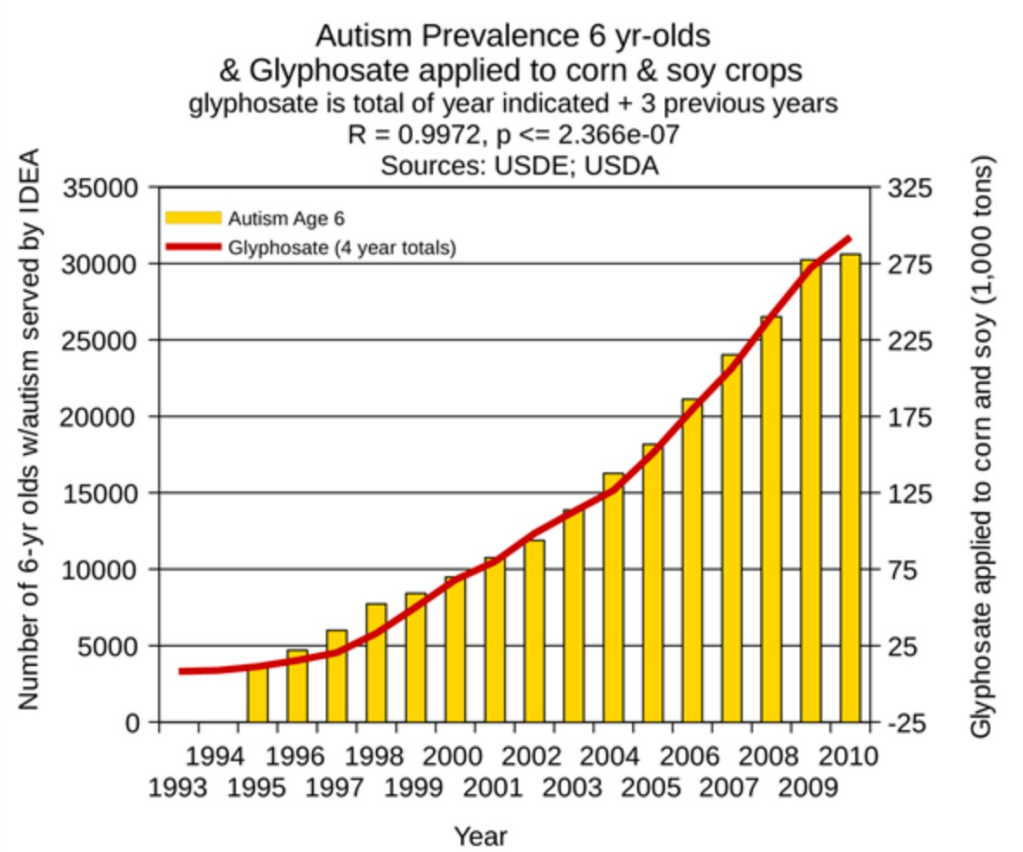
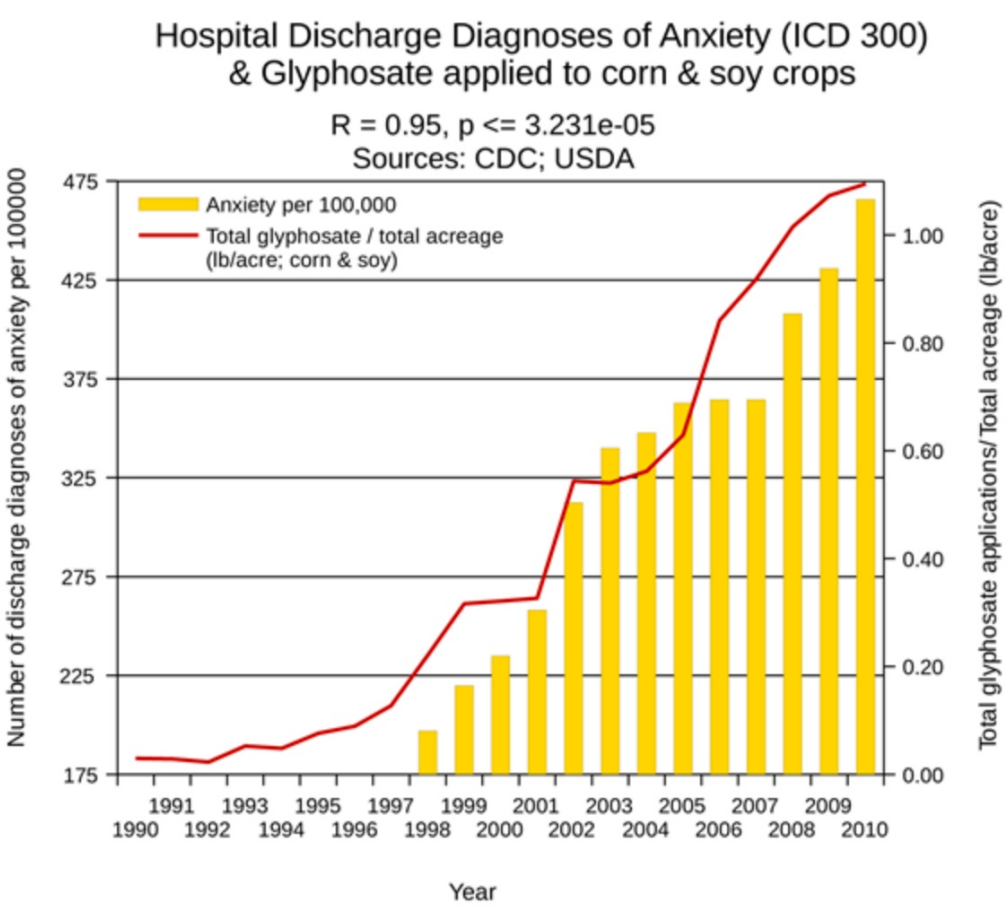
Aluminium and Glyphosate – Synergistic toxins. The melatonin-pineal connection.

