [15]. Contamination by persistent organic compounds cannot be denied and has been studied. Recent publications analyzed early pregnant mothers in Norway [16], together with 43 human placenta in the US [17] and 130 in Finland [18] for evidence of persistent organic pollutants such as the PCB's (widely used by the electrical industry), for polybrominated diphenyl ethers

(flame retardants) and organochlorine pesticides. All were observed at various levels. Also, studies of historically contaminated communities have monitored blood, urine and hair samples of residents for PCBs, organochlorine pesticides and Pb, Cd and Hg and found them present [19]. Recent work has examined pregnancies in areas of Vietnam that were heavily contaminated with the most toxic of the dioxins (2,3,7,8-tetrachlorodibenzo-p-dioxin) along with others that now are part of their food chain and so directly ingested [20]. This and their earlier work measured the concentrations of about 30 PCBs and dioxins in the mother's milk one month after giving birth. Analytical sensitivity nowadays is such that these were all successfully monitored but were present generally on a pico-scale (10^{-12} g/g). Nevertheless, the baby can be consuming the mother's milk daily. Also, as will be seen below, the mammary gland is quite effective, implying that the mother's and the fetal cord blood during and at birth did have concentrations several-fold higher. However, there were no indications of birth defects in these babies other than head size and infant growth effects [21]. A later study examining three year old children did show slight autistic traits [22]. Consequently, it is clear that at some level our bodies are becoming contaminated by everything that exists in the environment. Whether traces on such a low scale can be termed hazardous is debatable yet still disturbing. Also, on a positive side, the US study did suggest declining trends in the environment with these pollutants compared to previous studies [17]. To realize the magnitude of the problem, a brief reading of the 519 page, *4th National Report on Human Exposure to Environmental Chemicals* released by the American Center for Disease Control and Prevention illustrates the magnitude and growth of our apparent dependence on such organic structures [23]. Although many of these organic forms can cross the placenta and some even the blood/brain barrier, insufficient global patterns of subsequent effects exist for the present analysis [24]. Moreover, the traces of these potential neurotoxins that may be ingested differ in magnitude from the dosage of thalidomide that was inoculated. Nevertheless, this has not prevented statistical analyses that tend to suggest positive correlations with autism. One studied 69 autistic children in Southwest Pennsylvania indicating this was an area of raised air levels of styrene, Cr and possibly PAHs and methylene chloride [25]. Another more difficult hypothesis to readily discard is a possible correlation in Quebec between autism and antidepressants, especially serotonin taken during the 2nd and 3rd trimester periods [26]. Further suggestions of this type can be readily assessed by the medical profession by sampling different geographic regions that should show bias to certain societal more affluent groups that are not currently evident. As a result, there always remains in this analysis a possible role that any of the current neurological hazardous organic chemicals now in use may be posing a problem for some individuals. Nevertheless, there is little doubt that some of these chemicals with their highly complex chemical structures will contribute to the overall body burden and add to its baseline tasks.

Neurotoxic and toxic inorganic elements and their compounds

Due to the usefulness of metals and their compounds, their extraction from ores has a long history during which time their effects on people have become clearly documented. Of the neurotoxic elements and their compounds in the periodic table these involve mainly the six metals Al, As, Hg, Mn, Pb and Tl. Many other metals are toxic such as Ba, Be, Bi, Cd, Cr, Cu, Sb, Se, with Co, Mo, Ni, Sn and Zn normally showing minimal toxicity. Generally, the degree of toxicity depends on quantity and the chemical nature, inorganic structures often being less toxic than organo-metallic forms. Also valence can play a significant role, toxic for Cr (VI) compounds such as chromates, but not for those of Cr (III), such as chromium oxide, Cr_2O_3, and toxic for Hg (II), as $HgCl_2$, but not Hg (I), as calomel, Hg_2Cl_2. Solubility in water can also be very important as also intestinal absorption. The neurotoxins are intriguing in that five of the listed six, Al, As, Hg, Pb and Tl are all alien to the body in having no known biological purpose but all are ingested to various degrees by diet. The one exception is Mn that is an essential human element but is now listed by most controlling agencies as more of a developmental neurotoxin of concern mainly for children, pregnancy and industrial workers. However, if an element is essential for life, invariably if healthy, the body has protective mechanisms to control excesses. Examining biomarker analyses of blood, hair, excretions and nails, and during autopsies of the internal organs and the brain, these all show many of these metals to various degrees in the body. From the viewpoint of autism, five of these six elements require consideration as potential inorganic neurotoxins. The element thallium and its compounds are rarely encountered in diets and can be safely discounted as it would display strong regional dependences due to its more limited sources. Of the remaining five, Al, As, Hg, Mn and Pb, these are not significant to any degree in air now that lead-free gasoline is legislated globally for normal automobile use [15]. Moreover, dangers from proximity to polluting sources generally will become evident on a local area basis. The same can be said for drinking water that is significantly regulated in the US. It would therefore appear that to be widespread, these toxic elements generally have to be ingested either in the diet or administered medically. Dietary exposure to metals over the past 30 years was analyzed recently in a UK study [27]. It included these five metals among the 24 considered, usefully listing the sources of each. The study was further broken down into 4 age groups (1.5-4.5; 4-18 yrs; elderly-independent; elderly-institutionalized) and vegetarians. If anything, the study showed that exposure to these metals has decreased over the years and no health concerns are clearly apparent. As a result, if any of these metals is playing a role some increased change has to be recognized.

A considerable volume of data now is emerging from the widespread availability of analytical equipment such as the ICP-MS (Inductively coupled plasma-mass spectrometer) that can monitor most of the trace metals, and chromatographic separation that can detect pharmaceutical drugs, organic structures and also help in resolving the speciation of certain elements. Such examples could be the distribution of Cr^{III} and Cr^{VI}, or more importantly at present the fraction of elemental (amalgam) mercury from that of organic methyl mercury (from fish) in the body. To some degree, the concerns of impurities in diets have arisen through this reliability of monitoring and sample handling, and have led to improved product quality control. Throughout past history, the degree of contamination in diets was unknown and studies still emerge considering questions from the past arguing whether certain individuals such as Mozart actually died of mercury poisoning (use of laxative Hg_2Cl_2) [28], whether Napoleon was poisoned by trace metal elements [29], or whether the Roman Empire decline was partly due to their addition of old wine (acetic acid) as a sweetener to food being cooked or eaten from lead vessels (lead acetate formation) [30]. The majority of human analytical studies that are particularly interesting in the current medical context are the development of biomonitoring methods that now indicate to a physician the health level of the human body. In the case of the trace inorganic metals this usually involves either simple blood or hair analyses, or metal content of excrements or nails, depending on the element of interest. As a result, a significant volume of data exists concerning the distribution of trace metal concentrations throughout the body.

Neurotoxic organometallics

Biochemistry, more than the other branches of chemistry encounters

the organometallic structures that bridge the organic and inorganic fields. This bonding of inorganic metals to carbon structures has always been intriguing in its two natures. One, the true organometallics, is less exhibited and involves a direct metal-carbon bonding. Otherwise, many more structures are known that have instead loosely bound ligand groups binding the metal to the carbon for example via O-, N or S-atoms. The human body utilizes many of these latter-type structures in complex molecules such as metalloenzymes and proteins that are generally named bioinorganics. The role and need for Fe (hemoglobin), Se (anti-oxidant proteins), Zn, Cu, Mn (enzymes), Co (B_{12}) and even Cr, Mo, W (enzymes) by humans is well known. Rather interesting is the fact that the body has no use for true organometallics that contain direct carbon-metal bonding. For the neurotoxin elements being emphasized here, several of these can be synthesized in the laboratory to form the direct metal-carbon structures but do not form or exist in the human body (with the possible exemption of As, see below). Synthesized examples are $Al(CH_3)_3$ that is pyrophoric in air, $As(CH_3)_3$ that is highly toxic but rarely encountered, and $Hg(CH_3)_2$ that is one of the strongest neurotoxins known. Lead tetraethyl, $Pb(C_2H_5)_4$, of gas additive fame is man-made and not found in nature. It is now globally banned for automobiles but 100 tons/yr are still allowed as an additive to piston engine aircraft fuel. The MMT, methyl cyclo-pentadienyl manganese tricarbonyl, also man-made can be a manganese replacement for lead in gasoline but is also toxic. Its structure has been described theoretically and the bonding to the Mn atom is more of a ligand nature than covalent Mn-C. This additive is in the process of also being banned in most countries and is gradually being phased out mainly due more for its detrimental effects on emission control devices and engines than for health. Arsenic does have numerous methylated structures such as arsenobetaine, its ion $(CH_3)_3As^+CH_2COOH$, and closely related arsenocholine, $(CH_3)_3As^+CH_2CH_2OH$, that do occur in fish but are essentially non-toxic. This is mainly due to the fact that these fortunately are not metabolized or accumulated in the body and are excreted: the later form changing to the betaine structure in passage. These can also be present in natural gas and petroleum sources. Also arsenic is one metal of very few, if not the only one, that can become methylated in the body [31]. Quite often, these organometallics are never easy to synthesize in the laboratory and with mercury has to invoke reactions with Na/Hg amalgam. Consequently, it is quite remarkable that nature finds enzymic routes to readily synthesize these such as the mercury and arsenic methylation that occurs in fish [32,33]. The mono-methyl mercury ion, although molecularly quite heavy, is small in size, is totally alien to the body and was probably not even known to the human body until environmental levels in fish rose to their current levels over the past millennium. Our bodies, however, now have also encountered the intake of the ethyl analog received in the form of thimerosal in vaccines. This ligand-type organometallic has the C_2H_5HgS-group directly attached to the sodium salicylic acid benzene ring structure that can metabolize to the ethyl mercury ion. Now well documented, these organo-mercury forms manage to mimic a true organic and be transported very efficiently through a placenta. However, as will be seen, they can also be transported through the blood/brain barrier.

The Concept and Dilemma of Neurotoxin Thresholds

Once the ability of measurement was acquired, this then facilitated the establishment of health related "Minimum Risk Levels" such as those now in place by the medical profession concerning, for example, blood pressure and cholesterol levels. As a result, a huge global undertaking now has been in place for more than a decade to better establish human toxicity levels for most of the elements and various organic molecules. This is difficult to establish directly unless there are adequate examples with people and they generally must be assessed from animal data coupled to model extrapolation. This then approximately establishes the NOAEL toxicity level dosages (No Observable Adverse Effect Levels) and LOAEL (Lowest Observed Adverse Effects Levels) that form the basis of setting ideal recommended "safe levels". It is of course based on the concept that the body has historically evolved to be able to accept a certain level of toxicity, which is true. Even so, there is a school of thought that feels the true safe level for a neurotoxin is zero but whether that is achievable is questionable. The difficulty in medicine arises in being able to adequately ensure that a recommended "safe level" is sufficiently well below the NOAEL threshold, yet remains consistent with a normal human diet or lifestyle. Listed in Table 1 are the test results for blood analyses of average people around the world, some in rural and some in more industrialized environments. These are just a random sample of recently published values and are intended mainly to illustrate several general points. Due to the large quantity of data collected in such studies, these require statistical analysis and mean (arithmetic average), geometric mean and median (middle data point) values are often quoted as well as standard deviations or quartile ranges. These convey the spread of the distribution and establish the occurring ranges for the majority of people. What is immediately apparent from the table is the actual presence and very broad distribution of all these elements in most humans. Distributions are not symmetrical but often have a long tail to higher concentrations. The difficult toxicological question then is to establish recommended thresholds for medical guidance. This is attempting to ensure that all the population distribution lies well below the laboratory determined or otherwise estimated toxicity curve values (NOAEL). Ideally then, the average value of the population distribution should be at least a hundred times lower than the NOAEL onset level to ensure that the fraction of outliers or upper tail constituents remain safe. As mentioned, it is true that mankind has always survived with a baseline set of values due to the existence of all the metals in the environment entering our diet through earth's natural processes of dispersion. Core drilling investigations into ice, peat bogs and sediments try to establish the approximate natural ancient levels of trace elements in the environment. This can then quantify the ratio of anthropogenic to natural contributions. Although this ratio has always been much larger than unity since industrial growth for most metals, now for some a decline has been occurring as modern day regulations finally address such environmental situations. However, some metals, mercury for one, remain high in spite of major efforts to extensively remove its role in global commerce. Only coal combustion, some medical use and freelance gold mining remain unregulated with regards to mercury. The current mining of gold/silver using amalgam extraction now is being fully assessed in this regard as a requirement of the United Nations 2013 Minamata Convention that is endeavoring to finally address this contribution [68-70]. Even so, these final contributions, although still significant, remain a small fraction of anthropogenic mercury already in the environment. This remains high, due to past historical accumulations and exists from the anthropogenic recycling (evasion, evaporative emission) from the extensive gold and silver mining and industrial emissions of the past. As a result, it could be several centuries before old anthropogenic mercury pollution is finally sequestered and levels fall to low and more acceptable values. The magnitude of anthropogenic over fully natural background levels remains difficult to assess [71]. Analyzing Arctic lake sediments, results implied a factor of three [72]. Another effort studying ocean surface mercury levels reports a 4-fold increase in mercury concentrations over the past 600 years. Additionally the latter's model estimated that in that time period only

