Autism genes are selectively targeted by environmental pollutants including pesticides, heavy metals, bisphenol A, phthalates and many others in food, cosmetics or household products.

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Abstract

The increasing incidence of autism suggests a major environmental influence. Epidemiology has implicated many candidates and genetics many susceptibility genes. Gene/environment interactions in autism were analysed using 206 autism susceptibility genes (ASG's) from the Autworks database to interrogate ~1 million chemical/gene interactions in the comparative toxicogenomics database. Any bias towards ASG's was statistically determined for each chemical. Many suspect compounds identified in epidemiology, including tetrachlorodibenzodioxin, pesticides, particulate matter, benzo(a)pyrene , heavy metals, valproate, acetaminophen, SSRI's, cocaine, bisphenol A, phthalates, polyhalogenated biphenyls, flame retardants, diesel constituents , terbutaline and oxytocin, *inter alia* showed a significant degree of bias towards ASG's, as did relevant endogenous agents (retinoids, sex steroids, thyroxine, melatonin, folate, dopamine, serotonin). Numerous other suspected endocrine disruptors (over 100) selectively targeted ASG's including paraquat, atrazine and

other pesticides not yet studied in autism and many compounds used in food, cosmetics or household products, including tretinoin, soy phytoestrogens , aspartame, titanium dioxide and sodium fluoride. Autism polymorphisms influence the sensitivity to some of these chemicals and these same genes play an important role in barrier function and control of respiratory cilia sweeping particulate matter from the airways. Pesticides, heavy metals and pollutants also disrupt barrier and/or ciliary function, which is regulated by sex steroids and by bitter/sweet taste receptors. Further epidemiological studies and neurodevelopmental and behavioural research is warranted to determine the relevance of large number of suspect candidates whose addition to the environment, household, food and cosmetics might be fuelling the autism epidemic in a gene-dependent manner.

Key words: Autism; gene/environment; pesticides, heavy metals, pollutants; pregnancy

Introduction

According to the Center for disease control (CDC) http://www.cdc.gov/ncbddd/autism/data.html the USA incidence of autism spectrum disorders rose 2.2 fold from 2000 to 2010 [1]. In the UK, a five-fold increase in autism in the 1990's , reached a plateau in the 2000's up to 2010 [2]. This increased prevalence is likely partly due to environmental influences, of which there are many candidates. Many chemical classes or specific chemicals related to autism have been reviewed by Rossignol or Sealey and co-authors [3,4]. These include pesticides, heavy metals, diesel, particulate matter, and other traffic and air or smoking pollutants, as well as Bisphenol A, phthalates , solvents and polychlorinated or polybrominated biphenyls found in household objects such as feeding bottles, fragrances or flame retardants. Certain drugs used in pregnancy, including valproate, selective serotonin reuptake inhibitor antidepressants (SSRI's), acetaminophen, dexamethasone, terbutaline oxytocin and prostaglandins have also been linked to the

development of autism. These and other environmental risk factors are referenced in Table 1, which also includes details of animal studies related to autism, where available. Evidently certain compounds have been more extensively studied and further work is needed for many. It should also be appreciated that, as in genetic studies, replication is a problem in epidemiology, but also that gene/environment interactions may partly explain some disparities (i.e. compound X affects autism if it influences, or is influenced by susceptibility gene(s) products Y, Z etc., or gene Y shows association only if compound X is relevant). This is exemplified for paraoxonase 1 (***PON1***) variants, which metabolise organophosphate pesticides. ***PON1*** is associated with autism in US studies, where organophosphate use is extensive, but not in Italy where organophosphate use is low [5].

Autism related genes are preferentially expressed prenatally in the frontal cortex suggesting that an inherent genetic susceptibility may be confined to this period [6] . Many of these compounds are endocrine disruptors which have been linked to a variety of diseases, including autism, attention hyperactivity deficit disorder, obesity and diabetes, whose incidence has increased in recent decades. Their annual burden of health cost in the European Union has been estimated at over 100 billion Euros [7,8] .

A number of compounds detailed in Table 1, or related compounds have also been shown to produce autism-relevant behavioural effects in laboratory models when administered prenatally, although not all have been studied. These include pesticides, fungicides or herbicides (atrazine, chlorpyrifos, cypermethrin, the DDT metabolite Dichlorodiphenyldichloroethylene (DDE), endosulfan, linuron, prochloraz, procymidone, . tetrachlorodibenzodioxin and vinclozolin) heavy metals (aluminium, cadmium, lead, arsenate, manganese, or mercury) bisphenol A and phthalates and other pollutants (perfluorooctanoic acid, 4-methylbenzylidene camphor, 2-ethylhexyl 4-methoxycinnamate, butylparaben, polychlorinated and polybrominated biphenyls (flame retardants) and

particulate matter) as well as dexamethasone, fluoxetine, terbutaline, thalidomide and valproic acid .Others such as Rotenone and fungicides (pyraclostrobin, trifloxystrobin, famoxadone or fenamidone) as well as fluoxetine, carbamazepine and venlafaxine, or valproate also produce transcriptome changes consistent with autism (See Table 1 for references).

Genes associated with autism are catalogued at the Autworks database using a confidence score derived from analysis of the Genotator association database [9,10] . 206 genes are regarded as prime autism susceptibility candidates and these genes and network analyses are available at the autworks site from the Wall lab at Harvard University http://tools.autworks.hms.harvard.edu/gene_sets/580/genes .

This same set of genes has recently been shown to be localised and enriched in many barriers including the blood brain barrier, as well as skin, intestinal, placental and trophoblast barriers. Several also play an important role in relation to respiratory cilia that sweep noxious particles from the airways. These barrier-related genes are thus in a position to modify the access of numerous environmental agents to the blood and brain and their role in respiratory cilia is relevant to particulate matter and airborne pollutants [11].

Given the strength of the various environmental associations with autism, and its increasing prevalence over recent years, it is possible that the environmental influences that target these genes may afford clues as to the combined and conditional causes of autism.

Epigenetic changes have been observed in autism, and these too may be related to environmental agents [12,13] as reported for Bisphenol A and heavy metals (see Table 1) and for flame retardants and other endocrine disruptors, including soy formula and phytoestrogens such as genistein [14-16] and also for other nutritional agents such as Vitamin D and folic acid[17-19]. However, epigenetics is not the subject of this study, which

is limited to the 206 autism-related polymorphic genes reported from gene association studies.

Chemical influences on the 206 Autworks susceptibility genes (ASG's) were analysed using the Comparative Toxicogenomics Database (CTD) [20] which records over 1 million interactions between diverse chemicals and genes or proteins. Previous work using this database has already shown a link between autism or other disease-related genes and environmental risk factors [21]. For example, asthma has been linked with p,p'-DDT, and autism with o,p'-DDT, both metabolites of the organochlorine insecticide dichlorodiphenyltrichloroethane (DDT)[22].

The results suggest that the toxicogenomic effects of many chemicals associated with autism selectively target the ASG's, showing a close relationship between genes and environment.

Table 1

Compounds that have been implicated in autism in epidemiological studies, or where different blood, hair or tissue levels have been reported. Where available, relevant animal studies are also noted.