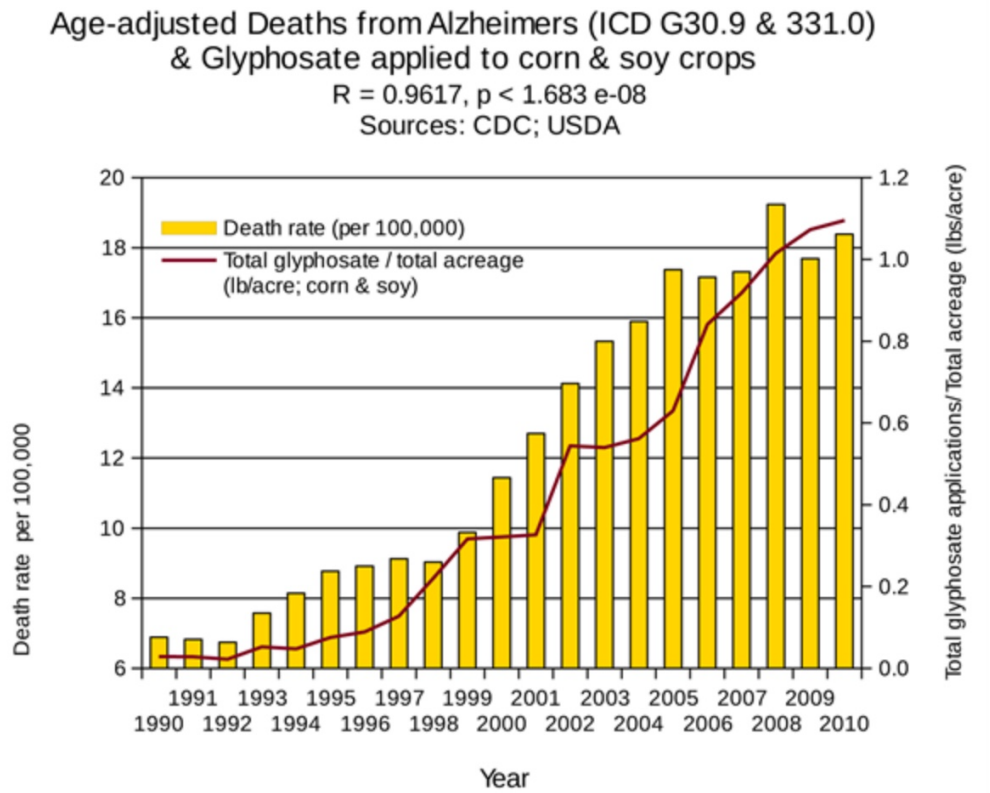
Dr Fiona Dann Ray MSc Applied Toxicology, MSc Chiropractic.

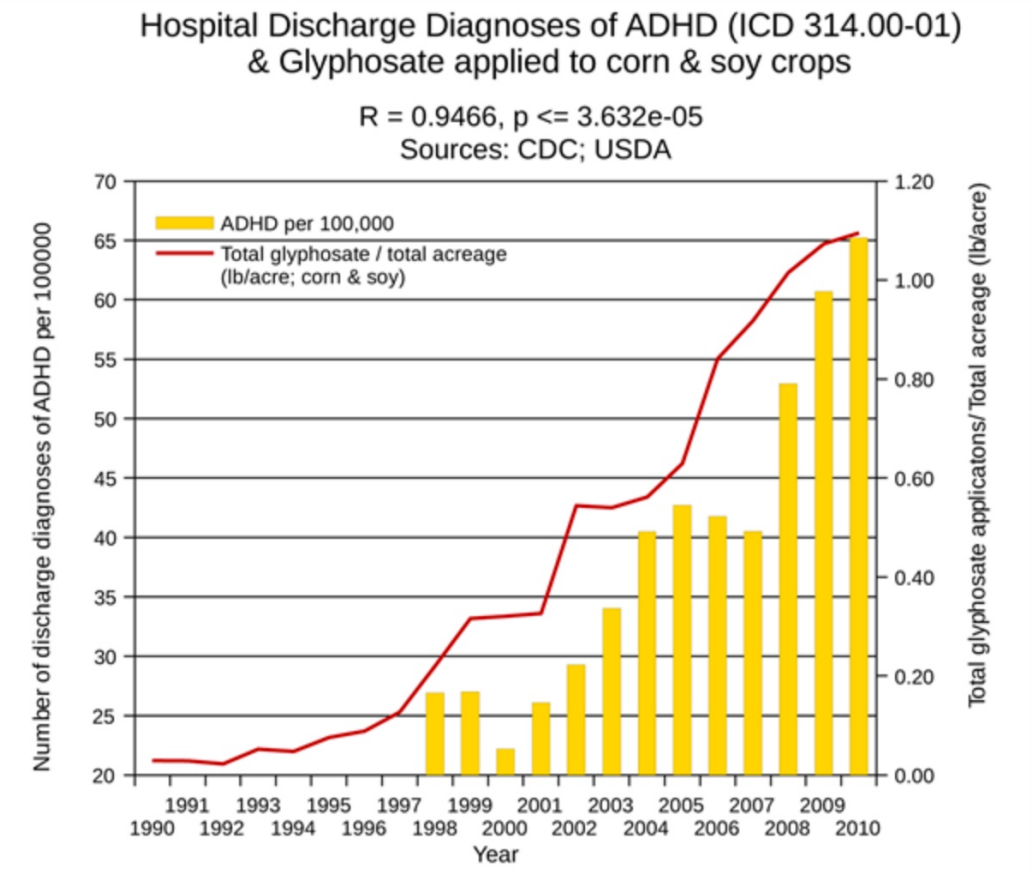
Aluminium toxicity and glyphosate toxicity have both received recent attention as being damaging to human health. Particular concern has been directed toward neurological toxicity. It's not only autism rates that have shown correlation with increased glyphosate use, a whole host of neuropsychiatric disorders, sleep disturbance and mental health issues have too.
These interesting graphs show the problem, with quite a few conditions increasing in line with glyphosate use:

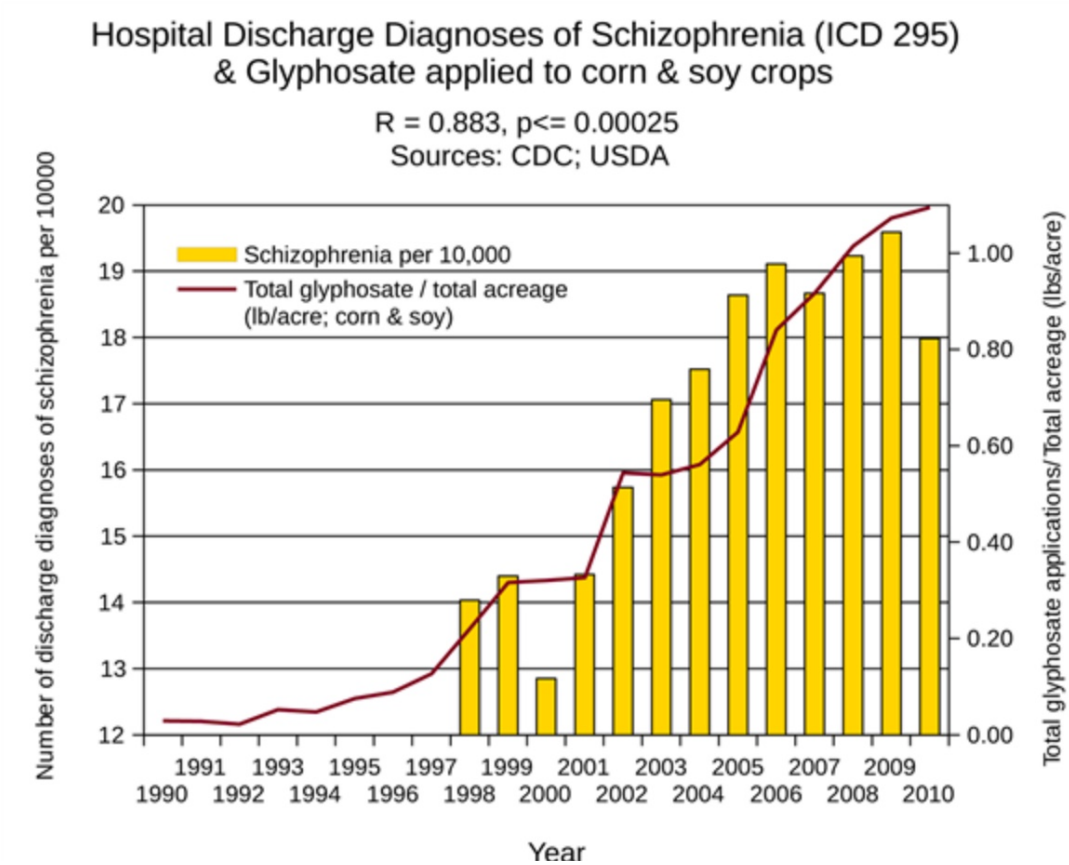


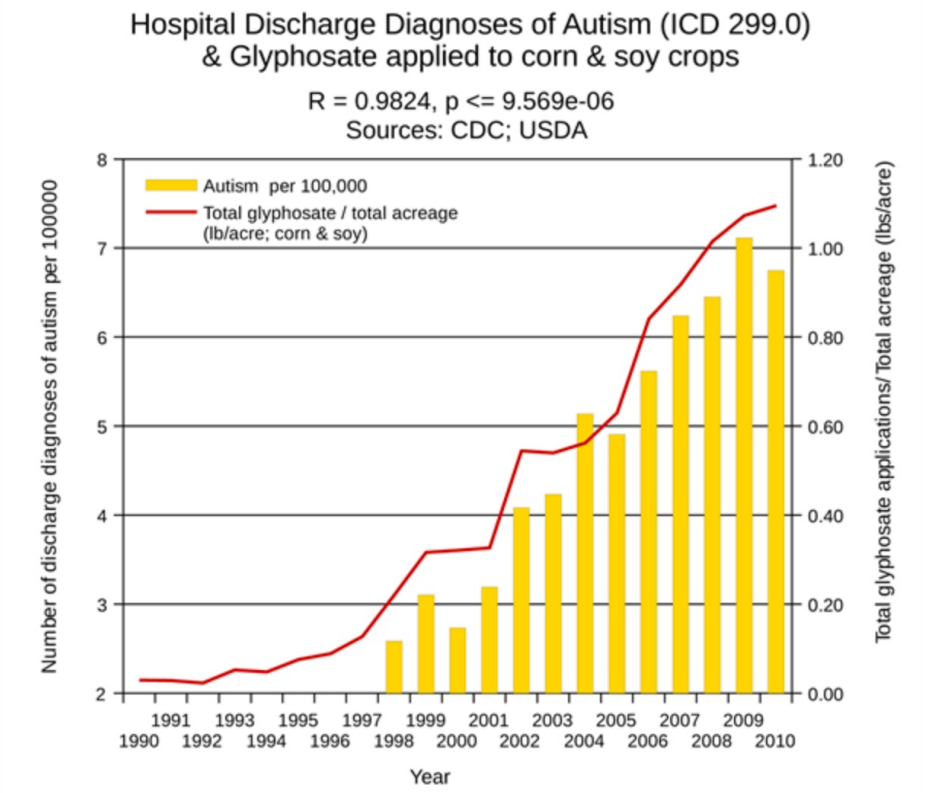
The year on year increase in glyphosate use and Autism prevalence track closely.