Metal	USA Adult Safe Limits	Global Adult Population Concentrations	References
Neurotoxins			
Al	<6[a]	1.6 Serum (Mean), (63 sample size, Canada)	Wang1991 [34]
		3.8 ± 1.7 Serum [Mean, Range 1.5-10], [351 sample size, France]	Pineau1993(35)
		3.8 ± 1.7 Serum [Mean, Range 1.5-10], [351 sample size, France]	Sharp1993(36)
		37 ± 9 Men, Blood (Mean), (37 sample size, Turkey)	Akay 2008 [37]
		214 ± 508 Blood (Geo. mean, Range 0-2638), (50 sample size, polluted, S. China)	Li 2014 [38]
		4.6 Blood (Geo. mean, Range 3.8-17), (172 sample size, Cement Plant, NY)	Dong 2015 [39]
As	<12[a], <10[b]	13 ± 13 (Mean), (144 sample size, Catalonia, Spain)	Ferre-Huguet 2009 [40]
		7.0 ± 5.9 [Mean, Range 0.6-56], [1601 sample size, Bangladesh]	George 2013(41)
		5.9 (Median, Range 0.8-41), (184 sample size, Norway)	Birgisdottir 2013 [42]
		0.55 ± 2.7 (Mean, Range 0-18), (50 sample size, polluted S. China)	Li 2014 [38]
		4.0 (Geo. mean, Range 2.6-8.5), (30 sample size, 25-45 yrs, USA)	Ettinger 2014 [43]
		5.7 (Geo. mean, Range 4.0-9.5), (30 sample size, 25-45 yrs, S.Africa)	Ettinger 2014 [43]
		11 (Geo. mean, Range 2.5-21), (30 sample size, 25-45 yrs, Ghana)	Ettinger 2014 [43]
		9.2 (Geo. mean, Range 6.4-19), (30 sample size, 25-45 yrs, Jamaica)	Ettinger 2014 [43]
		16 (Geo. mean, Range 11-27), (30 sample size, 25-45 yrs, Seychelles)	Ettinger 2014 [43]
		2.2 (Geo. mean, Range 2.0-6.5), (172 sample size, Cement Plant, NY)	Dong 2015 [39]
		4.8 (Mean, Range 0.01-30), (1183 sample size, Urban Brazil)	Freire 2015 [44]
Hg	<9[a], <2.0[b]	14 ± 10 (Mean, Range 2-90), (89 sample size, Medical Patients, CA, USA)	Hightower 2003 [45]
	<5.8[c], <0.8[d]	2.7 (Geo. mean, Range 0.2-36), (1811 sample size, NYC, USA)	McKelvey 2007 [46]
		12 ± 11 (Mean, Range 5-58), (20 sample size, Cambodia)	Agusa 2007 [47]
		0.8 (Geo. mean, Range 0.2-33), (16780 sample size, USA)	Caldwell 2009 [48]
		4.6 Men (Mean, Range 0.2-22), (137 sample size, Finland)	Airaksinen 2010 [49]
		2.8 Women (Mean, Range 0.1-20), (162 sample size, Finland)	Airaksinen 2010 [49]
		1.1 (Mean, Range 0.3-3.5), (273 sample size, Sweden)	Bjermo 2013 [50]
		1.1 Women (Geo. mean, Range 0.1-9.8), (480 sample size, 10 Euro. Countries)	Pawlas 2013 [51]
		1.4 ± 1.4 (Mean, Range 0.1-12), (593 sample size, Metro Brazil)	Kuno 2013 [52]
		4.0 (Median, Range 1.2-13), (184 sample size, Norway)	Birgisdottir 2013 [42]
		1.2 ± 1.4 (Mean, Range 0-5.9), (50 sample size, polluted S. China)	Li 2014 [38]
		0.8 (Mean, Range 0.1-5.8), (80 sample size, 50-59 yrs, Urban Poland)	Prokopowicz 2014 [53]
		0.07 (Geo. mean, Range 0.0-24), (30 sample size, 25-45 yrs, USA)	Ettinger 2014 [43]
		0.05 (Geo. mean, Range 0.0-35), (30 sample size, 25-45 yrs, S. Africa)	Ettinger 2014 [43]
		1.6 (Geo. mean, Range 0.01-11), (30 sample size, 25-45 yrs, Ghana)	Ettinger 2014 [43]
		2.4 (Geo. mean, Range 0.2-8), (30 sample size, 25-45 yrs, Jamaica)	Ettinger 2014 [43]
		28 (Geo. mean, Range 9-70), (30 sample size, 25-45 yrs, High fish, Seychelles)	Ettinger 2014 [43]
		1.3 (Geo. mean, Range 1.1-6.2), (172 sample size, Cement Plant, NY)	Dong 2015 [39]
		4.2 (in 2005) to 3.1 (in 2011), (2000 sample size, >20 yrs, Korea)	Seo 2015 [54]
		14.5 (Mean, Range 2-119), (1183 sample size, Urban Brazil)	Freire 2015 [44]
Mn	<18[a], <20[b]	18 ± 12 (Mean, Range 7.5-88), (73 sample size, Mexico)	Santos-Burgoa 2001 [55]
		8.9 (Geo. mean, Range 4.7-17), (215 sample size, Sardinia)	Bocca 2011 [56]
		7.6-10.8 (Geo. means), (Listing of 7 earlier studies,1990-2010)	Bocca 2011 [56]
		9.2 Men (Mean, Range 1.6-45.5), (3857 sample size, USA)	Oulhote 2014 [57]
		10.6 Women (Mean, Range 2.7-62.5), (3863 sample size, USA)	Oulhote 2014 [57]
		21.4 ± 7 (Mean, Range 12-44), (50 sample size, polluted, S. China)	Li 2014 [38]
		9.3 (Mean, Range 5-19), (7545 sample size, USA)	Jain 2015 [58]
		14.5 (Mean, Range 2-119), (1183 sample size, Urban Brazil)	Freire 2015(44)
Pb	≤ 40 (<6 yrs)[a]	110 ± 59 (Mean, Range 25-310), (73 sample size, Mexico)	Santos-Burgoa 2001 [55]
	≤ 90 (>7 yrs)[a]	17.9 (Geo. mean, Range 3-38, >100(10)), (1811 sample size, NYC, USA)	McKelvey 2007 [46]
	<35 d, <19[e]	32 ± 35 Men (Mean), (≈ 25 sample size, 16-35 yrs, Catalonia, Spain)	Ferre-Huguet 2009 [40]
		10 ± 10 Women (Mean), (≈ 25 sample size, 16-35 yrs, Catalonia, Spain)	Ferre-Huguet 2009 [40]
		27 ± 16 (Mean, Range 1.3-131), (539 sample size, Metro Brazil)	Kuno 2013 [52]
		19 Women (Geo. mean, Range 5.5-130), (480 sample size, 10 Euro. Countries)	Pawlas 2013 [51]
		13 (Mean, Range 6-29), (273 sample size, Sweden) Bjermo 2013(50)	Bjermo 2013 [50]
		25 (Median, Range 8.6-65), (184 sample size, Norway)	Birgisdottir 2013 [42]
		159 ± 160 (Mean, Range 0-650), (50 sample size, polluted, S. China)	Li 2014 [38]
		22 (Mean, Range 9-48), (80 sample size, 50-59 yrs, Urban Poland)	Prokopowicz 2014 [53]
		0.8 (Geo. mean, Range 0.2-6), (30 sample size, 25-45 yrs, USA)	Ettinger 2014 [43]
		1.5 (Geo. mean, Range 0.6-3.8), (30 sample size, 25-45 yrs, S. Africa)	Ettinger 2014 [43]

		3.1 (Geo. mean, Range 0.0-32), (30 sample size, 25-45 yrs, Ghana)	Ettinger 2014 [43]
		1.0 (Geo. mean, Range 0.2-2.6), (30 sample size, 25-45 yrs, Jamaica)	Ettinger 2014 [43]
		2.6 (Geo. mean, Range 1.5-7), (30 sample size, 25-45 yrs, Seychelles)	Ettinger 2014 [43]
		11 (Geo. mean, Range 9.6-35), (172 sample size, Cement Plant, NY)	Dong 2015 [39]
		26 (in 2005) to 20 (in 2011), (2000 sample size, >20 yrs, Korea) Seo 2015(54)	Seo 2015 [54]
Tl	<1.0[a], <0.6[b]	0.021 (Median, Range 0.004-0.034), (106 sample size, France)	Cesbron 2013 [59]
Toxins			
Cd	<4.9[a], <1.0[b]	0.8 (Geo. mean, Range 0.2-9.7), (1811 sample size, NYC, USA)	McKelvey 2007 [46]
	<1.2[f]	0.33 ± 0.13 Men (Mean), (≈ 25 sample size, 16-35 yrs Catalonia, Spain)	Ferre-Huguet 2009 [40]
		0.30 ± 0.16 Women (Mean), (≈ 25 sample size, 16-35 yrs Catalonia, Spain)	Ferre-Huguet 2009 [40]
		0.1 ± 0.15 (Mean, Range 0.1-1.7), (539 sample size, Metro Brazil)	Kuno 2013 [52]
		0.45 Women (Geo. mean, Range 0.1-4.4), (480 sample size, 10 Euro. Countries)	Pawlas 2013 [51]
		0.19 (Mean, Range 0.09-1.08), (273 sample size, Sweden)	Bjermo 2013 [50]
		0.45 (Median, Range 0.11-1.8), (184 sample size, Norway)	Birgisdottir 2013 [42]
		2.4 ± 2.1 (Mean, Range 0-8.3), (50 sample size, polluted, S. China)	Li 2014 [38]
		0.7 (Mean, Range 0.2-4.5), (80 sample size, 50-59 yrs, Urban Poland)	Prokopowicz 2014 [53]
		0.15 (Geo. mean, Range 0.01-1.2), (30 sample size, 25-45 yrs, USA)	Ettinger 2014 [43]
		0.0 (Geo. mean, Range 0.0-1.1), (30 sample size, 25-45 yrs, S. Africa)	Ettinger 2014 [43]
		1.1 (Geo. mean, Range 0.0-0.01), (30 sample size, 25-45 yrs, Ghana)	Ettinger 2014 [43]
		1.2 (Geo. mean, Range 0.0-3.1), (30 sample size, 25-45 yrs, Jamaica)	Ettinger 2014 [43]
		0.5 (Geo. mean, Range 0.0-1.6), (30 sample size, 25-45 yrs, Seychelles)	Ettinger 2014 [43]
		0.30 (Geo. mean, Range 0.27-0.94), (172 sample size, Cement Plant, NY)	Dong 2015 [39]
		1.5 (in 2005) to 0.86 (in 2011), (2000 sample size, >20 yrs, Korea)	Seo 2015 [54]
		0.25 non-smokers (Mean, Range 0.0-9.0), (1059 sample size, Urban Brazil)	Freire 2015 [44]
		0.81 smokers (Mean, Range 0.0-9.8), (117 sample size, Urban Brazil)	Freire 2015 [44]
Cr	<5.6[b]	24 (Mean, Range 7-55), (61 sample size, USA)	Herring1960 [60]
		0.55 (Median, Range 0.33-0.87), (106 sample size, France)	Cesbron 2013 [59]
		93 ± 33 (Mean, Range 34-154), (50 sample size, polluted, S. China)	Li 2014 [38]
Cu	<1500[b]	1030 (Mean, Range 500-1930), (61 sample size, USA)	Herring1960 [60]
		1036 (Geo. mean, Range 776-1495), (215 sample size, Sardinia)	Bocca 2011 [56] 812-1640 [Geo. means], [Listing of 9 earlier studies,1990-2010]
		812-1640 (Geo. means), (Listing of 9 earlier studies,1990-2010)	Bocca 2011(56)
		783±77 Men (Mean, Range 602-1000), (149 sample size, China)	Wang 2011(61)
		849 ± 87 Women (Mean, Range 695-1068), (163 sample size, China)	Wang 2011 [61]
		670 ± 90 (Mean, Range 140-850), (50 sample size, polluted, S. China)	Li 2014 [38]
Sb	<3.5[b]	1.9 ± 1.1 (Mean, Range 0.14-4.4), (50 sample size, polluted, S. China)	Li 2014 [38]
Se	70-130[b]	64 ± 18 (Mean, Range 14-166), (1380 sample size, Poland)	Klapcinska 2006 [62]
		86 ± 13 Men (Mean, Range 62-141), (149 sample size, China)	Wang 2011 [61]
		95 ± 15 Women (Mean, Range 64-143), (163 sample size, China)	Wang 2011 [61]
		140 (Geo. mean, Range 106-185), (215 sample size, Sardinia)	Bocca 2011 [56]
		74-132 (Geo. means), (Listing of 12 earlier studies,1990-2010)	Bocca 2011 [56]
		128 (Mean, Range 109-150), (1045 sample size, U.K.)	Spina 2013 [63]
		127 ± 21 (Mean, Range 60-222), (1601 sample size, Bangladesh)	George 2013 [41]
		95 (Median, Range 63-153), (184 sample size, Norway)	Birgisdottir 2013 [42]
		190 (Mean, Range 144-253), (7545 sample size, USA)	Jain 2015 [58]
		170 (Geo. mean, Range 160-220), (172 sample size, Cement Plant, NY)	Dong 2015 [39]

a Mayo Clinic Medical Laboratories [64]
b Micro Trace Minerals Laboratory [65]
c United States Environmental Protection Agency
d Schulz [66]
e World Health Organization, Geneva
f Toxicology Profile, Cd [67]