Herbicides	Human studies	Animal studies
2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD : Agent orange defoliant contaminant)	Breast milk concentrations associated with autism in 3 year old Vietnamese children [23]. Dioxin toxicity, including TCDD, also related to autism and neurodevelopmental problems in a follow-up Vietnamese study. [24] Dioxin and polychlorinated biphenyl maternal blood levels also related to autistic traits in a German study [25]. polychlorinated dibenzo-p-dioxin exposure during the brain growth spurt — extending from the third trimester of pregnancy to age 2 related to autism: Reviewed in [3]	relatively low doses of four endocrine disruptors , atrazine (10mg/kg), perfluorooctanoic acid (0.1mg/kg), bisphenol-A (50 µg/kg), 2,3,7,8-tetrachlorodibenzo-p-dioxin (0.25 µg/kg) alone or combined in a mixture, from gestational day 7 until weaning produce behavioural toxicity , which for mixture effects was predominantly seen in male mice offspring [26].
Pesticides	At sub-cytotoxic concentrations, Rotenone and fungicides (pyraclostrobin, trifloxystrobin, famoxadone or fenamidone) produce transcriptional changes in mouse cortical cultures *in vitro* that are similar to those seen in brain samples from humans with autism, ageing or neurodegeneration (Alzheimer's disease and Huntington's disease)[27]. Residential proximity to acephate and oxydemeton-methyl and pyrethroids, neonicotinoids, and manganese fungicides linked to poorer neurodevelopment in children (Center for the Health Assessment of Mothers and Children Of Salinas (CHAMACOS) study). [28]	
Dichlorodiphenyltrichloroethane (DDT) metabolite metabolite: Dichlorodiphenyldichloroethylene = (DDE)	Farm families exposed to pesticides show an increased autism incidence : Reviewed in [3]	High doses of endocrine disrupting mixtures, (di-n-butylphthalate, diethylhexylphthalate, vinclozolin, prochloraz, procymidone, linuron, epoxiconazole, and DDE) or (bisphenol A, 4-methylbenzylidene camphor, 2-ethylhexyl 4-methoxycinnamate, and

		butylparaben), when administered prenatally to rats have been shown to modify the expression of genes related to glutamatergic function, the migration and pathfinding of GABAergic and glutamatergic neurones and of autism-related genes in the offspring [29].
Dicofol (Organochlorine)	Exposure during pregnancy linked to autism in the offspring: Reviewed in [3]	None found
Endosulfan (Organochlorine)	Exposure during pregnancy associated with autism : Reviewed in [3]	Endosulfan or cypermethrin ((0.1 or 0.5mg/kg) administered orally to 10 day old mice subsequently altered the levels of brain protein relevant to brain development, and produced neurobehavioral abnormalities manifested as altered adult spontaneous behaviour and ability to habituate to a novel home environment. These effects persisted for several months [30]. Supported by *in vitro* and *in vivo* studies in mice showing deleterious effects on pre and postsynaptic dopamine,GABA and glutamate function in the frontal cortex [31]
Chlordan (Organochlorine mix of cis- and trans nonachlor)	Maternal blood or urine sample levels of trans-nonachlor associated with subsequent childhood autistic behaviour (Health Outcomes and Measures of the Environment) Study (Cincinnati, Ohio) [32]	None found
Chlorpyrifos	Umbilical cord plasma levels linked to autism in the offspring: Reviewed in [3].	Chlorpyrifos (on gestational days 14-17 at the sub-toxic dose of 6 mg/kg) induces relevant

	Proximity to organophosphates at some point during gestation was associated with a 60% increased risk for autism, which was higher for third-trimester exposures or second-trimester chlorpyrifos application [33].	behavioural effects in mice offspring when administered during pregnancy , showing male preference and [34] increases brain markers of oxidative stress in the offspring in a strain (gene) - and age-dependent manner [34-36]
Organophosphates and pyrethroids	This study linked combined rather than individual exposure to diverse pesticides, globally showing association with autism [33]. The most abundant of which was chlorpyrifos (20.7%), followed by acephate (15.4%), and diazinon (14.5%). Of the pyrethroids, one-quarter of the total was esfenvalerate (24%), followed by lamda-cyhalothrin (17.3%), permethrin (16.5%), cypermethrin (12.8%), and tau-fluvalinate (10.5%). Of the carbamates, approximately 80% were methomyl or carbaryl, and of the organochlorines, 60% of all applications were dienochlor. Paraoxonase (**PON1**) variants associated with autism are less able to metabolise diazinon [5]' High urinary concentrations of the pyrethroid metabolite, 3-Phenoxybenzoic acid, observed in autistic children [37].).	(For cypomethrin, See endosulfan above)
Heavy metals		Gestational exposure to

		heavy metals in drinking water, from the first day of pregnancy to day 10.5 (cadmium, 10 parts per million (ppm); lead, 300 ppm; arsenate, 0.5 ppm; manganese, 10 ppm; mercury, 20ppm) or valproic acid (600 mg/kg i.p. on gestational day 8.5 produces multiple behavioural , neurodevelopmental-related abnormalities that persist into adulthood in male mice offspring , effects that are accompanied by epigenetic changes in gene methylation [38]
Aluminium	Elevated hair concentrations of aluminium, arsenic, cadmium, mercury, antimony, nickel, lead, and vanadium observed in autistic children [39].Aluminium concentrations also elevated in urine samples [40]. Autism incidence correlated with the use of aluminium adjuvants in vaccines across several countries [41]. The use of polybrominated diphenyl ethers, aluminium adjuvants, and the herbicide glyphosate have increasing trends that correlate positively to the rise in autism (not the case for lead, organochlorine pesticides or vehicular emissions)[42].	The prenatal administration of aluminium to mice in "vaccine-relevant amounts" produces weight gain and reduced exploratory activity in the light/dark test box in male and female adults (6 months) and reduced open-field activity in male mice [43].
Antimony	High hair levels found in autistic children [39,44]	None found

Arsenic	Autism prevalence linked to proximity to industrial facilities releasing arsenic, lead or mercury [45]. high levels of mercury, lead, arsenic, antimony and cadmium in hair samples of autistic children [44]	See heavy metals and epigenetic effects (above) [38]
Cadmium	Retrospective air levels in birth areas related to autism in 2 year old children: Reviewed in [3]	See heavy metals and epigenetic effects (above) [38]
Chromium	Living in areas with higher air levels of styrene and chromium during pregnancy associated with increased autism risk (National Air Toxics Assessment , Pennsylvania USA [46]: Higher urinary Chromium levels in children with autism (Turkish study)[47]	None found
Copper	High serum copper levels in autistic children and/or low Zn/Cu ratio observed in several studies [48-51]	Increased copper levels lead to local zinc deficiencies in mice. Prenatal copper overload reduces ProSAP/Shank protein levels in the brain and decreases the expression of the N-methyl-D-aspartate receptor subunit (GRIN1), thus influencing a pathway in excitatory synapses associated with autism [52]
Iron	Low prenatal iron levels associated with autism [53]: Low iron levels also observed in autistic children [54,55]	Adult offspring from iron-deficient rat dams show deficits in pre-pulse inhibition of acoustic startle and in passive avoidance learning [56] .
Lead	Birth residence air levels associated with autism : Reviewed in [3]. Data from 4486	See heavy metals (above) [38]

	autistic children residing in 2489 census tracts in five sites of the Centers for Disease Control and Prevention's Autism and Developmental Disabilities Monitoring Network showed a potential link between ambient lead concentrations and autism prevalence and that exposure to multiple metals (lead, arsenic mercury) may have synergistic effects on autism prevalence[57].	
Manganese	Perinatal exposure to lead, manganese, mercury, nickel, diesel particulate, methylene chloride, and the overall metal score associated with autism [58] Birth residence air levels of manganese chloride associated with autism Reviewed in [3]. poorer neurodevelopment in children linked to manganese-containing fungicides[28]. A synergistic effect of blood manganese concentrations and glutathione transferase (GSTP1) polymorphisms has been observed in relation to autism risk [59]	See heavy metals (above) [38]
Mercury	Birth residence air levels associated with autism: Reviewed in [3]	See heavy metals (above) [38]
Molybdenum	High hair levels found in autistic children [39,44]	None found