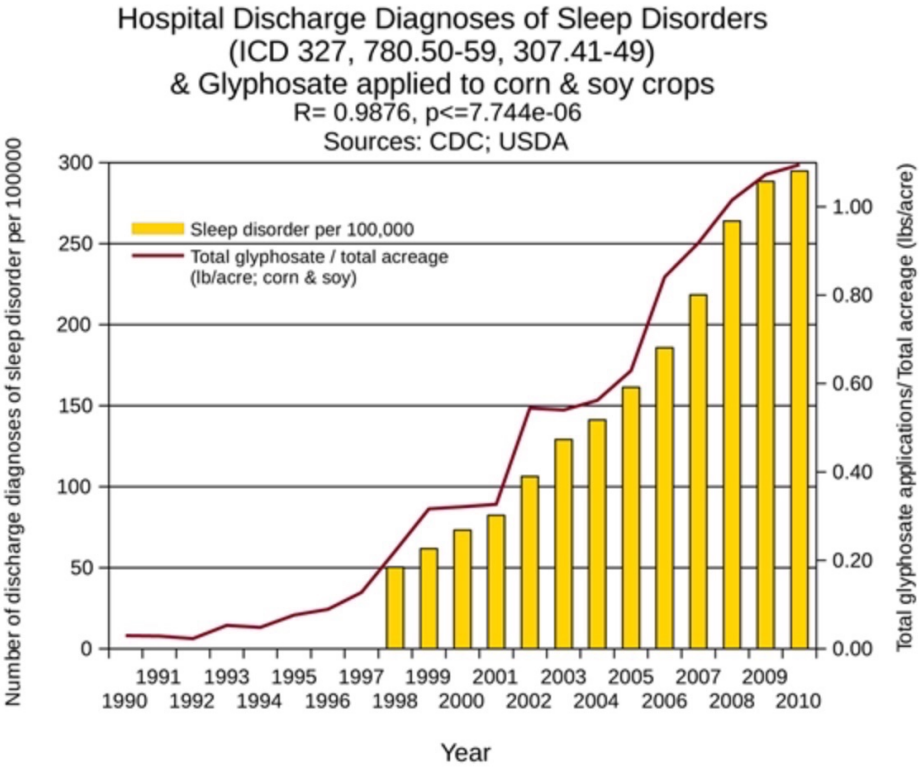

Hospital Discharge Diagnoses of Anxiety (ICD 300)
& Glyphosate applied to corn & soy crops
R = 0.95, p <= 3.231e-05
Sources: CDC; USDA
Anxiety per 100,000
Total glyphosate / total acreage
(lb/acre; corn & soy)
Number of discharge diagnoses of anxiety per 100000
Total glyphosate applications/Total acreage (lb/acre)
475
425
375
325
275
225
175
1.00
0.80
0.60
0.40
0.20
0.00
1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010
Year


Age-adjusted Deaths from Alzheimers (ICD G30.9 & 331.0)
& Glyphosate applied to corn & soy crops
R = 0.9617, p < 1.683 e-08
Sources: CDC; USDA
Death rate (per 100,000)
Total glyphosate / total acreage
(lb/acre; corn & soy)
Death rate per 100,000
Total glyphosate applications/Total acreage (lbs/acre)
20
18
16
14
12
10
8
6
1.2
1.0
0.8
0.6
0.4
0.2
0.0
1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010
Year


Hospital Discharge Diagnoses of ADHD (ICD 314.00-01)
& Glyphosate applied to corn & soy crops
R = 0.9466, p <= 3.632e-05
Sources: CDC; USDA
ADHD per 100,000
Total glyphosate / total acreage
(lb/acre; corn & soy)
Number of discharge diagnoses of ADHD per 100000
Total glyphosate applicatons/ Total acreage (lb/acre)
Year


Hospital Discharge Diagnoses of Schizophrenia (ICD 295)
& Glyphosate applied to corn & soy crops
R = 0.883, p<= 0.00025
Sources: CDC; USDA
Schizophrenia per 10,000
Total glyphosate / total acreage
(lb/acre; corn & soy)
Number of discharge diagnoses of schizophrenia per 10000
Total glyphosate applications/ Total acreage (lbs/acre)
Year