Table 1: Human blood: Average toxic metal concentrations: standard deviations and ranges, µg/l.

half of the total emitted anthropogenic mercury has been sequestered in marine sediment [73]. Such global modeling of mercury's cycle illustrates the remaining uncertainties but does indicate a small loss component [74,75]. The most recent assessments confirm this reality that mercury's environmental levels are a significant factor of several-fold over what should be the natural baseline and will remain so for an extended period [76]. As a result, the baseline levels of Hg and other metals in our diet have been raised over time and are no longer the desired orders of magnitude below their NOAEL levels especially for those people on the outlier higher edge of any distribution. Consequently, the question of safe levels with some of the trace metals is an obvious area of concern. For the fetus or young child this becomes even more of a problem due to their smaller body weight. Human NOAEL levels generally are derived from animal studies in which known dose levels are administered. The result is expressed in units of grams of the toxic consumed per kilogram body mass per day. Then,

through approximate animal/human models this is translated to a human dietary intake and then reduced further by an additional factor to add a degree of safety and allowance for possible errors. This is then converted via a pharmacokinetic model of dietary distribution into the particular biomonitoring scale value reported to a physician. In the case of mercury, EPA (US Environmental Protection Agency) and later other agencies chose instead of animal studies to use the extensive data base acquired from a decade's long study of the population of the Faeroe Islands, known to live on a high fish (whale meat) diet. From observed cases there, that were in fact displaying neurological effects, a dangerously high blood mercury level was assessed directly. This was then converted in reverse and scaled to dietary intake. An EPA oral recommended dose (RfD) of 0.1 μg Hg/kg/day was derived. The necessary conversion model involved estimated body absorption (95%), the fraction of this that enters the blood (5.9%), bodily elimination rate (71 days), body blood volume (5 liters) and body mass (67 kg). Assuming a supposedly normal person of 75 kg weight, EPA thus transformed the data to biomonitored values of either 5.8 μg/l in blood or about 1.0 μg/g in hair. The blood value is about 10-fold below the NOAEL value to allow for errors and the approximations involved. The question that arises with this and any toxic is whether it is consistent with measured values in healthy adults and whether it is meaningful in cases of pregnancy [77]. As noted in Table 1, the various USA "Safe levels" have been tabulated and are used as guidelines by testing laboratories. Looking simply at the average levels in many distributions the majority of people have trace metal levels in their bodies that are acceptable. However, there are many broad distributions where some do have levels several standard deviations higher than the norm. It is therefore useful to examine whether significant changes have occurred in recent decades concerning the neurotoxic and toxic metals. Moreover, there is a very important aspect that has never really been addressed by the medical profession that has gathered all this data. This involves the collection of the individual metal distributions in people. Each metal is analyzed and statistically evaluated as a full people sample. The interpretation simply answers whether for a particular toxin the average lies roughly in the safe range limits. The body however is ingesting all these toxins to various extents and is required to safely process them. As a result, a summation or direct matching of all the toxins in each individual would be more meaningful but has not been assessed in any of these collective studies. These are obviously solely addressing the commonly encountered average levels, and that toxicity results from only one metal. Numerous toxins at various levels can of course be reasonably assumed and with the additional uncertainty also of synergistic effects.

Has Anything in the Human Toxic Metal Baseline Changed?

When a chart is consulted of all the metabolic reactions occurring in the body, it is hard to see any direct role for the metals, the major channels being mainly organic reactions. Nevertheless, without the presence of numerous metals in trace quantities it fails: their role is crucial. The obvious major metal elements are Ca, Mg, Na and K but about 22 others are in trace quantities. Their roles generally are to become incorporated into enzymes or in catalytic processes or be present in a molecule such as the central core atom of Co in vitamin B_{12} without which we would die. It is interesting that all the required trace metals for life are found in the top part of the periodic table including only the first row of transition elements together with Sr and Mo. They are generally defined as trace if the needs are less than 200 mg/day. Because of diet, the body contains traces of many others, roles for which have never been found such as Ag, Au, Ba, Cs, Ge, Hg, Sb, Sn, Ti, Tl and Zr to name some. In fact, it is still not entirely settled whether the traces of Al, As, Cd and Pb may have some as yet unknown functions. Some, such as As, Ni and V play roles in lower organisms and plants, but none yet noted in humans. In other words, the body has come to terms with being constantly contaminated from conception with materials it does not need. Moreover, a recent study fed sets of mice with a very low dose of one or more of the toxins As, Cd, Hg or Pb in each set. In each case, although the dosage was regarded sub-chronic and somewhat negligible, it was noted that the presence could be complex showing synergistic effects and also in disturbing the normal body balance of the other essential metals [78].

In the present analysis a neurotoxin is needed, and might be aided and supplemented by a toxic. As a result, it is not necessary to examine every metal element. However, it is obvious that the six neurotoxins require consideration together with the most commonly encountered metal toxins. As seen in Table 1, these can now all be readily monitored using ICP-MS methods in blood, hair and urine samples and in dietary intake foods. Such analyses with their potential complexities of sample handling, interferences and analysis preparation concerns now have been developed into accepted standardized methods. Nevertheless, for reliable results at these generally very low levels, an experienced laboratory and technical staff is required [79]. For this reason, some published data can still be erroneous due to the difficulties and should be supported by other results. Also, reasonably applicable scaling factors now have been derived to utilize any of the biomonitoring methods for either blood, hair, nails or urine. However, for some of these metals it is fair to say in spite of considerable effort that few NOAEL levels are known reliably and the recommended USA safe levels are those in current use by most test facilities. In many cases their foundations are not entirely clear and they have been tentatively established over the years and sometimes lowered for additional assurance as concentrations of metals in the environment have fallen. At present, it is generally accepted that they do probably lie in reasonably safe zones. How a physician handles such data has to be difficult. The quoted safe limits at least have provided an initial valuable benchmark set of measures against which health might be judged. It does remain in an approximate state though that definitely has uncertainties. Consequently, the exercise of assessing the potential health risk factors for these metals is worth examining on an individual basis looking for any noticeable changes in the environment over the past decade or so.

Aluminum

Of the metals labeled as neurotoxic, Al is minimally regarded so by the medical profession because this is unfortunately based on previous oral data. Also, this is why there are few values for Al in Table 1. It is still not generally included in a blood/metals analysis. This may change now that Al is a major component in many vaccines. Two very encyclopedic reports on its health risks and its toxicity profile present summaries of the very many experiments on animals and note the behavior seen in humans [80,81]. These stress the difference between whether it is orally ingested or is inoculated into the body. This is particularly important because the adjuvant in most US vaccines replacing mercury now is aluminum. The temporary oral MRL (minimum risk level) of about 1.0 mg Al/kg/day dietary intake has been suggested and is based on an average diet value. Drinking water now is ≤ 0.2 μg/l in most regions and negligible. However, these values are of minor importance because of the very low intestinal absorption for dietary aluminum compounds (<1%) with ready excretion from the body. On the other hand, injected aluminum is 100% absorbed which now should raise general concern.

Several major analyses in fact have implied correlations with autism and Alzheimer's disease [82,83]. There is no evidence of neurological effects from the use of antacid medications, antiperspirants and other oral sources. Nevertheless, in regions of the world with areas of high aluminum deposits and content in the drinking water, it is quite well documented as a neurotoxin. However, this can be hard to validate because such water also often contains Pb and Mn [84]. Consequently, orally consumed aluminum appears to be of minor concern but the re-introduction of aluminum into vaccines is a major change that needs to be addressed because it is recent. The body burden of aluminum is mainly present in the skeleton and lungs. Normal oral rejection is on a time scale of several days. Nevertheless, experiments with animals and human autopsies clearly indicate that although inorganic, low levels of aluminum can cross into the brain and central nervous system. One interesting human isotopically labeled experiment is noteworthy. Injected as ^{27}Al citrate, although 72% was excreted within 5 days from the body, about 4% remained after 3 years and 2% after 10. The body appeared to be releasing the Al from different sites that had half-lives of about 1.4, and 40 days, and 7 and 50 years. A similar experiment with rabbits indicated a brain half-life of about 150 days. Other experiments with rats used aluminum citrate that was ^{14}C labeled. The brain half-life in humans is difficult to assess but is considered prolonged [85]. From autopsies it is clear that a slow blood/brain transport for inorganic aluminum does exist with a much slower egress that now is regarded to be on about a 20 year half-life scale. Whether it ever equilibrates is unknown. Experiments with rats indicate transfer across the placenta and into the fetal brain of their pups [86]. Although not proven, indications of Al in human fetal brain autopsies have conveyed that it is possibly dangerous for pregnant mothers even to use any aluminum products and moreover should be administered only with adjuvant-free vaccines [87]. Also, the case against Al as being possibly involved in Parkinson's or Alzheimer's diseases still remains very controversial [83,88-91]. Consequently, Al is a neurotoxin and its potential damage to an embryo/fetus or child clearly may exist and so requires consideration.

Arsenic

Arsenic in blood is cleared quite quickly and this may not be a good measure of its toxicity [92]. Based on an oral MRL of 5 μg/kg/day, with drinking water (<10 μg/l), this has suggested safe blood levels of (<1 μg/l), with hair and nails (<1 μg/g), and urine (<100 mg/l), analysis by the latter method being preferred depending on the duration of the toxicity. Measurements in a South China industrial region for both hair and blood samples were in agreement giving a mean value of 0.75 ± 3.2 μg/g for hair and 0.55 ± 2.7 μg/l for blood (Table 1) [38]. Otherwise from the general population distributions in Table 1, the Acceptable Hospital level of <10 μg/l for blood would seem appropriate [65]. Additionally, arsenic ingestion is more complex in that the biological As in seafood (mainly arsenobetaine) is only mildly toxic, is not digested and is excreted [31]. Since total As generally is monitored this is a complication and moves to measure only inorganic As have been suggested. Additionally, some regions of the world can experience high As level drinking water at least 5-fold above recommended US standards. Nevertheless, arsenic is being ever more tightly regulated and has been constantly decreasing in the US diet over the past two decades.

Mercury

With mercury, an extensive analysis of toxicity was undertaken by the US Agency for Toxic Substances and Disease Registry [93]. In these reports, an NOAEL value for blood content is suggested of about 60 μg/l and it was concluded that levels 4-fold lower could be used as an MRL value. However, as mentioned above, EPA reduced this value further to 5.8 μg/l for a safe blood level. In commercial laboratory testing and in various hospital facilities suggested levels are <9 μg/l but lowered by others to <2 μg/l and even more so in Europe to <0.8 μg/l, which would seem an unrealistic low value at present [64-66]. As seen in Table 1, such recommendations become meaningless when the value falls well within the average population distribution. With the Hg cases noted in Table 1, the two very high mean values of 14 or 28 μg/l were extreme examples of either groups of people visiting the doctor with dietary mercury poisoning or living on a high ocean-fish diet in the Seychelles' Islands [43,45]. Nevertheless, many other distributions have been noted that extend to high blood mercury values and particularly place women at high risk [94-97]. Again one is left with a disturbing quandary. If such people still appear healthy what conclusion can be drawn?

In the case of mercury there is greater complexity due to its chemical diversity. It can enter the body in one of four entities; liquid elemental, elemental vapor, inorganic single or divalent salts, and in organic forms such as the methyl mercury or ethyl mercury ion. These all differ in their degree of bodily toxicity and neurotoxicity. In other words it is necessary to define exactly the state of the mercury in any discussion of its behavior and identify its source. The case of liquid elemental ingestion is rare and usually intentional or accidental. Surprisingly, in medical history it was even used to unblock intestinal difficulties, passing rapidly through the body with negligible absorption. However, those cases where it has been injected intravenously by syringe differ and are quite interesting. Although a liquid metal, it does have a slight solubility in water at equilibrium of about 60 μg/l at room temperature [98]. Otherwise, within the body tissue it will have difficulty vaporizing and will remain as liquid clusters. Of those studies reported, blood levels can become very high but remain in the body as a toxin. Chelation can reduce the quantity and patients can be released from treatments with no obvious neurological damage [99,100]. Excessive ingestion and injection, where blood mercury may be as high as 800 μg/l finally become a case of body toxicity leading to death [101]. Since the solubility of liquid mercury in blood plasma can only be 60 μg/l, higher reported analysis values possibly imply either a dispersion of essentially colloidal nanoparticles of elemental mercury or the mercury divalent ion if some form of enzymic oxidation has occurred. This would need chromatographic analysis to resolve. It is known that nanoparticles such as ZnO and SiO_2 cannot penetrate the blood/brain barrier [102]. One very interesting case of attempted suicide involved injection of 3 ml of liquid Hg into an arm vein. An operation removed the vein with some of its mercury and over several years of reconstructive surgery and chelations the patient remained healthy and totally functional. However, her blood mercury remained very high for 10 years (209 μg/l) and at this point she did have one pregnancy with a spontaneous abortion. Nevertheless, the following year she became pregnant again with a blood mercury level of about 174 μg/l and this time gave birth to a healthy daughter (cord blood 190, amniotic fluid 8 μg/l). The mother's milk (281-318 μg/l) could not be used, but the baby was raised quite healthily on formula foods. The baby's blood at 4 months was 17 μg/l with the mother's still at 154 μg/l, but with both showing no neurological effects and both living normally [103]. This clearly indicated that the neural system survived high levels of elemental mercury even through the embryonic and fetal stages. The cord blood indicated that the baby had been heavily exposed and had excreted mercury into the amniotic fluid. It would indicate that elemental mercury in the blood has great difficulty in crossing the blood/brain barrier and may in this case have had a more colloidal rather than vapor nature. After birth this baby

gradually began to shed the excess mercury and remained normal. It is also surprising that they appear not to have had normal toxic organ poisoning responses.