Nickel	High birth residence air levels: Reviewed in [3]: In four studies, weak associations were found for nickel and autism spectrum disorder (Review) [60].	None found
Tin	Higher urinary levels of lead, thallium, tin , and tungsten in autistic children [61]	None found
Tungsten	Higher urinary levels of lead, thallium, tin , and tungsten in autistic children [61]	None found
Vanadium	Elevated hair concentrations of aluminium, arsenic, cadmium, mercury, antimony, nickel, lead, and vanadium observed in autistic children [39]	None found
Zinc	Zinc deficiency and copper excess and/or low Zn/Cu ratio have been observed in autism in several studies [48-51,62-64]	Prenatal zinc supplementation attenuates autistic-like behaviour in animal models of autism [65,66]
Air Pollution		
1,3-butadiene	Exposure during pregnancy associated with autism [67]	None found
Carbon monoxide	Exposure in children during previous 4 years linked to autism : Reviewed in [3]	None found
Diesel particulate and diesel	Birth residence air levels linked to autism: Reviewed in [3]. Perinatal exposure to diesel has been associated with autism, particularly in male children [58].	Exposure to diesel exhaust particles during pregnancy and nursing in mice increases locomotor activity and repetitive behaviours in the offspring, which did not show deficits in social interactions or social communication [68]. Mice acutely exposed to diesel exhaust (250-300μg/m3 for 6h) show microglia activation, increased lipid peroxidation, and neuro-

		inflammation, particularly in the hippocampus and the olfactory bulb. Adult neurogenesis was also impaired. In most cases, the effects of were more pronounced in male mice [69].
Formaldehyde	Exposure during pregnancy associated with autism [67]	None found
Methylene chloride	Birth residence air levels linked to autism : Reviewed in [3] and [70]	None found
Nicotine (smoking)	ADHD symptoms and autistic traits scores have been associated with elevated levels of regular smoking; cannabis use; and nicotine, alcohol, and cannabis use disorders [71] . Perinatal or prenatal smoking has been associated with autism [72-75], although in adulthood, lower smoking levels have been observed in adulthood [76]	None found
Nitric oxide	Air pollution linked to autism incidence [77]	None found
Nitrogen dioxide (NO_2)	Birth residence air levels linked to autism: Reviewed in [3]. NO_2 levels during gestation or during the first year of life related to autism [78] . Child exposure to Ozone, carbon monoxide, NO_2, and SO_2 in the preceding 1 year to 4 years increases the risk of diagnosis for autism spectrum disorders (Taiwan) [79]	None found
Nitrous oxide (N_2O)	?	A review has shown that exposure to N_2O, even at non-toxic doses, can

		modulate central neurotransmission and targets many neural substrates directly implicated in neurodevelopmental disorders, including the glutamatergic, opiate, cholinergic, and dopaminergic systems [80].
Ozone	Exposure in children during previous 4 years associated with autism : Reviewed in [3] Child exposure to Ozone, carbon monoxide, NO_2, and SO_2 in the preceding 1 year to 4 years increases the risk of diagnosis for autism spectrum disorders (Taiwan) [79]	None found
particulate matter <2.5 μm (PM2.5) particulate matter <10 μm (PM10) There appears to be a divergence between North American and European studies (perhaps related to different levels/types of pollution?)	Birth residence air levels linked to autism: Reviewed in [3].Meta-analysis: PM2.5 and NO2 exposure during pregnancy associated with increased risk of autism. Ozone exposure during the third trimester also weakly associated (Canada) [81]. Prenatal and postnatal exposures to PM2.5 and to a lesser extent nitrogen oxides are associated with increased risk of autism (literature review) [82]. Higher maternal exposure to PM2.5 during pregnancy, particularly the third trimester associated with greater risk of a child with autism spectrum disorder (USA) [83]: Also seen for PM10 in the third	Lateral ventricular dilatation observed in young male mice exposed to ultrafine particles (<100nm) (a phenomenon also seen in autism and schizophrenia). Glial activation was also observed [88]. Such exposure also induced inflammation/microglial activation, reductions in size of the corpus callosum (CC) and associated hypomyelination, aberrant white matter development and/or structural integrity with ventriculomegaly (VM), elevated glutamate and excitatory/inhibitory imbalance, increased amygdala astrocytic activation, and repetitive and impulsive behaviours [89].

	trimester (USA) [84]. PM2.5 and PM10 also associated with autism during gestation (USA) [78]. Ozone and PM 2.5 air levels as well as nitric oxide and nitrogen dioxide in area of birth residence related to autism (USA) [77]. The effects of air pollution may be gene-dependent: the MET receptor tyrosine kinase rs1858830 CC genotype and air pollutant exposure may interact to increase the risk of autism spectrum disorder(USA) [85] . Early life exposure to low levels of nitrous oxides or PM10 from road traffic does not appear to increase the risk of autism spectrum disorders (Swedish study and a large European study)[86,87].	
Quinoline	Birth residence air levels linked to autism: Reviewed in [3]	None found
Smoking	Several, but not all studies have implicated prenatal or perinatal parental smoking with autism in children [72,73,90-94]. Maternal passive smoking during pregnancy has been associated with children's autistic behaviour [95]	None found
Styrene	Birth residence air levels associated with autism: Reviewed in [3]	None found

	and [70]. Living in areas with higher air levels of styrene and chromium during pregnancy associated with increased autism risk [46]	
Sulphur dioxide SO_2	Exposure in children during previous 4 years linked to autism: Reviewed in [3]: Child exposure to Ozone, carbon monoxide, NO_2, and SO_2 in the preceding 1 year to 4 years increases the risk of diagnosis for autism spectrum disorders (Taiwan) [79]	None found
Trichloroethylene	Retrospective air levels in birth areas associated with autism in 2 year old children: Reviewed in [3] and [70]	None found
Vinyl Chloride	Retrospective air levels in birth areas related to 2 year old autistic children: Reviewed in [3]	None found
Parental occupational exposure		
Xylene	Reviewed in [3]. In a study relating risks for autism in children related to in utero exposure to monitored ambient air toxins from urban emissions in Los Angeles county , autism incidence was increased in relation to 1,3-butadiene, meta/para-xylene , other aromatic solvents, lead, perchloroethylene, and formaldehyde [67]. Exposure to lacquer, varnish, and xylene occurred more often in the parents of children with ASD compared to	None found