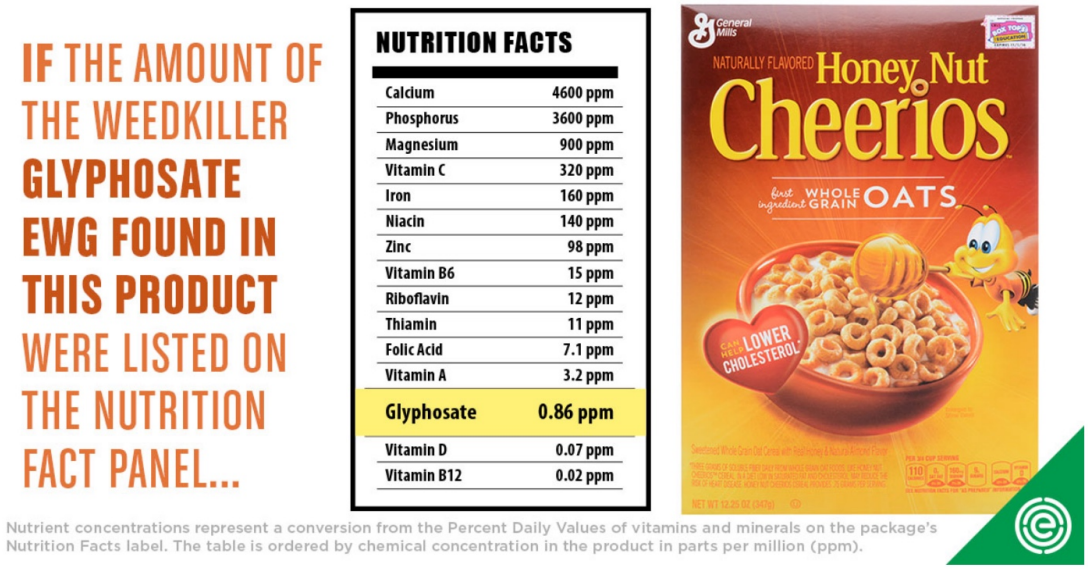


All graphs from Seniff et al 2015[1]

Glyphosate key facts.

Glyphosate is the active ingredient in Roundup, a herbicide and pesticide used everywhere from playgrounds to cereal crops. Many GMO crops such as soy and

corn have been bred to be resistant to Roundup so that the herbicide can be used on them to eliminate other weeds and pests, increasing crop yield. Roundup is often sprayed on grain crops pre-harvest to 'dry' the grain. Residues are not removed by cooking or washing, and are stable for a year or more[2]. Residue of Round-up is found on foods made from sprayed crops. For example, if Glyphosate was included on the nutritional information for a cereal product in the USA, it is higher than several vitamins!
Image from Environmental Working Group [3]



Roundup is a mix of glyphosate, surfactants and other substances. It becomes more toxic than Roundup itself. Indeed the safety studies on glyphosate on it's own found very little toxicity to mammals. These studies have two major issues. They only lasted 3 months, and they studied Glyphosate on its own, not as it is used as Roundup Ready and other preparations[4]. The addition of the other ingredients, many toxic by themselves, changes the effect of glyphosate. When the surfactants (including polyethoxylated alkylamines – POEA's) were studied they were found to be not only toxic by themselves, but worked synergistically with glyphosate to increase the toxicity by at least 125 fold, so 125x more toxic than glyphosate by itself. The author's comment was "Despite its reputation, Roundup was by far the most toxic among the herbicides and insecticides tested"[5], [6].

The Shikimate pathway.

Glyphosate acts on the shikimate pathway, not possessed by mammalian cells. However it is present in gut microbes and in plant cells, potentially disrupting the gut flora and the production of nutrients we depend on, such as aromatic amino acids such as tryptophan, phenylalanine and methionine. Tryptophan is a precursor to serotonin, which is a precursor to melatonin.

Low levels of these amino acids have been seen in the autistic and Alzheimer's disease population. Indeed, plasma analysis in the autistic group found the relative tryptophan level to be low enough to disrupt serotonin synthesis. Low serotonin levels can cause constipation, common in autism, as well as neurodevelopment issues and mental health issues. Increased glyphosate usage tracks the increase in ASD in the USA.

Glyphosate is a known depletor of intracellular glutathione, the major cellular and mitochondrial defense against free radicals. Glutathione levels are generally low in those with Autism.

Glyphosate residues are found in the urine of humans, and in the urine and organs of cows. Similar levels were found in organs as were found in urine, so some retention indicated, and residues were also found in malformed day old piglets[7].

Glyphosate and aluminium – the mechanism of synergistic toxicity.

We are exposed to aluminium on a daily basis through our diet. Aluminium is a very common constituent of soil minerals. The gut has evolved multiple mechanisms to exclude these forms of aluminium and is remarkably good at it. Estimates of aluminium absorption from the gut vary between 0.02-1% of dietary intake for the normal gut[8]. Roundup/ Glyphosate alters this. It is a microbicide. The effect of glyphosate exposure on gut bacteria is to disrupt the normal healthy balance. Indeed, the manufacturers Monsanto were awarded a patent in 2010 for the use of glyphosate as an antibiotic, with beneficial bacteria being more susceptible to it's effects than pathogenic bacteria are[9].

Overall there is an increase in the level of Clostridium difficile in the gut. One of the major toxins produced by C.difficile is p. cresol, which has been implicated in Autism in both human and mouse studies. p.Cresol increases aluminium absorption across the gut via transferrin. Pigs fed a diet of Roundup Ready corn and soy had inflamed stomachs, suggestive of gut dysbiosis. The associated leaky gut would lead to increased absorption of aluminium complexes (Al-citrate, Al- glyphosate) across the gut barrier[10].

Glyphosate also has been shown to be a direct aluminium chelator, forming aluminium cages with glyphosate molecules[11]. It is a similar mechanism to citrate binding of aluminium, that leads to increased absorption across the gut barrier[12], with increased urinary levels seen. It is reasonable to assume, that like calcium – also bound by glyphosate, dietary aluminium reaches the circulation. Increased passage of glyphosate-assisted aluminium across the blood brain barrier is a possible cause of increase in CNS levels of aluminium[13].

Glyphosate, Aluminium and Hypoxia

Glyphosate and aluminium work synergistically to induce anaemia, therefore relative hypoxia, and an increased effect of aluminium on neurons. Hypoxic conditions are common with premature birth, and lead to increased uptake of

aluminium to the pineal gland. Melatonin, which usually protects the pineal gland from the effects of stresses such as hypoxia, is exhausted. The effect on the pineal gland is to increase it's vascular permeability, and vulnerability to serum based toxins such as aluminium and glyphosate, disrupting secretory function, and the availability of melatonin. The pineal gland is rich in transferrin, which is inhibited by melatonin, so hypoxia plus glyphosate would lead to increased aluminium uptake. In preterm infants, where Al exposure form parenteral nutrition is a concern, increased pineal Al levels are a real issue.