This situation possibly differs from the inhalation of mercury vapor, which consists of separate gaseous elemental atoms that can be readily absorbed by the mouth membrane and lungs into the blood stream. One review suggested a whole body half-life of about 40 days for this, but a very long and still uncertain lifetime of years for any that managed to be in the brain [104]. The consequences of this form of exposure are well documented through hazardous metallic mercury spills, by industrial exposures as with those working in the chloralkali industry, gold miners who use smelters to separate the gold from its amalgam with mercury, and the nature of dental amalgams in the body [105]. If exposure is extended, such as in gold mining (>50 μg/l blood mercury) or dentistry, neurological effects can become apparent as neuromotor defects such as hand tremors or postural sway indicating some neural invasion as well as renal damage [106-108]. Occupational exposure has been correlated with some tremor among US dentists [109]. Moreover, safety agencies now recommend not restoring teeth with amalgams [110]. One heavy vapor exposure from amalgam recycling was clearly evident from very high urine mercury, but no signs of intoxication. Nevertheless, later, dying 17 years after exposure and chelation, the brain and some organs still clearly were seen to be rich in mercury content. However, no signs of neural loss were apparent in the brain [111].

Low levels of exposure as in dental amalgams do contribute to body burden but the inorganic elemental Hg appears to be tolerated. One approximate mass balance for a significant load of amalgam restored surfaces (thirty) indicated mainly fecal excretion, coupled to smaller oral cavity absorption, and urine contributions indicating mainly kidney rejection with a half-life of about 45 days. However, compared to a control group, the mercury body burden could become a non-negligible 60 μg/day [112]. Inserting radiolabeled ^{203}Hg into the teeth of sheep and monkeys, it was shown in a series of papers that within a month the mercury was distributed over the major organs, and could transfer to the fetal blood and amniotic fluid within 2 days of maternal dentistry. Also in humans it was reported that dental mercury could cross the mammary gland into breast milk. There is no mention of it crossing the blood/brain barrier [113-116]. It does seem that the elemental Hg or even its ion Hg^{2+} if the mercury is oxidized in the blood can be controlled by enzyme and protein transporters that cleanse the organs. Although the component of mercury as tooth amalgam is not of concern as a neurotoxin, it still will contribute as an additional component of the body's burden. It has been linked to potentially being involved in fatigue and depression type symptoms [117]. As a result some Scandinavian Countries now have banned its use in dentistry and the World Health Organization is seeking a global ban.

The inorganic molecules of mercury of which there are actually few for such a metal are mainly divalent. Calomel, Hg_2Cl_2, is the major monovalent compound, but is insoluble in water and as a result has low toxicity. Historically, it was used as a laxative and antiseptic but finds few uses today. The ore, cinnabar HgS, also is very insoluble in water and non-toxic. However, it can cause renal inflammation in rats and may be an additional burden in the body if consumed [118]. Of the divalent salts, the nitrate and chloride are both water soluble and highly toxic. The nitrate was used to treat felt and was the basis for the "Mad as a Hatter" phrase. The dichloride is thermally stable but is corrosive, volatile and very toxic. It and elemental mercury are emitted from coal combustion. In the form of its radiolabeled $^{203}HgCl_2$ it has been used with pregnant hamsters in toxicity comparison studies with organic mercury compounds, primarily the methyl and ethyl ions [119]. The dichloride displayed a short bodily half-life in the animals of 2.2 ± 0.4 days and so was administered on day 9 of gestation with analysis on day 15. The fetal level of inorganic Hg^{2+} mercury was very low in both the parent and fetus' brains. The maternal analysis showed major accumulations in the kidney, placenta and liver in that order with major excretion in the urine. The fetus indicated twice the level in the liver than the brain, the fetal dose appearing to be about 0.2% that of the mother, with 3% of the dosage retained in the placenta. With inorganic mercury, this was noted also with rats but seemed to accumulate in the fetal brain easier than the maternal brain [120]. In this case the accumulations in the kidney, liver and brain were 53, 39 and 1.7% in the maternal rats and 24, 49 and 16%, respectively, in the infants. Although not sufficiently definite, the studies appear to confirm that all forms of inorganic mercury have difficulty in crossing the BBB. Moreover, autopsy data can be difficult to interpret for mercury at such low levels due to changes in the brain that can occur after death and also in its handling and analysis [121].

As a result, the organic forms of mercury are seen to have the most dangerous neurotoxin nature. These have been studied now quite extensively especially as the CH_3Hg^+ that exists in fish, and the $C_2H_5Hg^+$ ion that is still used as the adjuvant in those vaccines utilizing it in the form of thimerosal from which structure it metabolizes in the body. There is a very significant recent literature of noteworthy studies and reviews on the neurological behavior of these in the body and their potential effects during pregnancies [122-129]. The major findings now are reasonably consistent and provide a foundation of understanding. It has long been established, presumably due to their organic nature that these two mercury structures manage to partially leak through the blood /brain barrier (BBB). Whether administered orally or by injection they are efficiently absorbed approximately equally. Following studies on rabbits, one similarly examined hamsters that used an oral dose of radiolabeled $^{203}CH_3HgCl$. This indicated after 13 days a full body half-life of about 8 days and a clear presence of CH_3Hg^+ in the brain [119]. The kidneys retained most of the mercury but that in the brain as organic mercury was only one-tenth lower. Although demethylation was evident in the pregnant hamster main organs, no inorganic mercury was evident in the adult or fetal brains. Levels in the fetus were an order of magnitude higher for organic compared to inorganic mercury. A more detailed study administered both forms of the organic mercury ions to infant monkeys obtaining the distributions in the brain [123]. This showed that the two mercury-alkyls have quite different toxicologies, the $C_2H_5Hg^+$ having whole blood and brain half-lifes of about 7 and 24 days, respectively, compared to 19 and 60 for the methyl mercury. Moreover, although brain levels were about 3-fold lower for ethyl, it left a much greater fraction (34 vs. 7%) of inorganic Hg^{2+} in the brain that has a still ill-defined but certainly long half-life for egress. Apparently, the methyl ion de-alkylates to Hg^{2+} less than the ethyl structure in the brain. These general findings had also been reported in pregnant rat studies [122,124]. This fetal behavior was also assessed from infant brain autopsies [130,131]. Through the consumption of fish, one human study was examined with 27 volunteers [132]. They ate fish at a tolerable level for 14 weeks followed by 15 weeks without. Blood and hair samples were monitored throughout giving an approximate hair/blood biomonitoring ratio of about 340 and a half-life consistent with the 60 days obtained earlier, and with a value of 80 days from a recent toxicity model [133]. A smaller more recent similar study indicated a wider variation, being individual dependent with values of 43-128 days [134]. As a result, it is clear that both of these organo-mercury compounds pass through the placenta and can leak into the brain. Their brain lifetimes are significant and the fetal brain can obviously be placed at high risk. Consequently, since sources of mercury in vaccines and fish diets are common, mercury requires a fuller assessment.

Manganese

For the element Mn, this is essential for health and under normal conditions is unlikely to be toxic in an average diet because of the natural body controls. It is generally in a range of 4-15 μg/l in blood with an average of 9 μg/l in the USA. No absolute MRL (minimum risk level) has yet been obtained but a CDC (Center for Disease Control) toxicology assessment has suggested an Interim Guidance Level of 0.16 mg/kg/day based on a 70 kg person with an 11 mg/day diet [135]. As a cup of black tea can contain 0.4-1.3 mg Mn and the fact that the British appear to show no pronounced effects from their heavy tea consumption custom, this removes some concern for normal dietary intake. It is cleared quite rapidly from the blood but this remains its best biomarker. Nevertheless, manganese as the Mn^{2+} ion can cross the blood/brain barrier and the identity of the appropriate transporters have been quite extensively discussed [136,137]. Suggestions are that egress may be a slower process with the possibility of accumulation with repeated excessive exposures [138,139]. A recent large Shanghai study of mothers and newborns tentatively concluded that high Mn levels in the cord blood could possibly start to affect the newborn neurologically [140]. Whether any excess intake of manganese is adding to the body-burden of toxics that constantly have to be removed has to be seen. However, from the point of view of whether Mn has changed its role in the environment the use of the MMT addition to gasoline now has been phased out. Excess exposure to the general public should now be minimal.

Lead

Although lead has been known to be very toxic for well over a century, it took a long time to reduce its anthropogenic presence in the environment. The significant efforts undertaken in recent decades are now reflected in one of the major improvements to health relating to any of these elements of concern. Until recently, children in the US had lead blood-levels over 100 μg/l and the World Health Organization (WHO) indicated that 143,000 children died in 2004 from such poisoning and many more undoubtedly were affected neurologically. Blood levels of 50 μg/l now are recognized as sufficient to be of concern for affecting children. Regulations removed lead tetraethyl addition to gasoline, and leaded glass ended as being a beverage container. The question of lead as solder in old water pipes may still be a historical problem in older properties, as well as the remnants of old lead containing painted surfaces. Nevertheless, the controls now are constantly reducing lead's anthropogenic contribution to the environment annually and have been a meaningful program of global sensibility. The average blood level in the US from 1976-1991 fell 78% from 128 to 28 μg/l [141,142]. The number of people with levels >100 μg/l fell to 4.3%, and during 1999-2002 this reduced further to 0.7%. A decade ago an average value for all adults in the US was <20 μg/l. Foods in fact contain low levels of lead and canning had been a problem. The present levels are reflected in Table 1 and show this global downward trend. The WHO agency now suggests <19 μg/l as a recommended target but medical testing laboratories still accept higher standards. No MRL values are quoted as it is still felt that lead at any level can affect health. The sensitivity shown by children arises from their 4-5 folds more efficient absorption mechanisms. However, the fact that lead dietary levels have been dramatically lowered and moving away from its toxicological effects curve tends to suggest it is now a lesser participant or collaborator in present neurological concerns. Globally, it is of less concern, however as seen in a recent drinking water mishap in Flint, Michigan it can become a local overnight dilemma. By switching their water source to one unknowingly more corrosive it has caused significant Pb toxic damage to that community, which may have significant consequences for a generation.

Thallium

An older toxicological report for thallium was published and remains appropriate [143]. A more recent brief discussion mentions the possible methylation and bioaccumulation in algae but this remains unstudied and not noticed in the food chain [144]. Although a potent neurotoxin, with a half-life in the body of about 3 days, it was used in the past as a rat poison and medically for various ailments, but thallium is not normally encountered nowadays to any degree. Moreover, since its use is mainly concentrated in various specialized industries (semiconductor technology), any detrimental effects would most likely be observed by a geographic distribution. Before its stringent regulation, a community in the vicinity of a thallium emitting cement plant was monitored over a two year period and did display elevated levels in urine samples. Nevertheless, from the 300 births recorded in that period no causal relationship with fetal damage was ever positively confirmed [145]. Hair is now regarded as the best biomarker with normal levels of ≤ 5-10 ppbw. Some concerns have been raised for farming in geochemical areas rich in thallium. A high daily intake of 1.9 mg Tl/day was estimated for one such Chinese location and could be hazardous [146]. A recent study indicated that isotopic separation of Tl in contamination questions can resolve whether its source is natural or not. Analysis of topsoil in the vicinity of a cement plant in Germany confirmed that the local Tl in the vicinity was anthropogenic [147]. There appears to be no other evidence in the literature concerning its potential as an environmental hazard or its being responsible for birth defects.

Cadmium

With cadmium, due to its toxic nature, significant animal and human data have been collected. A recent report summarized its toxicological aspects, as also a recent book [67,148]. Cadmium is not known for neurological damage but accumulates principally in the kidneys. As a result any MRL that is quoted relates to potential kidney damage. In this case, its effects could be studied both from human and animal data. The blood/brain barrier severely limits Cd access and natural body protein molecules such as metallothionein and cysteine are very efficient chelators [148]. Recent recommendations suggest 0.35 μg/kg/day as a safe dietary intake. This value has been very useful in validating the various pharmacokinetic models that are used to quantize the various distributions of an element in the body that then relate the dietary input to the actual biomonitoring value that is clinically observed. The Cd toxicology report illustrates the various approximations that are required for such a conversion and why uncertainties always remain in the field of toxicology. In this case the dietary intake translated to a recommended MRL of 1.2 μg/l for blood. A current median blood concentration for the average American is quoted as 0.33 μg/l. Dietary intake of Cd has been estimated to have dropped by one-third from the 1980's. This continuing decline is clearly evident examining the USA 1999-2008 average blood levels [67]. Consequently, Cd is another metal, not particularly toxic to the brain that also has been in constant decline in recent decades. In this case, it is partly the result of less smoking which can readily elevate Cd-blood content by 1.0 μg/l and also can affect fertility. As seen from Table 1, global levels do appear satisfactory except in the more heavily polluted industrial areas. Urine testing is another valuable biomarker for Cd. Germany recently reduced its previous standard for this now to 0.2 μg/l, further reflecting the declining trend [66].