	the parents of unaffected children (CHARGE study) [96].	
Others		
Bisphenol A	Exposure during the brain growth spurt — extending from the third trimester of pregnancy to age 2 linked to autism Reviewed in [3]. Higher bisphenol A and metabolite urine levels also reported in autistic children [97]. Children with autism spectrum disorder had significantly increased serum mono-(2-ethylhexyl)-phthalate , di-(2-ethylhexyl)-phthalate , and bisphenol A concentrations compared to healthy control subjects [98]	Following gestational exposure to BPA (400-μg/kg) in rats, male but not female offspring had increased numbers of neurons and glia in layers 5/6 of the medial prefrontal cortex in adulthood [99]. BPA exposure during gestation has long lasting, transgenerational effects (epigenetic) on social recognition and activity in mice. Brains from embryos (embryonic d 18.5) exposed to BPA had lower gene transcript levels for estrogen receptors, oxytocin, and vasopressin. The effects on vasopressin expression persisted into the fourth generation, at which time oxytocin was also reduced but only in males [100-102].
Perchlorate	Levels in drinking water linked to autism: Reviewed in [3]	None found
Phthalates	Exposure during pregnancy related to autism: Reviewed in [3]' PVC flooring (a source of airborne phthalates) in parent's bedroom associated with childhood autism [103]. Children with autism spectrum disorder had significantly increased serum mono-(2-ethylhexyl)-phthalate , di-(2-ethylhexyl)-phthalate , and bisphenol A concentrations	Endocrine disrupting mixtures, (di-n-butylphthalate, diethylhexylphthalate, vinclozolin, prochloraz, procymidone, linuron, epoxiconazole, and DDE) or (bisphenol A, 4-methylbenzylidene camphor, 2-ethylhexyl 4-methoxycinnamate, and butylparaben), when administered prenatally to rats have been shown to modify the expression of genes related to glutamatergic function, the migration and pathfinding

	compared to healthy control subjects [98]	of GABAergic and glutamatergic neurones and of autism-related genes in the offspring [29].
Diethyl phthalate and Di-butylphthalate	Among autism and development delay boys, higher indoor dust concentrations of were associated with greater hyperactivity-impulsivity and inattention [104].	
[di-(2-ethylhexyl) phthalate metabolites: (5-OH-MEHP [mono-(2-ethyl-5-hydroxyhexyl) 1,2-benzenedicarboxylate] and 5-oxo-MEHP [mono-(2-ethyl-5-oxohexyl) 1,2-benzenedicarboxylate)	Higher urinary concentrations in autistic children [105]. Decreased Diethylhexyl Phthalate glucuronidation in autistic children [106].	
Polychlorinated biphenyls (PCB)	Exposure during the brain growth spurt — extending from the third trimester of pregnancy to age 2 related to autism Reviewed in [3]. High serum levels of PCB's in banked second trimester maternal samples associated with an increased risk of autism (particularly so for PCB138/158 and PCB153) [107].	Polychlorinated biphenyl perinatally exposed rats show significantly impaired social recognition as indicated by persistent conspecific-directed exploration by juvenile animals regardless of social experience [108]. PCB-95 (2,2',3,5'6-pentachlorobiphenyl) induces dendritic growth in primary rat hippocampal neurons [109]. 4-OH-2',3,4',5,6'-pentachlorobiphenyl and bisphenol A inhibit the thyroid hormone-dependent dendritic development of Purkinje cells. 4-OH-2',3,3',5',6'-pentachlorobiphenyl, 4-OH-2',3,3',5,5',6'-hexachlorobiphenyl, 4-OH-2,2',3,4',5,5',6-heptachlorobiphenyl, progesterone and nonylphenol promoted the dendritic extension of Purkinje cells in the absence of thyroid hormone [110].
Polybrominated diphenyls (flame retardants)	polybrominated diphenyl ether-28	Global hypomethylation of adult brain DNA was

(Flame retardants)	(PBDE-28) or trans-nonachlor maternal blood or urine sample levels associated with subsequent childhood autistic behaviour [32]. Exposure during the brain growth spurt — extending from the third trimester of pregnancy to age 2 has been associated with autism (Reviewed in [3]). The use of polybrominated diphenyl ethers, aluminium adjuvants, and the herbicide glyphosate have increasing trends that correlate positively to the rise in autism (not the case for lead, organochlorine pesticides or vehicular emissions)[42]	observed in female offspring perinatally exposed to low concentrations of 2,2',4,4'-tetrabromodiphenyl ether 47 (BDE47) which coincided with reduced sociability (study in mutant MECP2 dams) [111]. BDE49 (2,2',4,5'-tetrabromodiphenyl ether) also inhibits mitochondrial electron transport at Complex IV and V at nanomolar concentrations in brain mitochondria and in neuronal progenitor striatal cells [112]
Soy infant formula	Data from the Simons Foundation Autism Research Initiative Simplex Collection (1949 children) suggested an association between the use of Soy infant formula and certain behavioural aspects of autism [113]	None found
Benzo(a)pyrene (Polycyclic aromatic hydrocarbon)	Impacts cognitive development in children who have been exposed in utero and impairs learning in animal models [114]	
Drugs used in pregnancy or to induce or delay labour.		
Acetaminophen (paracetamol)	Maternal use during pregnancy and in perinatal periods associated with autism in the offspring [115]: Use after measles-mumps-rubella vaccination also associated with autism	None found

	in children of 5 years of age or less [116]. Prenatal acetaminophen exposure was associated with a greater number of autism spectrum symptoms in males and showed adverse effects on attention-related outcomes in male and female children. (Spanish birth cohort study including 2644 mother-child pairs recruited during pregnancy)[117].	
Antibiotics	Maternal influenza infection was associated with or prolonged episodes of fever increased the risk of infantile autism. The use of various antibiotics during pregnancy was a potential, but relatively weak risk factor for Autism spectrum disorders/infantile autism [118] .It has been suggested that exposure to antibiotics may be related to deleterious effects on the microbiome [119]	None found
Selective serotonin re uptake inhibitors (Percentage use in the test group comprised 44% fluoxetine, 21% sertraline, 19% paroxetine, 8% citalopram, and 8% escitalopram)	Prenatal use in the first trimester associated with autism development in boys [120]. Fluoxetine has also been shown to alleviate serious and pervasive repetitive behaviours in the clinic in later life [121]	Psychoactive compounds are also environmental pollutants and mixtures can be found, at low concentrations, in drinking water. At such concentrations, a mixture of fluoxetine, carbamazepine and venlafaxine, or valproate produce expression changes in genes related to neuronal growth, development and regulation, and to autism in SK-N-SH neuroblastoma