Mineral deficiencies of cobalt and iron are key in anaemia. Both are common in Autism. Aluminium absorption uses iron channels as that is it's most similar ion. Ferric reductase, required for iron absorption in humans, has it's function markedly decreased for hours following glyphosate exposure in plants. Aluminium causes inhibition of heme protein synthesis.
Cobalt deficiency is found in conjunction with higher urine glyphosate levels in cows.

Glyphosate, aluminium and liver enzymes
Phase 1 liver detox processes are performed by CYP enzymes. These are heme protein dependant. Aluminium toxicity experiments on rats showed a 50% drop in enzyme levels, mostly due to aluminium replacement of iron at the centre of the heme proteins, rendering them non-functional. Glyphosate also acts against CYP enzymes, via nitrogen bonding to the heme protein. Here too, Aluminium and glyphosate act synergistically.
CYP enzymes are involved in melatonin metabolism, both in plasma clearance and in sulphation of melatonin. Impairment of CYP enzymes would impair sulphation.

Sulphation
In the gut, serotonin is a regulator of gut peristalsis, with low serotonin levels linked to constipation. Serotonin deficiency, as a result of low tryptophan (production of this hampered by inhibition of the shikimate pathway) can be linked to glyphosate exposure.
Children with autism have abnormal sulphation pathways, with very low levels of serum sulphate, and so low levels of sulphur containing amino acids. Studies on E.coli have found glyphosate inhibits enzymes involved in sulphur absorption and use. This inhibition leads to low incorporation of sulphur into biologically active molecules and leads to a pseudo-deficiency of sulphur in crops such as brassicas. It is likely that gut bacteria will be affected in the same way as E.coli.

Vitamin D deficiency is linked to poor CYP function – already known to be inhibited by Glyphosate. Low maternal vitamin D levels are implicated in a higher risk of autism. Vitamin D regulates the reuptake of sulphate in the kidney, with up to 80% reabsorption. Mice with poor vitamin D receptors levels/ function in the kidney had very low glutathione levels, sulphated proteoglycan in the skeleton and 50% lower serum sulphate. Deficiency in sulphated proteoglycans is linked to increase risk of colitis and Crohn's disease. Vitamin D as calcitrol is vital in the correct maturation and differentiation of enterocytes in the crypts and base of the villi. This is a result of Calcitrol's

function in delivering sulphate to the villi to produce heparin sulphate proteoglycans, essential for crypt enterocyte cell function.

Celiac disease, which has increased in incidence has also been linked to Glyphosate exposure. The reduced CYP action associated with Glyphosate has been implicated. Poor liver CYP function results in poor flow of bile acids through the circular pathway between liver and gut. The result of this is system-wide reduction in sulphate levels. Local inflammation to produce sulphate locally[14] is a short term fix with long term harmful effects. Fish exposed to Glyphosate showed reduced levels of digestive enzymes including protease. A major finding was '"disruption of mucosal folds and disarray of microvilli structure" in the intestinal wall, along with an exaggerated secretion of mucin throughout the alimentary tract. These features are highly reminiscent of celiac disease'[15]. Gut dysbiosis due to glyphosate exposure is key in the development of celiac disease. Re-testing of frozen serum samples from the 1940's and 50's compared to matched samples from the 2010's found a four fold increase in antibodies to gluten in the 2010's samples.
Below is a graph of glyphosate use vs. incidence of celiac disease, showing a temporal link between the two.

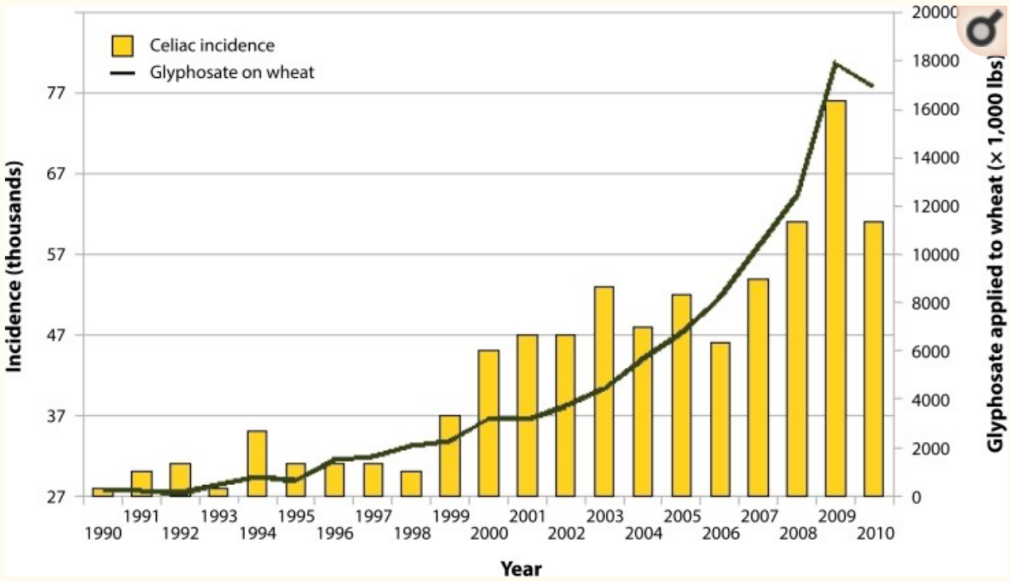


Figure 1

Hospital discharge diagnosis (any) of celiac disease ICD-9 579 and glyphosate applications to wheat (R=0.9759, $p \leq 1.862e\text{-}06$). Sources: USDA:NASS; CDC. (Figure courtesy of Nancy Swanson).