Chromium

Although chromium acquired much publicity as a potent toxin, this in fact relates specifically to the Cr(VI) valency that is associated particularly with the chromate industry. In nature and in the human diet chromium is Cr(III) and is essential to the body being particularly important in regulating blood sugar [149]. Its toxicological profile has been published on the Web [150]. This quotes several estimates for dietary intake of 20-45 μg Cr(III)/day or a blood level 0.1-0.16 μg/l (Institute of Medicine). The average USA intake appears uncertain and has been quoted by the WHO as about 25-224 μg Cr(III)/day (average 76) and also as 52-943 μg Cr(III)/day. It is toxic only in significant excess (100 mg/day dosage-EPA) and can be prescribed up to 200 μg/day to diabetics or the elderly who may be deficient. It accumulates mainly in the kidneys, liver and bone and is not known for neurological effects. No study has shown any connection to birth defects. However, a recent report from an industrial area of China has suggested a possible correlation between chromium exposure during pregnancy and low infant birth weight [151]. Chromium is easily excreted via urine and in fact is poorly absorbed (1-2%) from diet. Blood levels normally are quite low for non-industrially exposed persons. If there is concern with chromium, a speciation measurement using chromatographic separation is required to measure any potential Cr(VI) contributions. No increases have been noticed in its environmental presence.

Copper

Copper is an essential nutrient and deficiencies are rare and medically apparent if they occur. It is the third most abundant metal in the human body following Fe and Zn. Excesses can normally be controlled by the body and readily excreted. Kidney and liver toxicity result at high levels but there is no suggestion of neurological effects. Intake is from diet, both food and mainly water in some regions. Drinking water in the USA is regulated to be <1.3 mg/l. A toxicological report suggests a maximum recommended level (MRL) of 0.01 mg/kg/day that is a factor of three below the NOAEL level [152]. This equates to about 1 mg/day that is a median adult value for a US diet. The WHO suggests a recommended maximum intake of 10-12 mg/day, which may be more appropriate in some countries. Such values illustrate the uncertainties that flow throughout toxicology and the tendency to have a bias to greater safety when establishing boundary limits. Normal blood content for copper is in the range of 1.5 mg/l, which appears quite closely followed, values often being on the lower side. There is little concern about any possible increases having occurred in the last decade.

Antimony

Although a significant toxin, antimony is not regarded as an at risk element for the general public. It is in the human diet at very low levels in water and consumed on a low 5 μg/day scale from food. The body reacts vigorously to higher doses causing vomiting and is immediately apparent. There is little concern as to its potential neurological effects and birth development problems have never arisen from women working in its industrial environment. Its presence in the environment is controlled and not a public concern. This probably reflects why a current toxicology report is quite dated [153].

Selenium

Selenium has been added to this list of metals because it plays an important antioxidant role in the body [154,155]. It is an important micronutrient but nonetheless is a toxic element at higher concentrations. It is unusual in this manner having only a narrow concentration window of being beneficial. A dietary intake in the range of 40-400 μg/day is required with an optimal range of 200-300 μg/day now being suggested for good health [156,157]. This is larger than the previously recommended daily intake of about 55 μg/day. Concern arises due to the uneven occurrence of selenium in soils around the world. Geology exerts its control over crops and animals and in China for example areas exist with either soil too rich or poor in selenium, both extremes raising medical concern [158]. In regions of deficiencies there are even programs to try and introduce selenium into the food chain by enriching animal feed for egg and meat production or growing foods rich in selenium [159,160]. Due to this important role in living organisms the environmental health aspects on humans and animals, and the toxicology profile for selenium and its compounds have been very extensively documented [161,162]. These detailed reports are freely available on the Web. They indicate that a normal diet will usually provide about 70-150 μg/day of selenium from mainly grains and cereals, followed by meat, fish and poultry. Drinking water in the US is regulated to be ≤ 50 μg/l. In the body selenium has numerous roles that could be summarized as forming anti-oxidant proteins such as selenocysteine and selenomethionine that strongly interact with numerous toxic metals such as Hg, Cd, Pb and As, purging these from the body and brain. Organoselenium chemistry is rich in species. In fish it tends to form selenium bound proteins but has a more extensive speciation in vegetation. Its metabolism in the body can be varied and complex and still is not fully resolved [163]. As will be seen, it is a valuable defensive barrier in the brain particularly in neutralizing neurotoxins and protecting neuronal signaling [164].

Examining Table 1, the four metals that are solely toxins, Cd, Cr, Cu and Sb, do indicate some people on the outlier part of the distributions that might be considered as venturing onto toxicity curves. Nevertheless, these elements do not satisfy the necessary criterion of having changed noticeably since the 90s. Cr and Cu are needed biologically and are generally regulated well by the body, Sb is rare even in the human diet today and Cd although very toxic has been severely reduced over the last decade in the human diet. Of the six neuro-toxins, some elimination is also possible. It is reasonable to drop As, Mn and Tl based on similar arguments. Additionally, lead levels in diets have been so drastically reduced in the last decade in the US that their effects have to be less, rather than more, even in any synergistic mode [165]. This tends to leave only Al and Hg which need to be seriously considered further. Nevertheless, it should certainly be noted that even though not considered front runners, any substance that is a toxin is not entirely negligible. The body is in a constant conflict with all intruding toxins and carries this significant burden automatically without our knowledge. All make unnecessary contributions to the body's tasks, which humans unfortunately almost always take for granted.

Pregnancy, the Placenta, Cord Blood, Breast Milk

Rather surprising, and mainly because of the advances in analysis, it is only in recent years that more detailed reports have emerged concerning pregnancies and the extent of trace metals such as Al, As, Cd, Hg, Mn, Pb and Se in the maternal blood, the placenta, the birth cord blood and the mother's nursing milk. Either because they are regarded as non-essential to the body or have only a minor presence in diets, the species Tl, Cr, Cu and Sb have rarely been included in such studies. Representative global efforts that have been published in recent years for the other metals of interest are tabulated in Table

2. The purpose of such large surveys of pregnant women really has been to answer numerous rather basic questions, which they now have managed to do quite well. These uncertainties included the following aspects, but generally do not assess the neurological nature at birth of the babies:

- What are the concentrations and range of values of various toxic metals in a pregnant women's blood?
- What are the concentrations and range of values of various toxic metals in the fetal cord?
- How well is the placenta protecting the embryo/fetus from excesses in the mother's blood?
- Do blood cord levels of toxic metals pose a risk factor for the fetus?
- What are the concentrations and range of values of various toxic metals in breast milk?

The data presented in Table 2 do answer these questions but raise others that are difficult to interpret. The analyses depend heavily on statistics that search for correlations and attempt to reduce the data by taking numerous possible approximate confounding factors into account. Additionally, their main purpose is solely to establish a baseline of data that describes the majority of people and establishes a range of values that is acceptable and regarded as safe. This is still an exercise in process and remains difficult to extract any definitive conclusions from this ever growing large body of work. For the data that lie within the interquartile range it is fully acceptable, but for that extending to outlier ranges it is no longer of interest to the statistical analysis and the occurrence and consequences from such results is not normally examined. Emphasis remains solidly on the majority. Although lacking scientific rigor, these distributions at least do provide an approximate portrayal even though the data may be controlled by additional parameters beyond current understanding. The first thing noted in Table 2 is that a pregnant mother's blood can contain all of these metal neurotoxins and toxins. Also, of the various metals, variations from country to country do tend to reflect environmental quality and degree of industrialization. However, broad distributional ranges within any population are again very noticeable, displaying extreme values that are several standard deviations from the average. For these metals, there are examples in this data that lie approximately 4 (As), 15 (Mn, Pb, Cd), 30 (Al?) and 100-fold (Hg) above recommended average safe levels and obviously with some values that are encroaching onto toxicity dosage curves. It is noteworthy that such outlying values appear to have been taken from healthy women and it is unfortunate that their follow-up birth details were not discussed. By comparing fetal cord blood and mother's blood levels an approximate estimate can be made of the balance of trace metals that are established between them. It only relates to the ratio at birth but is expected not to vary significantly through the pregnancy probably tracking the mother's blood values that can be periodically measured. A recent review of more than 100 such studies examined this ratio of mother's blood to cord blood concentrations [192]. This not only included 14 metallic compounds but also innumerable toxic organics in environmental circulation. Although no values have been published for Al, a placenta and cord analysis did indicate a fractional barrier transfer possibly reflecting a halving of concentration in the fetal blood level [193]. All women's placentas appear in general to perform in a similar manner for a specific element. As a result, one can expect that the fetal blood, when compared to the mothers, has the following approximate percentage ratio: for Cd (≈ 17%), Tl (≈ 20%), Pb (75%), As (80%), Se (100%), but has enhanced enrichments apparent for Hg (160%) and Mn (200%). These enhancements imply that the influx to the fetus is greater than its rate of removal. Consequently, it is obvious that the placenta offers minimal protection for the fetus with regards to these metal elements. These are total element estimates and in reality the behavior of the placenta can show variations not only from mother to mother but also for each of the elements depending on its actual chemical form. For example, the cord to maternal blood ratio can be about 1.9 for methyl mercury and 1.0 for inorganic mercury [194]. Also with a 95 case sample and a general average ratio of about 1.4 for Hg, when exactly paired, the variation ranged from 0.4 to 3.2 [183]. Another study of the ratio of methyl mercury in the red blood cells of the cord and the maternal blood for 63 mother/newborns indicated an average value of about 1.6 but with a range of 1.1 to 2.2. This latter study also confirmed that the beneficial poly-unsaturated fatty acids also pass into the fetal blood [195]. Of the metals, Al, Mn, Pb and Cd, these naturally do not form organometallic molecules in the environment. Moreover, they tend not to methylate in any manner in the body and will have a dominant inorganic nature in the blood. As and Hg can be ingested from the environment in an organic form from fish (arsenobetaine, arsenocholine, methylmercury), and both As and Se can even become methylated within the body [126]. The organo-molecular form could explain the efficient transfer of methylated mercury through the placenta, but cannot explain that of Pb or the unusual high level of inorganic Mn except that this is an essential nutrient. Consequently, as seen in Table 2, like the mother's blood, that transferring to the developing fetus also can be regarded as toxic and neurotoxic. As a result, it is particularly interesting that although the placenta is an inefficient minimal filter, the mammary gland is a far better control concerning breast milk quality. From Table 2 it appears quite general for all these metals including Se that the concentrations in breast milk are uniformly reduced or of an acceptable level. Only in one exceptional case for Hg was the breast milk at toxic levels (300 μg/l). This was the very unusual situation where the mother had injected liquid elemental mercury into her vein and still gave birth [103]. Breast milk can even have lower metal content than feeding formulations. The trace minerals considered necessary for growth are Cu, Cr, Fe, Mn, Mo, Se, Zn together with F and I [196]. Breast milk is very adequate for these and any unneeded transmitted traces of Al, As, Hg, Pb and Cd are generally at levels of little concern although in some cases considerations of mercury content might be an issue [197-199]. This aspect has been raised recently by the monitoring of methylmercury in the breast milk of Japanese mothers on a staple fish diet [200]. It was seen that about half the mercury in the milk was in organic form and could be of marginal concern for a baby feeding every day. There are significant efforts to balance formula-milk correctly but concerns can still arise with contaminants such as Al being present at significant levels [201-205]. However, infant dietary estimates do show an increasing adequacy in infant foods [206]. Nevertheless, in spite of in-uterus dangers from toxins, mother's milk remains fully acceptable for the baby. Consequently, we are left with an intriguing conundrum as to why breast milk has more efficient barriers and better controls the toxins [207]. Logically, this tends to imply that the body accepts the inefficiency of the placenta knowing full well it has adequate further protections available for the fetus. Even evolutionary arguments that the fetus was never before encountering significant loads of metal toxins brought in by industrialization cannot explain this difference of the two filters.