		cells [122]. Neonatal fluoxetine administration in rats impairs motor coordination in neonates and decreased social behaviour in both juvenile and adult offspring [123]
Terbutaline β2-adrenergic receptor agonist, used as a tocolytic (anti-contraction medication) to delay preterm labour for up to 48 hours	Terbutaline exposure for >2 days during the third trimester associated with a fourfold increased risk for autism spectrum disorders (not observed with albuterol) [124]	In rats, maternal stress during pregnancy, or terbutaline administration to the neonates, on postnatal days 2-5 resulted in autistic-like behaviour in the offspring (stereotyped/repetitive behaviour and deficits in social interaction or communication[125]. Newborn rats treated with terbutaline (10 mg/kg) daily on postnatal days 2 to 5 or PN 11 to 14 showed a robust increase in microglial activation on postnatal day 30 in the cerebral cortex, as well and in cerebellar and cerebrocortical white matter. hyper-reactivity to novelty and aversive stimuli was also observed [126].
Oxytocin	Labour induction or augmented labour associated with an increased risk of subsequent autism (exogenous oxytocin and prostaglandins) [127]. Oxytocin also has reported benefits in the treatment of autism later in life, although meta-analysis of 12 randomized controlled trials suggested little consistent effect [128].	Oxytocin plays a generally beneficial role in sociability in animal models [129,130]. Autism related behaviour is observed in oxytocin or oxytocin receptor knockout mice [131].
Prostaglandins: Pharmacological methods for labour induction mainly include dinoprostone (prostaglandin E2: PGE2) or	Labour induction or augmented labour associated with an increased risk of	PGE2 modulates cerebellar development in the early postnatal period in rats and alters sensory threshold and

misoprostol (a prostaglandin E1 analogue)	subsequent autism (exogenous oxytocin and prostaglandins) [127]. PGE2 plasma levels increased in autistic patients [132]	social behaviour in juvenile males but not females [133].
Thalidomide	Prenatal use also associated with autistic features [134-136]	The prenatal administration of thalidomide in rats produces abnormal serotonergic neuronal differentiation and migration and behavioural effects partly consistent with autism [137,138]
Valproate	Maternal exposure during pregnancy associated with autism (reviewed in [139-141]	Valproate exposure in both rats and mice leads to autistic-like behaviour in the offspring, including social behaviour deficits, increased repetitive behaviour, and deficits in communication [141].
Other drugs		
Cannabis	ADHD symptoms and autistic traits scores have been associated with elevated levels of regular smoking; cannabis use; and nicotine, alcohol, and cannabis use disorders [71]	None found
Cocaine	Maternal use in the perinatal period associated with autism [142]	None found
dexamethasone	Reduced dexamethasone suppression in autistic patients [143]	Dexamethasone treatment during pregnancy in mice (gestational days 16-19) increases astrocyte density in the adult offspring Substantia nigra and ventral tegmental area in both males and females and increases tyrosine hydroxylase immunoreactivity in these areas in both sexes, but with a more pronounced effect on Tyrosine hydroxylase

		positive cell density in females [144].
Ethanol	Prenatal use associated with autism [135,145]	In utero exposure of mouse progeny to alcohol or methamphetamine causes postnatal neurodevelopmental deficits . mediated partly by oxidative stress [146].
Methamphetamine	Case report of autism related to prenatal exposure [147]	In utero exposure of mouse progeny to alcohol or methamphetamine causes postnatal neurodevelopmental deficits . mediated partly by oxidative stress [146].

Methods

206 Autworks autism susceptibility genes (ASG's) http://tools.autworks.hms.harvard.edu/gene_sets/580/genes [9] were analysed. Gene definitions are provided in supplementary File 1. Members of this gene set are highlighted in **bold** when they appear in the text. The gene symbols (applicable to human genes and mouse or rat homologues) were uploaded to the Comparative Toxicogenomics Database (CTD) [20] http://ctdbase.org/ . All interactions are referenced at CTD and can be accessed by uploading the gene symbols from the Autworks dataset. The results were downloaded and the number of ASG's and the total number of genes (autism and others) affected by each chemical or the number of chemicals affecting each autism gene were curated manually. Chemicals were broadly classified into groups (e.g. pesticides, metals, endocrine disruptors). Singletons (chemicals affecting only one gene) were ignored. Many clinical and research drugs were returned, but are not treated in this paper.

All chemicals possess a unique CAS registry number, from the American Chemical society Chemical Abstracts Service http://www.cas.org/content/chemical-substances allowing cross-referencing between CTD data and compounds in other databases. Overlaps were identified using the Venny tool http://bioinfogp.cnb.csic.es/tools/venny/ [148] .

The databases used for such classification, based largely on overlapping CAS numbers, included The TEDX List of Potential Endocrine Disruptors http://endocrinedisruption.org/ ; The EU list of endocrine disruptors http://eng.mst.dk/topics/chemicals/endocrine-disruptors/the-eu-list-of-potential-endocrine-disruptors/ ,the NIST Polycyclic Aromatic Hydrocarbon (PAH) Structure Index http://pah.nist.gov/ ,the national toxicity program from the US department of health http://ntp.niehs.nih.gov/index.cfm and the United States Environmental protection agency databases http://www.epa.gov/ .Persistent organic

pollutants (POPs) are as defined by the Stockholm convention http://chm.pops.int/Home/tabid/2121/mctl/ViewDetails/EventModID/871/EventID/514/xmid/6921/Default.aspx .

Compounds in cigarettes are defined by the Federal drug administration http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm297786.htm and the Tobacco Products Scientific Advisory Committee list of harmful or potentially harmful components in tobacco and/or tobacco smoke [149].

Compounds found in diesel exhaust are listed at Wikipedia http://en.wikipedia.org/wiki/Diesel_exhaust and at the United States department of labor Partial List of Chemicals Associated with Diesel Exhaust https://www.osha.gov/SLTC/dieselexhaust/chemical.html

Lists of chemicals in cosmetics, foods and pharmaceutical preparations were obtained from the National Research Council (US) Steering Committee on Identification of Toxic and Potentially Toxic Chemicals for Consideration by the National Toxicology Program [150], the UK Food standards agency listing EU approved food additives http://www.food.gov.uk/ and from the International fragrance association http://www.ifraorg.org/en/ingredients#.U_w5JWNWpZx . Food ingredients were also interrogated at FooDB http://foodb.ca/compounds a project from the Canadian Metabolomics Innovation Centre. Food additives are also listed at GSFA online http://www.codexalimentarius.net/gsfaonline/additives/index.html from the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and from the List of Indirect Additives Used in Food Contact Substances from the US Food and drug administration http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?rpt=iaListing and the EAFUS list (Everything Added to Food in the United States)

http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?rpt=eafusListing&displayAll=true .

The Consumer Product Information Database (CPID http://whatsinproducts.com/contents/about_cpid/1 was use for ingredients found in household products. Chemicals in household products were identified using the National Institute of health Household Products database http://householdproducts.nlm.nih.gov/cgi-bin/household/search .

It is important to appreciate that the only selection criteria were the 206 autism genes which were sent to forage chemical interactions in an extensive toxicogenomics database, and that the compounds returned are essentially unbiased by any other factor. However, certain compounds, such as dioxins, pesticides or heavy metals have been more intensively studied than others, due to their known toxic effects, while other relatively new chemical additions to the environment have been subject to less scrutiny. The total number of genes affected by each compound is therefore shown on each figure to allow appreciation of such effects.

Gene enrichment analysis.