Graph from Samsel et al 2013[16]

Brain Sulphation
Sulphation is also a vital part of brain health. Autopsy studies of Alzheimer's' brains showed the only lipid depleted was the sulphur containing sulfatide (myelin-specific sphingolipids)[17]. Children with autism have reduced heparin

sulphate in brain ventricles. Mice engineered to be deficient in heparin sulphate have all the features of mouse autism, and low serotonin in early brain development produces findings typical of autism such as 'fewer dendritic spines and reduced synaptic density, as well as excess cortical brain growth'[18].

The enzymes TPH1 and 2 synthesise serotonin from tryptophan. Vitamin D activates TPH2, which is the brain version and supresses TPH1 –the version outside the brain. If TPH1 is not supressed during development it effectively traps tryptophan outside of the brain, leading to a serotonin deficiency within the brain, and decreased levels of regulatory T-cells that protect the babies brain from attack by maternal antibodies. Boys are more vulnerable to TPH1/2 dysregulation, as oestrogen has a role in stimulating serotonin. This could well account for part of the sex difference in autism diagnosis.

Pineal Gland and sleep.

Sulphation is vital to the functions of the pineal gland. Supplemental melatonin taken up in the brain is almost all 6-hydroxylated and then conjugated with sulphate[19]. Pinealocytes when exposed to light in daylight hours upregulate the enzyme sulpherotransferase and boost their sulphur levels, then release sulphated melatonin at night. The median eminence has the highest level of melatonin receptors. It is next to the optic chiasma and hypothalamus. In people with autism, this area of the brain has a reduced level of grey matter, which would lead to disrupted pituitary function.

Melatonin, in addition to it's regulation of the sleep/wake cycle has neuroprotective properties, metal binding ability, and stimulates antioxidant enzymes. It stimulates ATP synthesis at the inner mitochondrial membrane. It is protective against oxidative stress and nitrosative damage. Aluminium taken up into the brain exacerbates iron-induced lipid peroxidation in the lysosomes (responsible for clearing cell debris). Melatonin is protective against this, and is also an aluminium binder. Reduced melatonin levels may well increase brain vulnerability to aluminium. The precursors to melatonin are tryptophan and serotonin, both of which are impacted by glyphosate.

The pineal gland is rich in nitric oxide synthases (eNOS ,nNOS and iNOS), with nNOS being expressed on a diurnal cycle for sulphate synthesis.
Aluminium does bio-concentrate in the pineal gland, binding to calmodulin at a far higher binding affinity that calcium can. This will adversely affect sulphate synthesis and melatonin production. The effect of the aluminium binding is to cause eNOS to detach from the membrane and switch to nitric oxide synthesis, instead of the sulphate synthesis that is needed by the pineal gland.

The pineal gland is also very vulnerable to calcification, which happens with increased age, and hampers the ability to accumulate sulphur during the day. People with Alzheimer's disease had 20% of the normal level of melatonin for their age, and also had far more calcification of the pineal gland.

Pineal gland function, given it's role in melatonin synthesis, regulation and transport is key for good quality, well regulated sleep.

Sleep has been postulated to be a time of removal of cellular debris, misfolded proteins and oxidised lipids. Increased interstitial space is seen during restorative sleep, with increased convective exchange of cellular and interstitial fluids, with increased Beta amyloid clearance[20]. Sulphation as the presence of heparin sulphate is vital for proper endocytosis and debris clearance and digestion through the endosomal-lysosomal pathway.

Poor pineal function and the associated poor sleep and poor supply of sulphate to the brain is a cornerstone of many neurological diseases and the associated sleep issues that are commonly seen with them. Aluminium and glyphosate, working both synergistically on the same pathway and by working on different pathways that then have an amplified effect cause major disruption and toxicity to the body and brain.

Summary

Aluminium and glyphosate have toxic effects in their own right, but together have a much greater synergistic toxicity.
The effects of Glyphosate on the gut such as inflammation, reduction in tryptophan and so serotonin and melatonin levels, villi damage, dysbiosis, increased Clostridium levels and increased gut permeability alongside increased aluminium transport across the gut in to the blood is just the start.
In the liver the inhibition of CYP enzymes, the reduced bile acid circulation, the effects of Al replacing Fe and the relative anaemia and hypoxia that can ensue adds to the damage.
Then in the brain, the pineal gland calcification, aluminium absorption, poor removal of cell debris and disruption to melatonin production due to the glyphosate induced damage to Sulphation pathways add up to increased damage with decreased protection.
This is a toxic mix for everyone from the gestating foetus to the elderly.

So what can you do?

1) Eat organic. Cereal crops are particularly heavy in glyphosate as they are sprayed just before harvest to help the drying process. Any crop seed sold as 'Roundup Ready' is also likely to have high residue levels – soy, corn etc. An experiment on a Swedish family found that eating organic dropped the glyphosate levels in their urine by a significant amount
2) Chlorella. Ultra micronised chlorella can cause an increase in urinary excretion of aluminium.
3) Increase intake of sulphur rich foods and supplements (NAC, MSM). A word of caution, some people may feel worse if given sulphur containing supplements – for some who have a genetic variant causing fast processing of sulphur, they produce a lot of ammonia, then get symptoms from that – confusion 'leaky brain' etc. For these people avoid sulphur supplements.
4) Supplement Melatonin
5) Supplement Glutathione (liposomal/ dermal)/ NAC
6) Detox – chelation of toxic metals and chemicals.