Fetal Brain Risk

Due to the greater loss of babies during pregnancy, it is obvious

Metal	USA Adult	Sample Size	Maternal	Cord	Milk	Reference
	Safe Limits	Country				
Al	<30a	172, Perth, Australia	65 Mean (<10-860)	-	-	Callan 2013(166)
		100, Jamaica	Mean	10.9±9.2 (2-28)	-	Rahbar 2015(167)
As	<10a	120, India	3.8 Mean (0.1-15)	-	2.2 (0.3-9)	Sharma 2005(168)
		62, S. Africa	0.6 Median (0.08-3.1)	0.46 (0.04-2.8)	-	Rudge 2009(169)
		36, Brazil	0.6 Median (0.3-3.8)	0.97 (0.44-4.5)	-	Rudge 2011(170)
		94, Nepal	Mean	1.5 (0.5-10)	-	Parajuli 2012(171)
		870/619/602, Italy	1.2 Median (0.2-33)	1.1 (0-54)	0.3 (0.04-12)	Miklavcic 2013(172)
		426/287, Slovenia	Median	0.6 (0.1-8.4)	0.04 (0.04-2.9)	Miklavcic 2013(172)
		219/209/123, Croatia	2.1 Median (0.3-37)	1.6 (0.3-32)	0.2 (0.04-119)	Miklavcic 2013(172)
		375/39, Greece	Median	3.3 (0.2-65)	0.8 (0.3-4.8)	Miklavcic 2013(172)
		172, Perth, Australia	1.9 Mean (0.4-15)	-	-	Callan 2013(166)
		237, Belgium	0.64 Geo. mean	0.54	-	Baeyens 2014(173)
		81, China	11.0 Median	10	-	Hu 2015(174)
		419, Bolivia	<3.3 Median (3.3-7.2)	<3.3 (3.3-6.5)	-	Barbieri 2016(175)
Hg	<2.0b	120, India	8.3Mean (0.2-50)-	4.6(0.1-28)	Sharma 2005(168)	
		1057, Hong Kong	4.9Median	8.8	-	Fok 2007(176)
		62, S. Africa	0.65 Median (0.1-8.8)	1.2(0.1-9.7)	-	Rudge 2009(169)
		1, USA	209-170 (Elemental Hg)	190	281-318	Pugach 2009(103)
		52, Austria	0.7Median (0.1-5.2)	1.1(0.2-6.8)	0.2	Gundacker 2010(177)
		36, Brazil	0.66 Median (0.06-4.4)	1.1(0.4-8.3)	-	Rudge 2011(170)
		15, Faroes	Median	12	2.3	Needham 2011(13)
		294, Baltimore, USA	Geo. mean	1.4(0.3-16)	-	Wells 2011(178)
		1652, Shanghai	Median	1.1(0.2-13)	-	Yu 2011(179)
		871/614/605, Italy	2.4 Median (0.05-40)	3.9(0.1-33)	0.2(0-28)	Miklavcic 2013(172)
		446/284, Slovenia	Median	1.5(0.2-14)	0.2 (0-2.9)	Miklavcic 2013(172)
		255/210/125, Croatia	2.0 Median (0.6-21)	2.9 (0.3-32)	0.2 (0-2.4)	Miklavcic 2013(172)
		391/44, Greece	Median	5.8(0.2-33)	0.6 (0-12)	Miklavcic 2013(172)
		257, China	0.84 Geo. mean (0.3-2.1)	1.5 (0.3-4.8)	-	Ding 2013(180)
		1575, Saudi Arabia	3.0 Mean (0.0-206)	3.4 (0.0-27)	-	Al-Saleh 2014(181)
		217, 1st Sem.,Mexico	3.3±2.0 Mean (0.4-12)	-	-	Basu 2014(182)
		264, 2ndSem., Mexico	3.1±1.9 Mean (0.4-13)	-	-	Basu 2014(182)
		248, 3rdSem., Mexico	3.7±3.5 Mean (0.3-31)	4.7±2.8 (0.8-17)-	-	Basu 2014(182)
		95, Nigeria	3.6 Mean (1.1-9.5)	5.1 (1.2-10.6)	-	Obi 2015(183)
		998, Saudi Arabia	0.89±1.8 Mean (<49)	0.97±0.7 (<6.4)	-	Al-Saleh 2015(184)
		100, Jamaica	Mean	4.4±2.4 (2-7.6)	-	Rahbar 2015(167)
		104, S. Korea	2.7±1.4 Geo.mean (<8.5)	4.4±1.5 (2.6-12)	-	Kim 2015(185)
Mn	< 20a	120, India	22 Mean (0.2-150)	-	7.4 (0.4-44)	Sharma 2005(168)
		62, S. Africa	17 Median (8.7-63.5)	35 (7.2-81)	-	Rudge 2009(169)
		36, Brazil	19 Median (7.0-40)	37 (22-66)	-	Rudge 2011(170)
		172, Perth, Australia	9.1 Mean (<0.1-50)	-	-	Callan 2013(166)
		239, Belgium	12 Geo. mean (4-40)	31 (7-80)	-	Baeyens 2014(173)
		75, CA,USA	21 Geo. mean (6.7-36)	40 (21-72)	-	Gunier 2014(186)
		172,Shanghai	54 Median (23-304)	77 (26-342)	-	Chen 2014(187)
		100, Jamaica	Mean	44±18 (30-85)	-	Rahbar 2015(167)
Pb	<19c	120, India	20 Mean (0.1-100)	-	6.0 (0.1-40)	Sharma 2005(168)
		62, S. Africa	23 Median (6-161)	15(1.4-95)	-	Rudge 2009(169)
		52, Austria	25 Median (10-84)	13(0.2-65)	-	Gundacker 2010(177)
		36, Brazil	14 Median (3.5-58)	13(7.5-26)	-	Rudge 2011(170)
		15, Faroes	Median	6	8.5	Needham 2011(13)
		294, Baltimore, USA	Geo.mean	6.6(2.5-155)	-	Wells 2011(178)
		1652, Shanghai	Median	41 (5-351)	-	Yu 2011(179)
		79, Nepal	Mean	32 (7-221)	-	Parajuli 2012(171)
		1575, Saudi Arabia	2.9 Mean (0.07-26)	2.6 (0.15-56)	-	Al-Saleh 2014(181)
		81, Mexico City	77±40 Mean (17-287)	-	0.8±0.7 (0.4-3.2)	Ettinger 2014(188)
		239, Belgium	11 Geo. mean	8.6	-	Baeyens 2014(173)
		205, China	39 Geo. mean (8.6-137)	32 (2.7-0.157)	-	Sun 2014(189)
		81, China	23 Median	22	-	Hu 2015(174)
		100, Jamaica	Mean	8.0±13 (2-17)	-	Rahbar 2015(167)
		104, S. Korea	10±14 Geo. mean (5-18)	7.1±14 (4.7-16)	-	Kim 2015(185)

		419, Bolivia	19.4 Median (7.8-51)	13.5 (3.8-43)	-	Barbieri 2016(175)
		121, Turkey	Mean	16±16 (<125)	15±12 (<46)	Dursun 2016(190)
Tl	<0.6a	239, Belgium	0.03 Geo. mean	0.02	-	Baeyens 2014(173)
		81, China	0.2 Median	0.04	-	Hu 2015(174)
Cd	<1.0b	120, India	3.0 Mean (0.0-15)	-	1.5 (0.0-7)	Sharma 2005(168)
		62, S. Africa	0.15 Median (0.04-0.9)	0.02 (0.0-0.32)	-	Rudge 2009(169)
		36, Brazil	0.10 Median (0.01-0.6)	0.01 (0.01-0.10)	-	Rudge 2011(170)
		15, Faroes	Median	0.33	0.23	Needham 2011(13)
		94, Nepal	Mean	0.39 (0.2-2.6)	-	Parajuli 2012(171)
		1575, Saudi Arabia	0.99 Mean (0.2-3.2)	0.78 (0.25-15?)	-	Al-Saleh 2014(181)
		237, Belgium	0.31 Geo. mean	0.07	-	Baeyens 2014(173)
		207, China	0.48 Geo. mean (0-3.2)	0.09 (0-0.3)	-	Sun 2014(189)
		81, China	0.9 Median	0.6	-	Hu 2015(174)
		104, S. Korea	0.6±1.5 Geo. mean (0.2-2)	0.01±0.05 (0-0.2)	-	Kim 2015(185)
		24, Turkey	Mean	(0-6.7)? range	0.02-1.6	Dursun 2016(190)
Se	70-130a	62, S. Africa	104 Median (63-203)	111 (50-202)	-	Rudge 2009(169)
		36, Brazil	64 Median (39-97)	76 (53-152)	-	Rudge 2011(170)
		15, Faroes	Median	105	16.4	Needham 2011(13)
		287, Baltimore, USA	Geo. mean	70 (42-114)	-	Wells 2011(178)
		94, Nepal	Mean	175 (92-397)	-	Parajuli 2012(171)
		172, Perth, Australia	102 Mean (37-374)	-	-	Callan 2013(166)
		870/619/602, Italy	117 Median (63-229)	113 (49-279)	18 (4.6-87)	Miklavcic 2013(172)
		426/287, Slovenia	Median	76 (38-194)	17 (1.7-69)	Miklavcic 2013(172)
		219/209/123, Croatia	90 Median (41-182)	96 (55-163)	18 (8.4-49)	Miklavcic 2013(172)
		375/39, Greece	Median	104 (32-229)	21 (0-168)	Miklavcic 2013(172)
		198, China	144 Geo. mean (68-456)	125 (51-225)	-	Sun 2014(189)

[a]Micro Trace Minerals Laboratory (65)
[b]Taylor et al., 2014 (191)
[c]World Health Organization, Geneva

Table 2: Pregnancies: Maternal blood, cord blood and breast milk toxic metal concentrations: averages and ranges, µg/l.

that the fetus encounters its greatest risks in that period. This in itself tends to suggest a toxic nature in that life is then at its smallest mass. In pregnancy, after fertilization, the blastocyst of cells attaches to the uterus with implantation being complete at day 9/10 and the placenta then starts formation. By day 12 the amniotic sac is formed, filled with fluid with the embryo floating and the placenta attached. The heart and blood vessels begin to develop by day 16/17 and the fetal heart begins to pump by day 20 with the first blood cells occurring the next day. At this point, organ formation and location begins and the neural brain plate initiates a folding (neurulation) to form the sealed and protected neural tube containing the brain which mechanism is completed by day 28 [208]. While in embryonic form, protective mechanisms still are not fully understood. It appears that while the placenta is forming, proteins and enzymes in the amniotic sac protect the embryo until the neural tube formation is complete and the neurons are then further protected by a cerebrospinal fluid and the blood/brain barrier (BBB) [209]. The latter is a densely knit layer of cells meant to keep everything out except the transporters of glucose, oxygen and necessary nutrients. Earlier beliefs were that this was immature at formation. Recent work has reassessed and questioned this long held concept, concluding now that the barrier is intact from the start [210]. Moreover, it is claimed that the embryonic brain has functionally effective tight BBB junctions and that some transporters are more active than in the adult brain [211]. In fact some mechanisms are now claimed in embryos that are not present in adults. Any leakages of unwanted chemicals that manage to be transported into the brain are intercepted by numerous metabolic enzymes and effective protein pumps that attach for their eviction [212]. All the organ formation is completed by 8 weeks when the embryo becomes a fetus with brain waves detectable by the 9th week. At this point the fetus weighs only 1 g and has a very small brain that only becomes one-quarter full size by birth time. Nevertheless, once the fetus starts accepting nutrients from the mother via the umbilical cord and placenta, its growing organs will begin to encounter toxic levels of numerous metals. The fetal kidneys and liver remain the initial main filters, but the fetus as it grows will be very dependent on its blood/brain barrier. Because of this, the body and brain genes know to regulate the necessary battery of cysteine and glutathione related enzymes and selenoproteins that can bind to any toxin leaking into the brain and transport this away with p-glycoprotein molecules [213]. These protective brain chemicals also tend to be strong antioxidants that can control inflammatory reactions and have the capability also for DNA repair. The micron size of cells is complex and contain many such proteins and recently these have been compared to nanomachines that have a life force of energy controlled by DNA coding and our genetic being [214]. Nevertheless, fetal malfunctions are actually quite common, and when they occur, generally do so through the initial 8-week period and sometimes before pregnancy is even recognized [215,216]. That the period from possibly day 18 to 28 are most hazardous for the fetus seems to be indicated by the degree of miscarriages and birth defects that occur. There is concern that this is increasing in frequency and that the full extent of its occurrence is not being reported. Data from Brazil indicate that of the 12% of preterm births, two-thirds are spontaneous abortions [217]. In the USA, 17% of pregnancies involve fetal loss, and 50% of such losses remain unresolved [218,219]. Also, about 40% of these can indicate abnormalities and the general consensus is that toxicity rather than genetics is the primary cause. A Polish study in an industrial area indicated that one quarter of the pregnant women in one study had previously had a miscarriage and now 75% of them had very high Hg cord blood (≤ 17 µg/l) [220]. A Korean study noted a higher reproductive risk for women working in the semiconductor industry

[221]. Additionally, cases of anencephaly and spina bifida have been clearly associated with fetal tube closure problems with a prevalence of 1.4% in pregnancies in some heavily industrialized parts of China and are considered a result of metal neurotoxins [7,208]. Autopsies of fetal brains in the heavily ocean-fish eating Seychelles Islands region also clearly indicate the presence of methyl mercury [130,131]. Any leakage through the fetal blood/brain barrier particularly with molecules such as CH_3Hg^+ has some potential for neurological damage.

From animal studies it is well known that the neurotoxic metals in some form can partially cross the BBB. This is also evident in human brain autopsies that monitor all the neurotoxins and toxins considered here [222]. Also, from the data above, it has been seen that the mother's blood can pass neurotoxins through the placenta to the fetus and its organs including its brain. In the case of mercury, for example, its pronounced affinity for sulfur is reflected in its chemistry. Unlike most metals this is much stronger than that for oxygen, but the other periodic table family member is Se for which mercury has an even greater affinity. This has been confirmed in experiments with mice when the presence of Se can attenuate the levels of CH_3Hg^+ in the fetal brain if on an equal or larger atomic basis [223]. Similarly, Se has been shown to reduce toxicity of CH_3Hg^+ and Hg^{2+} in mice [224,225], and is known to be necessary for DNA repair and during pregnancy [226,227]. Selenium appears to have general chelating properties in the body and brain due to its involvement in at least 25 selenoproteins and molecules such as selenocysteine that can provide oxidative stress protection [228]. It has been shown also to alleviate fetal growth parameters and induced Alzheimer's disease with rats fed with traces of $AlCl_3$ [229,230], and similarly with arsenic and mercury fed to rabbits [231]. It reduces Pb induced effects with rats and appeared to provide prenatal human fetal protection against Mn exposure [232,233]. It clearly is a major detoxifier. Consequently, it is apparent that the fetal brain is permanently at risk. It is fully dependent on a regimen of protective chemicals to ensure its safety. However, the basic requirement of this analysis is to understand why this normally automatic behavior has suddenly changed. Of the known neurotoxins only two appear to satisfy the required criteria. These are Al and Hg, and now merit final analysis.