The ASG's, selected by Autworks by confidence score based on Genotator, number 206 (0.77% from a human genome of 26,846 protein-coding genes). There were 10,766 unique chemicals in CTD, with 1,002,333 curated interactions (2015 data). If a chemical affects N genes, one would expect an equal proportion of ASG's (0.77%) to be contained within this gene set (Expected = N*(206/26846)). Chemical bias towards the ASG's is reflected by observed/expected ratios >1 and the corresponding p value derived from the hypergeometric probability test, which was corrected for false discovery [151], with a final cut-off at $P<0.05$. Most results are illustrated graphically. For individual compounds the data are illustrated by

N autism genes affected/total number of genes affected by the compound, followed by the fold enrichment and p values (e.g. Methionine (69/3724: 2.41 fold: P= 2.E-12).

Results

67861 chemical/gene interactions affected the ASG's. 4428 compounds affected 1 or more ASG's. 6338 chemicals did not interact with any autism gene**.** The number of ASG's targeted by each chemical varied from 1 to 141 (Tetrachlorodibenzodioxin). The number of chemicals affecting each autism gene ranged from 0 to 1669. 760 compounds with significant enrichment values affected ≥5 ASG's; 372 ≥10; 109 ≥25; 29 ≥50 ; 6 ≥100 . Enrichment values (observed/expected ASG's per total number of genes affected by each compound) for these significant chemicals, where the number of ASG's targeted > 5 ranged from 1.4 to 97.7.

No chemical interactions had been curated for ***HTR3C, KLF14, RP1L1*** *or* ***ZNF778***

Genes affected by compounds implicated in autism (Fig 1)

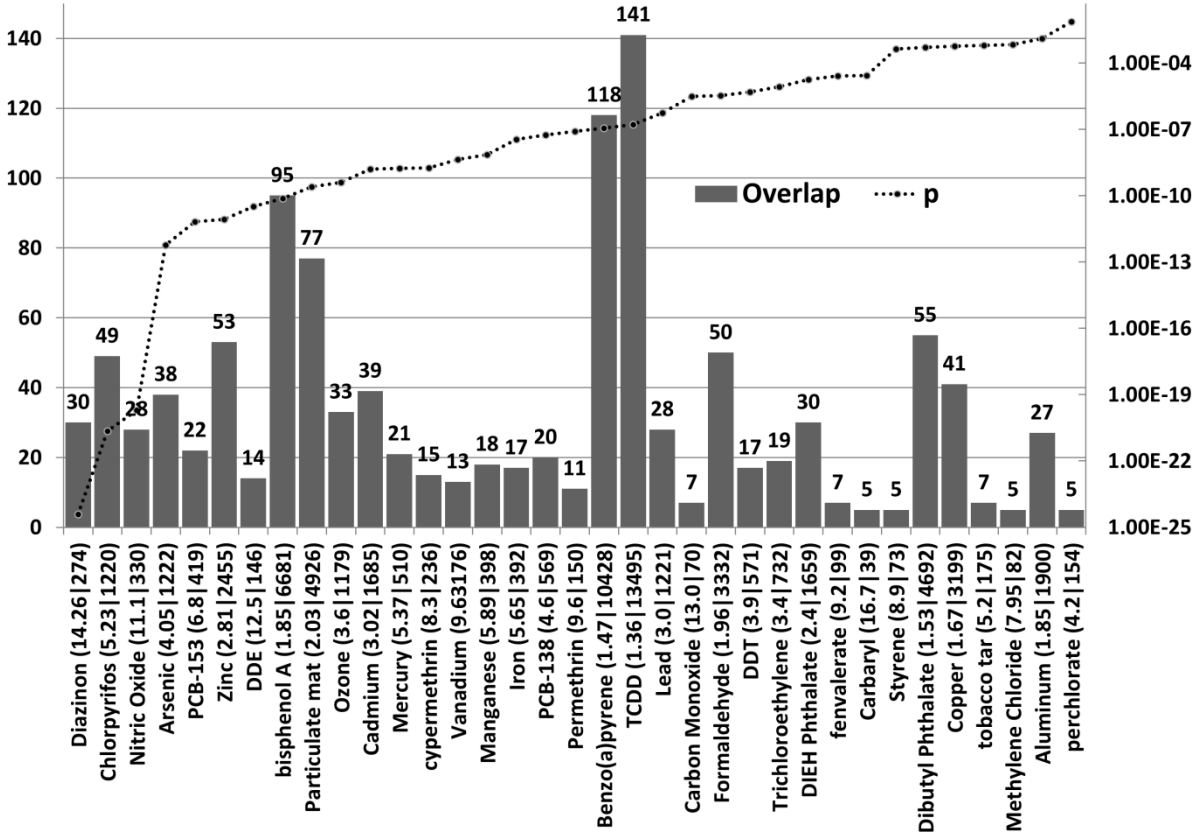
Of the named pollutants implicated in autism (see Table 1) 45 showed enrichment values at P < 0.05 (all except Nickel, diethyl phthalate, Nitrogen Dioxide and Vinyl Chloride)

Compounds with the most significant enrichment scores were pesticides (diazinon, chlorpyrifos, Dichlorodiphenyldichloroethylene (DDE: a DDT metabolite) and cypermethrin), and metals (arsenic, zinc, mercury and cadmium) Other highly significant pollutants included the flame retardant PCB-153, nitric oxide, Bisphenol A, benzo(a)pyrene, particulate matter and ozone (Fig 1).

Figure 1. The number of ASG's (where N>=5) affected by pesticides, herbicides, heavy metals and other named pollutants implicated in autism (left axis). The enrichment ratio and the total number of genes affected by each compound are shown after each compound name. For example Diazinon affects 274 genes in total, 30 of which are ASG's, yielding an

enrichment value (observed/expected) of 14.26. (Diazinon (14.26|274). FDR corrected p values are shown on the right hand Y axis, which is set at a maximum of p=0.05. TCDD= Tetrachlorodibenzodioxin. DDT = dichlorodiphenyltrichloroethane: DDE= Dichlorodiphenyl Dichloroethylene (DDT metabolite). DIEH Phthalate = Diethylhexyl Phthalate , PCB-153 =2,4,5,2',4',5'-hexachlorobiphenyl; PCB-138 =2,2',3',4,4',5-hexachlorobiphenyl (Both PCB's are flame retardants).

3-phenoxy benzoic acid (pyrethroid metabolite), Dicofol , Sulphur Dioxide, Chlordan , acephate ,cyhalothrin, quinoline, 3-xylene and 1,3-butadiene overlaps were also significant but affected less than 5 ASG's (not shown) .



Drugs with the most significant enrichment scores included SSRI antidepressants (fluoxetine, sertraline, paroxetine, citalopram); thalidomide, drugs of abuse (cocaine, methamphetamine,

and ethanol); nicotine, steroid drugs (dexamethasone and hydrocortisone) and drugs used to induce (Dinoprost, misoprost, oxytocin) or prevent (terbutaline) labour in pregnancy, as well as thalidomide, acetaminophen, thimerosal and valproate (Fig 2). There have been multiple conflicting studies relating to the risks and benefits of Thimerosal containing vaccines, which have resulted in its withdrawal in many countries [152]. Thimerosal was removed from childhood vaccines in the USA in 2001.