References:

[1] Seneff, S. , Swanson, N. and Li, C. (2015) Aluminium and Glyphosate Can Synergistically Induce Pineal Gland Pathology: Connection to Gut Dysbiosis and Neurological Disease. *Agricultural Sciences*, **6**, 42-70. doi: 10.4236/as.2015.61005

[2] Morley W. A. (2018) Environmental Subconcussive Injury, Axonal Injury, and Chronic Traumatic Encephalopathy. *Frontiers in neurology*, *9*, 166. doi:10.3389/fneur.2018.00166

[3]https://cdn3.ewg.org/sites/default/files/u352/EWG_Social_Share_HoneyCheeriosGlyphLabel_PP07.jpg

[4] Seneff, S. , Swanson, N. and Li, C. (2015) Aluminium and Glyphosate Can Synergistically Induce Pineal Gland Pathology: Connection to Gut Dysbiosis and Neurological Disease. *Agricultural Sciences*, **6**, 42-70. doi: 10.4236/as.2015.61005.

[5] Mesnage, R., Bernay, B. and Séralini, G.E. (2013) Ethoxylated Adjuvants of Glyphosate-Based Herbicides Are Active Principles of Human Cell Toxicity. Toxicology, 313, 122-128. http://dx.doi.org/10.1016/j.tox.2012.09.006

[6] Mesnage, R., Defarge, N., de Vendômois, J.S. and Séralini, G.E. (2014) Major Pesticides Are More Toxic to Human Cells Than Their Declared Active Principles. BioMed Research International, 2014, Article ID: 179691

[7] Seneff, S. , Swanson, N. and Li, C. (2015) Aluminium and Glyphosate Can Synergistically Induce Pineal Gland Pathology: Connection to Gut Dysbiosis and Neurological Disease. *Agricultural Sciences*, **6**, 42-70. doi: 10.4236/as.2015.61005.

[8] DeVoto, E., & Yokel, R. A. (1994). The biological speciation and toxicokinetics of aluminum. *Environmental health perspectives*, *102*(11), 940–951. doi:10.1289/ehp.94102940

[9] Morley W. A. (2018). Environmental Subconcussive Injury, Axonal Injury, and Chronic Traumatic Encephalopathy. *Frontiers in neurology*, *9*, 166. doi:10.3389/fneur.2018.00166

[10] Froment, D.P., Molitoris, B.A., Buddington, B., Miller, N. and Alfrey, A.C. (1989) Site and Mechanism of Enhanced Gastrointestinal Absorption of Aluminum by Citrate. Kidney International, 36, 978-984. http://dx.doi.org/10.1038/ki.1989.290

[11] Purgel, M., Takács, Z., Jonsson, C.M., Nagy, L., Andersson, I., Bányai, I., et al. (2009) Glyphosate Complexation to Aluminium(III). An Equilibrium and Structural Study in Solution Using Potentiometry, Multinuclear NMR, ATR-FTIR, ESI-MS and DFT Calculations. Journal of Inorganic Biochemistry, 103, 1426-1438. http://dx.doi.org/10.1016/j.jinorgbio.2009.06.011

[12] Coburn, J.W., Mischel, M.G., Goodman, W.G. and Salusky, I.B. (1991) Calcium Citrate Markedly Enhances Aluminum Absorption from Aluminum Hydroxide. American Journal of Kidney Diseases, 17, 708-711. http://dx.doi.org/10.1016/S0272-6386(12)80356-8 [Citation Time(s):1]

[13] Shaw, C.A. et al., 2014. Aluminum-induced entropy in biological systems: Implications for neurological disease. *Journal of Toxicology*, 2014.

[14] Samsel, A., & Seneff, S. (2013). Glyphosate, pathways to modern diseases II: Celiac sprue and gluten intolerance. *Interdisciplinary toxicology*, *6*(4), 159–184. doi:10.2478/intox-2013-0026

[15] Samsel, A., & Seneff, S. (2013). Glyphosate, pathways to modern diseases II: Celiac sprue and gluten intolerance. *Interdisciplinary toxicology*, *6*(4), 159–184. doi:10.2478/intox-2013-0026

[16] Samsel, A., & Seneff, S. (2013). Glyphosate, pathways to modern diseases II: Celiac sprue and gluten intolerance. *Interdisciplinary toxicology*, *6*(4), 159–184. doi:10.2478/intox-2013-0026

[17] Han, X.M., Holtzman, D., McKeel Jr., D.W., Kelley, J. and Morris, J.C. (2002) Substantial Sulfatide Deficiency and Ceramide Elevation in Very Early Alzheimer's Disease: Potential Role in Disease Pathogenesis. Journal of Neurochemistry, 82, 809-818. http://dx.doi.org/10.1046/j.1471-4159.2002.00997.x

[18] Seneff, S. , Swanson, N. and Li, C. (2015) Aluminium and Glyphosate Can Synergistically Induce Pineal Gland Pathology: Connection to Gut Dysbiosis and Neurological Disease. *Agricultural Sciences*, **6**, 42-70. doi: 10.4236/as.2015.61005.

[19] Seneff, S. , Swanson, N. and Li, C. (2015) Aluminium and Glyphosate Can Synergistically Induce Pineal Gland Pathology: Connection to Gut Dysbiosis and Neurological Disease. *Agricultural Sciences*, **6**, 42-70. doi: 10.4236/as.2015.61005.

[20] Xie, L., Kang, H., Xu, Q., Chen, M. J., Liao, Y., Thiyagarajan, M., … Nedergaard, M. (2013). Sleep drives metabolite clearance from the adult brain. *Science (New York, N.Y.)*, *342*(6156), 373–377. doi:10.1126/science.1241224