Autism and Genetic Changes, Which Comes First?

Over the last decade it has been realized that the condition of autism no longer has a specific genetic cause but is one of an immune and neuro-inflammatory disorder resulting from environmental toxins and impaired detoxification mechanisms [234]. Moreover, it may be on a scale of severity that relates to the time period of the aggravating mechanism. Autism now has been shown to be neither inherited nor run in families as a result of their genetic similarities [235,236]. There appears to be certain randomness in its occurrence as seen by its distribution over a broad population. Moreover, human genetic susceptibilities cannot make sudden changes that can explain the epidemic nature that has been observed. However, if damaged, genes can display change. Additionally, it remains uncertain that the concept of genetic susceptibility concerning metal toxicity even exists [237]. To relate child behavior at age two to the *APOE* genotype in cord blood as recently reported is not simple [238]. The group with high mercury cord blood levels later displayed behavioral changes, but the statement that this gene modified the toxicity of the methyl-mercury has to remain very speculative. There are now many hundreds of publications addressing the nature of autistic individuals and although interesting their observations actually can add very little to this current assessment. Many studies of course are directed to establishing a useful biomarker for autism. Otherwise, the value in their many comparisons between autistic and neurologically unaffected children becomes rather debatable. Since autistic children are operating on an altered genetic basis this is rather an apple/orange comparison and cannot be meaningfully analyzed. The fact that some autistic children have modified levels of trace elements simply confirms the change that has occurred in their DNA and body chemistry. Moreover, genetic analysis of autistic children examines their current state and can only examine their modified DNA structure. This would seem not capable of providing any causal information or when or how damage occurred. Changes modify their digestive and different dietary needs [239] as well as result in possible seizure and sleeping disorders. Because of this, it would seem, as with thalidomide babies of the past that damage has occurred in this case during the brain formation period. However, due to the body's remarkable ability for protection, repair and survival, autistic babies are born and live. They have suffered some damage and have been modified to a differing life state. Realistically, present suggestions of cures are insincere and of minimal probability. Rather, as is currently being developed by the mothers, acceptable new life styles are emerging that are compatible with these children [240]. No different from diabetic or gluten intolerant individuals, they need to find ways to make their bodies function better to permit a tolerable and meaningful life. Additionally no two autistic children are exactly alike but they are each a normal autistic child defined by its own DNA. For many, dietary changes to gluten, casein free and low sugar content and re-establishing appropriate bacteria and intestinal enzymes in their digestion appears to be most beneficial. The myriad of data currently collected on autistic children generally only reflects the degree of change that has occurred. It does not indicate whether the body is deficient or abundant in anything. That can only be re-established by trial and error, it is now a different body from that normally accepted as average [241-244].

Hair has become a useful biomarker as an alternate for blood analysis for several metals and particularly for mercury where the two are well correlated, with blood being a real time measure and hair an integral of the recent period. However, for young autistic children it can be deceptive although in some cases excretion via the hair can be impaired. Measures of an autistic baby's first haircut and later confirmed, indicated reduced mercury in the hair, the most reduction correlating with greatest severity of autistic symptoms [245]. However, this marker seems to die out with age and one study of 15 sibling pairs, 2-6 years old, having one normal and the other autistic showed no difference in hair mercury [246]. Other studies have shown inconsistencies with sometimes higher and sometimes lower metal levels and a lack of correlation [247-250]. From a chemical and scientific analysis of the data it would seem that autism may simply be a randomly induced effect of a neurological toxic overdose. What is seen genetically is the aftermath of this calamity and not a pointer to cause.

An autistic Epidemic: Why Now?

That autism's rate of occurrence has increased is evidenced in the number of publications addressing this situation, and the fact that Volume 1 of the journal *Research in Autism Spectrum Disorders* published by Elsevier appeared in 2007. As indicated at the beginning of this assessment, the most important clue to resolving its cause is to explain the trigger in its growth that occurred in the 90s and that is still present today. Also, rates of autism appear to be the largest in America, China and Japan. Because this is an occurrence with an outcome of neurological damage it most likely has to be caused by an anthropogenic neurotoxin and be ingested by the body. Moreover, it has to be the most dangerous for the fetus in pregnancies but much less

so for adults. It also appears that initial damage is initiated during the gestation period and first year of childhood when the brain is growing rapidly to three-quarter full size. Because a global aspect appears to be involved, this assessment has heavily emphasized chemistry particularly as genetic involvement clearly is a secondary component. Moreover, a global solution is necessary and requires an overview of all conceivable aspects. Several major global factors now have been identified that together would appear sufficient to be acceptable on a scientific basis. These explain why the testing of single causes has never yielded strong correlations; it appears that multiple causes collectively carry the blame.

As extensively detailed above, by elimination, only the two neurotoxins Al and Hg adequately fit the necessary criteria. These two elements are very different chemically as outlined earlier. Until its re-introduction into about eight or so of the major children's vaccines as a replacement adjuvant for mercury, the only concern with Al in diet centered mainly on long-time accumulation and possible relevance to Parkinson's and Alzheimer's diseases. Now, the body burden for aluminum has been changed significantly for 2-6 month old infants in a critical period of maximum brain development. It has been proven that there is a carrier for aluminum through the BBB with a slow efflux mechanism. This is a higher load than at other ages due to body weight considerations and the vaccination frequency schedules for different countries also is consistent with their reported occurrence levels of autism. One assessment considering the vaccine content of from 125-625 μg Al/dose concludes that Al in vaccines alone can be an at risk situation for young babies [82].

Mercury's main entrance into the body is by one of three major sources; tooth amalgams, vaccines and fish in the diet. Interestingly, although quite different they all require the body to eliminate them. As two authors asked, "is there a safe level for mercury?" [9]. It is a good question when you regard toxicity as a dose/body size/residence time mechanism. Mercury has the ability to damage or kill cells so that even if concentrations are below the NOAEL toxicity level dosages (No Observable Adverse Effect Levels) this does not account for any short-time presence and cumulative aspects. Additionally, in certain molecular forms, mercury is one if not the most neurotoxic metals known that has ready access to the body. As reviewed above, tooth amalgams do release inorganic elemental Hg into the body organs and blood. Even if oxidized to the divalent ion Hg^{2+}, although free to pass through the placenta, evidence implies it cannot penetrate either the adult or fetal blood brain barrier and is even minimized in breast milk. It is a toxin, and treated so by the body, flushing it from the various organs with a half-life of about 45 days but adding to the body's many tasks. In studies of mercury vapor toxicity long term signs of neural loss were not apparent [111]. As a result, of the three sources of mercury, tooth amalgam is of minor concern but still an unnecessary toxin.

The two other sources of mercury are most intriguing in that although from totally different sources they are remarkably complimentary. This arises from the fact that they become closely related producing the organic ions in the body of $HgCH_3^+$ and $HgC_2H_5^+$. Reluctantly holding on to its presence in numerous vaccines, thimerosal is the water soluble sodium salt of thiosalicylic acid, that has its -SH group substituted by $-SHgC_2H_5$. It has been the predominant adjuvant and preserver in vaccines for more than half a century. Its dilemma has resulted ironically from the great success of vaccines. As seen in Figure 3, although in 1975, a childhood regimen of inoculations in the USA was about 10, it is now moving above 40, necessarily requiring more frequent physician visits and often involving multi-doses given at the same time. This is currently close to twice the number of inoculations of any other Country [251]. The fact that blood mercury levels appear to rapidly revert to normal after an inoculation, as do urine and stool samples, was what alleviated concern over its safety [252-254]. Now it is realized that thimerosal metabolizes to free $HgC_2H_5^+$, a strong neurotoxin, that being organic manages to permeate into the brain. There it has been shown to have a possible half-life of about 24 days before being transported out. Another problem that arises is that during this time a reasonable percentage de-ethylates leaving Hg^{2+} in the brain that then has difficulty in egress and has a lengthened half-life of at least several years [104]. Consequently, it is clear that the fetus, with its small mass and a cord blood level that certainly can be high, is easily placed at risk. Published assessments that have estimated this level of risk readily conclude it outweighs and can question any benefits [9,255,256]. An additional study that implied fetal risk involved the practice of systematically inoculating pregnant women with a thimerosal flu vaccine to protect the fetus from any potential viral damage. Due to the nature of flu risk in the 2009/2010 season a double inoculation was recommended. The study examined the normal reported fetal losses through the prior period 1990-2008 and for the following 2010/2011. The disturbing results were that the two separate injections in the 2009/2010 season increased a normal low average value for fetal losses by far more than an order of magnitude and could only be explained by a synergistic effect using thimerosal based vaccines [257]. Consequently, it was prudent for the medical profession to begin to remove mercury to alleviate public concerns that were actually based on very plausible published analyses. However, with ever increasing recommendations of vaccine regimens it has been noted that mercury inoculation loads still remain very high [258]. Hopefully, mercury will continue to be removed soon from all vaccines within the US and also from those currently exported that do still contain mercury. The evidence is overwhelming that it is prudent and moral to remove all toxins from vaccines administered to all young people and all women until menopause. However, the problem is that vaccines are not the only player on the field which has always been the only consideration.

Possibly of even greater concern is the methylated mercury that bioaccumulates in fish. It is known to be highly toxic like its ethylated form but the two do differ in various neuro-kinetic ways. $HgCH_3^+$ has a longer half-life in the blood (19 days) and brain (60 days) [123,129]. Its concentration can be 3 times larger in the brain for equivalent dosages but it de-methylates less (about 10%) so each tend to leave a reasonable fraction of inorganic Hg^{2+} behind for long periods. As noted already, fetal brain autopsies have confirmed mercury's presence and that it can pass through the fetal BBB [130,131]. Mechanisms of its neurotoxicity have been examined and illustrate its possible damage and death to neural cells by oxidative stress, and its detoxifying mechanisms noted with -SH groups on cysteine type enzymes [259]. Consequently, fish in diet has come to the forefront with even adults now quite commonly being diagnosed with mercury poisoning [45]. As indicated in Table 1, many adults do have blood levels significantly above EPA's suggested safe blood level of 5.8 μg/l although it is to be remembered that this value is about 10-fold below what is thought to be the NOAEL level. However, in these dietary mercury poisoning cases, adults with blood levels of 90 μg/l and children whose blood values are 40-fold the national mean value have been observed [45]. This is an undeniable societal change and in recent years doctors have had trouble in recognizing and accepting mercury toxicity due to its previous rarity [260]. I can document the case of one woman who had to fly to a better equipped hospital before they would finally acknowledge her case of mercury poisoning induced by a fish diet.

In the US two things have influenced a greater consumption of

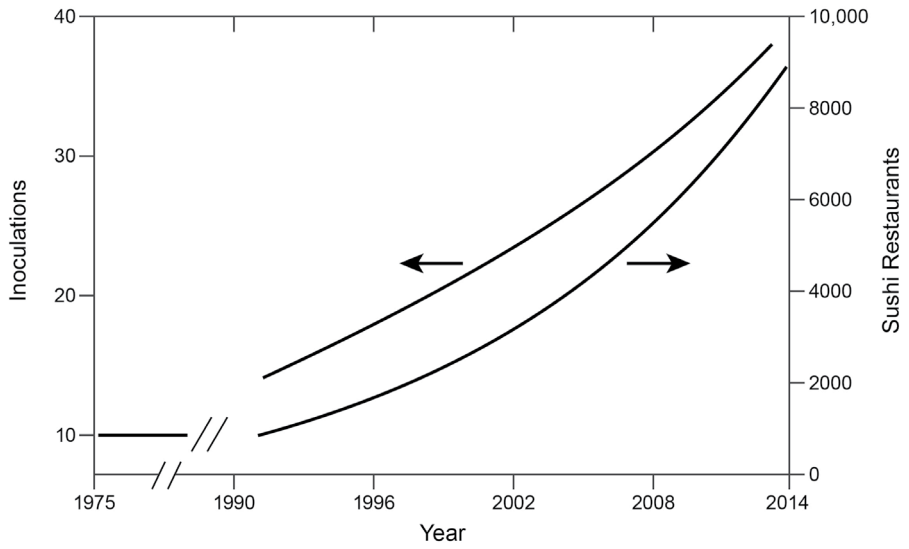

Figure 3: Annual growth rate of the number of childhood inoculations (0-16 years) and the number of Sushi restaurants in the United States.

fish. One is the concern involving health, exercise and weight control. Gymnasiums have opened everywhere and many young people have embraced frequent exercise and a greater concern over diet. Coupled to this, and in the correct triggering period with respect to autism, is the wide acceptance of the Japanese Sushi culture of eating fish. In particular, this includes eating the larger predatory varieties such as tuna, known to be dangerously high in methyl mercury content. Sushi has become extremely popular and one publication labeled the USA as now a "Sushi Nation". Fish matched the health aspect of being nutritious with less sugar, less fat and with fewer calories. Introduced slowly in the early 90's, sushi restaurants, a more social environment for eating fish delicacies, have grown very rapidly in the USA over the past 20 years with now possibly 9000 restaurants and also an equivalent number of food supermarkets selling sushi products. It is reported to be a business with an annual 15% growth rate and this for previous years is approximately indicated in Figure 3. Global fishing of tuna has always been popular but now the annual catch has risen to 4 million metric tons. Eaten as fresh fish, this is consumed mainly by Japan (80%) with 9% in America. Other widespread consumption is of canned tuna: for example, USA (24%), Japan (9%), UK (9%) and Spain (9%). Sushi has become popular globally and its consumption has been indicated as having a 300% growth in the UK over the past 5 years. Few studies yet have emerged assessing this cultural change. However, two that were noted conclude that sushi consumption does in fact pose a potential risk for mercury exposure, and that similarly canned tuna varieties need Governmental regulation particularly for the safety of pregnant women and infants [261,262]. Measurements of fish clearly indicate that not only have mercury levels increased in tuna over the past 50 years but that it has contributed the most to dietary mercury exposure [263,264]. Additionally, the monitoring of avid seafood consumers has shown that their blood mercury levels are significantly elevated [265]. With such consumption, and the current knowledge that CH_3Hg^+ is readily absorbed and can be transported into the brain, the question arises why we are not observing an even greater epidemic of neurological problems.