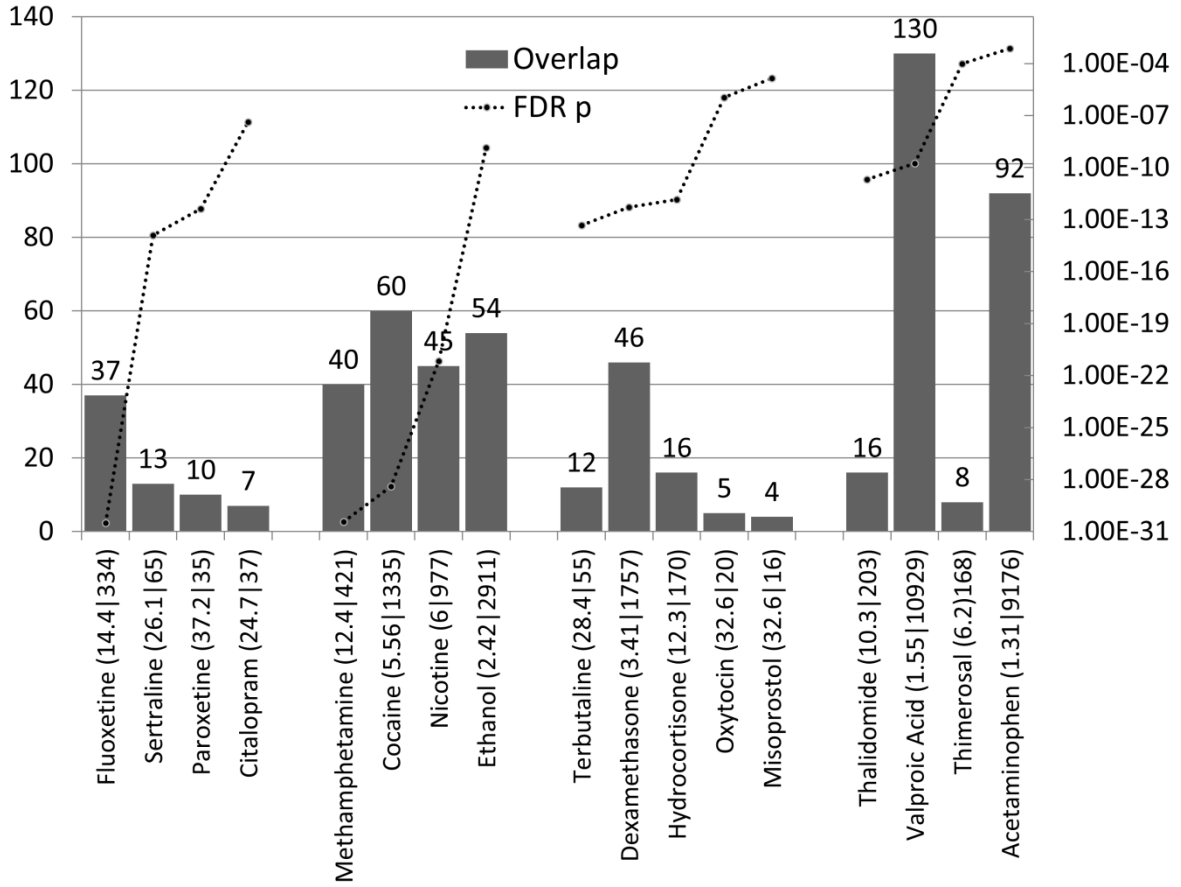
http://www.cdc.gov/vaccinesafety/Concerns/thimerosal/index.html .

Thimerosal affects 8 autism genes (***GSTM1, IL6, MAPK1, MAPK3, PTK2, RFC1, SLC1A1*** and ***TNF***) and its relatively minor enrichment effects (compared to many industrial and other pollutants) may well be limited to those with particular polymorphisms in this set. It should be noted that recent meta-analyses do not support a significant effect of thimerosal in relation to autism [153,154] and that the rise in the incidence of autism has continued since its withdrawal[155]. 79 other compounds significantly oriented their effects towards > 10 ASG's, 39 >20 ASG's and 16 > 30 ASG's and these are likely of greater concern.

Together, these results show that many industrial, agrochemical and household pollutants or drugs implicated in autism target multiple ASG's. One evident interpretation is that polymorphisms therein may modify sensitivity to autism-related chemicals. This is discussed in a later section. Using a similar experimental approach Kauchik et al constructed a protein/protein interaction (PPI) network of autism related genes and found that the effects of drug mixtures (environmental contaminant concentrations of carbamazepine, venflaxine and fluoxetine) or clinical concentrations of valproate on gene expression in fish brains or in human neuronal cell cultures tended to target the same networks as those identified in the autism PPI interactome [156].

Figure 2.

The number of ASG's affected by drugs implicated in autism (left axis), and p values (right axis). The enrichment ratio and the total number of genes affected by each compound are shown after each compound name. First batch = SSRI antidepressants, second = drugs of abuse, third = drugs used during labour, fourth =others.



Other pesticides, fungicides and herbicides

Many pesticides, other than those reportedly related to autism (see Fig 1), are used agriculturally or in the home, often together or at different seasons. 41 of these targeted multiple autism genes ($P < 0.05$) (Fig 3). In the various classes, Cycloheximide, Maneb, Vinclozolin and mancozeb were the most significant fungicides; Paraquat, Cyanazine, Atrazine and herbimycin the most significant herbicides and Methoxychlor, Dieldrin, Endosulfan and chlorpyrifos oxon the highest scoring insecticides.

Figure 3.

The number of ASG's affected by diverse pesticides (left axis), and p values (right axis). The enrichment ratio and the total number of genes affected by each compound are shown after each compound name. The compounds are divided by class: "Others" includes diverse broad-spectrum pesticides and Cyanimide, which is widely used in agriculture to promote uniform opening of buds, early foliation and bloom in fruits. Metdithocarb= methyldithiocarbamate.