Because of prior concerns over the risks associated with mercury, several decades-long studies have been in place particularly monitoring those societies such as in the Faroe and Seychelles' Islands. In these locations, people live predominantly on a seafood diet rich in whale meat or ocean fish, respectively, that have significant mercury content. Such studies in fact formed the basis of the current NOAEL level that is used in dietary directives. What has become apparent in these groups with high blood mercury content is that the body has numerous mechanisms for moderating methyl-mercury levels and transporting it from the brain and body. Mercury is an unusual element in that it has a low affinity for oxygen but has significant affinities for oxygen's other family elements of the periodic table, namely sulfur and selenium. The main chelating molecules to treat mercury poisoning historically introduced the term mercaptan into organic chemistry. This nomenclature now structurally implies the presence of an –SH group. Such thiols or dithiols are valuable for treating inorganic mercury toxicity and aid in cleansing the body, which with this element remains very demanding [266,267]. Nevertheless, such molecules are present and produced constantly in the brain as, for example, cysteine ($CH_2(SH)CH(NH_2)COOH$), an amino acid. This also is the precursor for the glutathione enzyme that has a similar -SH group, and is a major egress transporter of many neurotoxic metals that get into the brain. For a long time, selenium, although a neurotoxin itself has been known to be very beneficial to the healthy body and is always present in blood. In fact deficiencies can be a concern [227]. It also exists in the brain in the form of more than 25 selenoproteins important in maintaining cellular balance and as transporters [233]. These proteins together with glutathione enzyme are known to be heavily involved in mercury and toxin removal from the body [213]. Earlier in the Faroe Islands, the possible role of selenium in such a protective manner was discounted in one study, a result possibly disguised by the high levels of each [268]. However, the importance of selenium with respect to mercury now seems to have been proven beyond doubt in numerous detailed studies utilizing rats. Administering ^{82}Se enriched sodium selenite with mercuric chloride in equal molar quantities indicated their bonding onto a protein [269]. Another study fed rats a diet either rich or deficient in Se with either no, low or high levels of methyl-mercury confirming selenium's protective mechanism. Moreover, a reversal of toxicity was noted on switching from a low to rich Se diet [270]. One study had pregnant rats fed methyl-mercury cysteine and seleno-methionine throughout gestation, the two amino/mercaptan type structures of Hg and Se found in fish. Several sets of rats

were compared that were either controls, fed only Hg or Se, or fed with a Hg:Se atomic ratio less or greater than unity. The results confirmed the protective nature of having an excess of Se [223]. Most recently a very extensive study repeated these concepts and similarly fed rat pups, 14 days old, for 10 consecutive days. Some had a high dose of the methyl mercury-cysteine to ensure neural degradation and/or also some with the highest dose possible of the seleno-l-methionine. Four groups of pups were studied: controls, those fed with only the mercury, those fed only selenium and those fed both mercury and selenium [271]. Brain cerebrum content was analyzed on day 11. Those fed predominantly Se showed high brain content indicating efficient uptake by the brain with no neural damage. Those fed methylHg showed very significant neural brain damage in a selective rather than uniform distribution. Those co-exposed to both the mercury and selenium showed no neural damage at all. Also, the data indicated brain Se higher in the co-exposed pups than for those with Se only and that the Se did not prevent methylHg uptake by the brain. In fact brain total mercury had increased (1.4 times higher) and inorganic brain mercury level (1.9x higher) than seen with mercury feed only. Clearly, over the 10 day period of daily administration some demethylation was occurring and the selenium had sequestered and neutralized the potency of the methylHg and inorganic Hg^{2+} by attachment for either egress transport or longer term quarantine. This method of feeding could also be disturbing any partial balance across the brain and through the time period letting more mercury and selenium through with continual demethylation. These studies would now appear to provide some explanation as to why numerous people are exhibiting high blood mercury levels with apparently no consequence. It has implications concerning the types of fish eaten and helps to explain differences seen between the Faroe and Seychelles studies. The former group primarily consumes whale meat that has an approximate Se:Hg molar ratio of about 0.25:1.0 whereas the latter eat ocean fish with an Se:Hg ratio with Se 5-20 fold larger than Hg [272]. This also has importance for regions such as Australia and New Zealand that consume shark and its particular magnitude of the Hg:Se ratio [273,274]. One risk-benefit analysis for Portuguese blue shark with low Se levels concluded it should be eaten no more than once per year [275]. This Se effect has also been noted in Japanese whaling regions [276]. Due to the factor of 2.5 difference in their atomic weights, similar concentrations measured in mass units for Hg and Se will imply 2.5 times more atoms of Se are present. Referring back to Table 2, it can be noted there that the pregnancy blood ratios in most cases is Se>>Hg which undoubtedly is the cushion of safety embraced by a fetus. A recent UK study providing pregnant women with either a placebo or a 60 μg/day Se supplement confirmed its health benefits by reducing hypertensive conditions [277]. Similarly, a double blind study on elderly patients provided with Se and CoQ10, two anti-oxidants clearly indicated their improved health [278]. Nevertheless, too high a dosage of sodium selenite produced toxicity in adult mice and their pups [279]. Consequently, although there are nutritional benefits for the mother and fetus due to the poly-unsaturated fatty acids in a fish diet, this now is becoming a delicate balancing act with the contents of Hg and Se neurotoxins known to be dangerous. As a result, a pronounced dilemma is that pregnant mothers require careful counseling on what is acceptable on the side of safety [280,281]. It would appear that considerations of both Hg and Se fish content are important but still there is a need to bias to eating the smaller fish with lower Hg content [282-288]. Suggestions that a high fish diet has health benefits that outweigh the toxicity cannot be accepted by anyone at present without these further considerations [289-291]. Also it would seem that relying on the body to efficiently always maintain its housekeeping may be a risk not only at the beginning of life but throughout.

Autism, Probable Causal Occurrences and Corrective Suggestions

Because the environment is full of toxic and neurotoxic molecules it has been felt that the cause for autism might continue to remain a mystery. This certainly would have been true if the triggered start of the epidemic had not been so evident. However, sifting through all the possible chemicals few options are seen to fit the facts. Now, only two major contributing factors have emerged that clearly show sufficiently high risk and fit the triggering time frame. As clearly identified in Figure 3, and with the support of numerous previous analyses, the high current levels of inoculations coupled to the global love of sushi would appear to be more than adequate for explaining the rise in autism. From birth to death our bodies are involved in a 24/7 work-load of reducing all toxins from the body under the directions of genetic formulae. If these simply become overloaded by the level of toxicity or fail briefly in any manner, it is obvious from current medical knowledge that neurological damage will rapidly follow. Humans are most vulnerable to toxicity when they are at their smallest. From the data presented herein, it is apparent that the fetal blood can readily rise to toxic levels and from then on the fetus is totally dependent on its blood/brain barrier and the rate of formation of detoxification molecules within the brain cavity. Obviously in most pregnancies these manage to be adequate, but mishaps can occur and it is this that possibly leads to many miscarriages and neurologically damaged children. How the overloading stress breakdown finally occurs, before or after birth will depend on existing baseline body toxic levels and the final disruptive excess that occurs. Whether this results from too high a level of toxicity in the brain that overwhelms the protection or a glitch in the genetically controlled production rates of detoxification molecules has yet to be ascertained. Nevertheless, a causal factor that is hard to deny has been identified. The fact that Alzheimer's neurological disease now also is appearing to result from a fault in brain protein production may also have a similar type mechanism [292].

What can be done? What has been realized herein is no major eureka breakthrough but a final realization of what has been suspected by many for a long time in separate disciplines and through many experiments and analyses. However, nothing has been acknowledged. The Greeks more than 2000 years ago realized such problems introducing the phrase, "Moderation in all things". As seen, we appear to be paying a price for our 21st century life-style coupled to the sins of the past with the love for gold and silver. Each factor involved has to accept that although not singly responsible, the summation of all, possibly with additional synergistic effects of other trace toxins, is sufficient to explain this unfortunate and heart-breaking epidemic.

As currently desired by the United Nations, tooth amalgams should be ended. Even if not a factor in autism it adds unnecessarily to the whole body burden and any less toxin in the body has to be an improvement. Also new safer materials now are available for dentistry. Whether aluminum is safe or not in vaccines, it is a neurotoxin, it adds to body burden, and can enter the brain where it has a reasonably long half-life. The extent of its potential role in autism, Parkinson's and Alzheimer's diseases still remain unknown but it may be a player. Vaccines need to be fully mercury and aluminum free and a reassessment of vaccine policy is desperately required. The regimen of vaccines has become too large, in the US twice that of any other country, is still constantly growing annually, and inoculations are too closely scheduled [251]. Even when adjuvant free they can still have strong adverse reactions on some. They should be toxin free and only the most important given gradually to those in most need. Great care certainly should be taken during pregnancy,

and especially also before, by all women of child-bearing age. Their vaccination schedules should be minimal and sufficiently spaced not to stress the body. In Canada the flu vaccine given to pregnant women is mandated to be adjuvant free. Several countries are now realizing the maternal benefits of immunization against preventable diseases during pregnancy [293]. However, it is imperative that a new generation of adjuvants that are non-toxic be introduced [294-296].

Fish consumption is a more serious problem than most realize and is difficult to resolve. The large carnivorous fish such as tuna, shark, swordfish, mackerel, tilefish and whale that have very high mercury content should not be eaten by pregnant women then or before pregnancy and should be labeled to this effect as being very dangerous [297-299]. Alternate diets can be readily suggested to satisfy any nutritional need. The average adult can possibly tolerate certain mercury levels but long term risks still remain unknown. Now, fish mercury calculators exist on the web to indicate mercury ingestion from what can be listed as eaten. In fish, bioaccumulation is the problem and the older and/or larger fish have higher mercury content. Food preparation and source can vary the concentrations but as indicated in one study this can become dangerous gourmet eating [300]. Mercury content for all fish types now is known and adjustments can be made in fish diets to keep mercury content low. With fish this is not a simple short-lived problem that will disappear. Due to the nature of mercury's past anthropogenic re-cycling, the problem may remain in the Oceans and lakes certainly for this century. China avoids this fish problem to a certain degree by farming about 70% of its fish needs [301]. Other countries may have to do similarly. Canada for one, projects that by 2050, fish advisories may apply to all its lakes [302]. For young women of child-bearing age and those pregnant, it might be beneficial to be tested and establish one's baseline in all the toxic trace metals including selenium in particular and carefully manage this over time.

Hypothesis or Theory?

Medical research is demanding because of the complexities of the body and the difficulty in isolating individual parameters. It depends heavily on large samples and statistical analyses. These may be valuable in establishing major trends but to resolve something as a 1% or less effect becomes very difficult. This is the situation with autism. Its cause would appear to have an infinite number of possible explanations especially in this age of innumerable pharmaceutical drugs, obnoxious chemicals, polluted air and water and genetic engineering. For about 30 years the current autism epidemic has been examined in extensive human and animal studies aided by the rapidly developing analytical monitoring methods. This review has benefited from this wealth of research that has more clearly indicated what may or may not be a contributor.

The major scientific clue has always been the triggered onset and growth rate of autism. Additionally, the witness of people being diagnosed with severe mercury poisoning from eating high fish diets cannot be ignored. It is not too much a stretch of the imagination to ask if this can happen to an adult what it might do to a small fetus. The development of vaccine therapy and the invention of pharmaceutical drugs has been a wonderful achievement lengthening many lives. However, like many things it has to be controlled and regulated especially when toxic adjuvants are added for enhancement effects. Likewise, the fish we eat are now contaminated worldwide in the lakes and oceans and will not return to natural levels possibly for many centuries.

To all of this is the trend of society to believe mainly in single causes. However, it is now being realized that synergism exists and a cause may be the result of several factors. This is certainly the suggested case here where each individual player pleads innocence but does not realize that a collection of contributors, each operating for the benefit of mankind, is resulting in a high price for society. This review began as a hypotheses but the scientific data is very strong and appears to establish it as a theory that now welcomes further examination.

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