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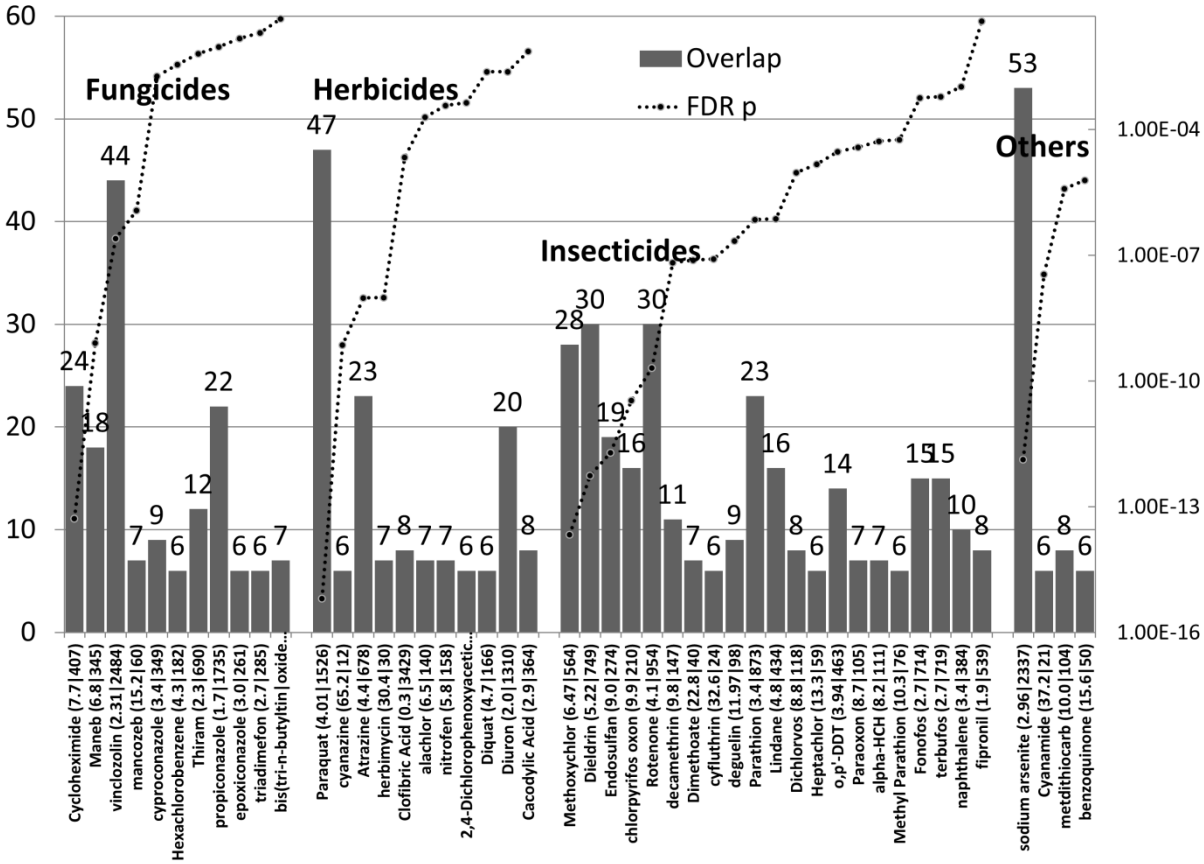


Other metals

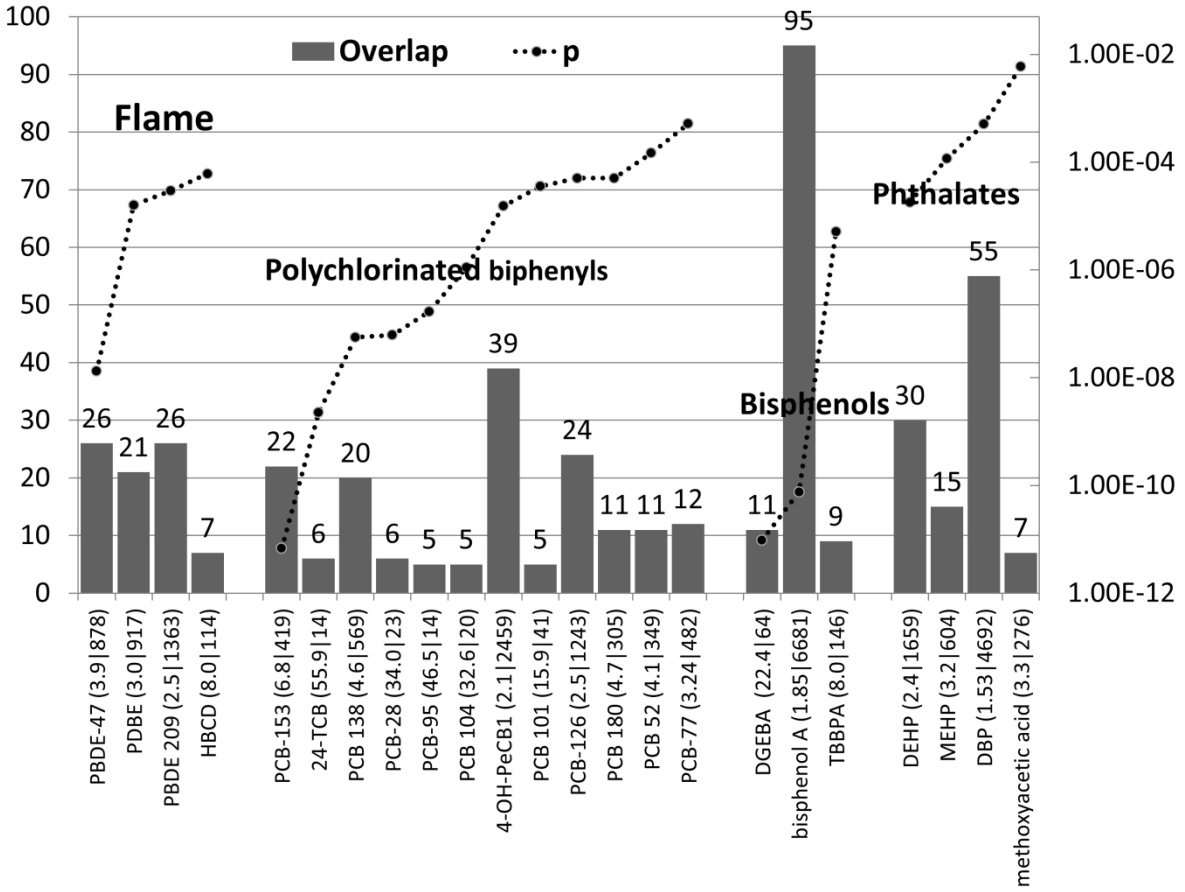
For the most part, other metals significantly orienting their effects towards the ASG's were salts of those already shown in Fig 1 (arsenic, zinc, cadmium, mercury, lead, copper, aluminium) (not shown)). Asbestos, Crocidolite (28/682: 5.4 fold: p= 2.1E-12) is blue asbestos, a product linked to many cancers but not studied in relation to autism. The metals also included the highly toxic tributyltin (10/228: 5.7 fold: p=2.45E-05), a suspected carcinogen, cobaltous chloride (49/3281: 1.95 fold: p= 4.92E-06. Titanium dioxide (50/3449: 1.8 fold: p=8.3E-06) and silicon dioxide (37/2789: 1.7 fold: p=0.0006) are included in the EAFUS and cosmetics lists and treated in these sections.

Poly-halogenated biphenyls, flame retardants, bisphenols and phthalates .

4 known flame retardants (all polybrominated biphenyls) and 12 polychlorinated biphenyls showed significant enrichment values in relation to the ASG's as did several bisphenols and phthalates (Fig 4). During the revision of this paper, high serum levels of PCB-153 and PCB-138 in banked maternal second trimester serum samples were shown to be related to increased autism risk [107]. Both are enriched in ASG's (Fig 4).

Figure 4.

The number of ASG's affected by diverse polyhalogenated biphenyls, bisphenols and phthalates (left axis) and p values (right axis). The enrichment ratio and the total number of genes affected by each compound are shown after each compound name. Flame= Flame retardants. Methoxyacetic acid is a di(2-methoxyethyl) phthalate metabolite. PBDE-47 =2,2',4,4'-tetrabromodiphenyl ether; PDBE =pentabromodiphenyl ether; PBDE 209 =decabromobiphenyl ether; HBCD hexabromocyclododecane; PCB-153 =2,4,5,2',4',5'-hexachlorobiphenyl; 24-TCB =2,4,2',4'-tetrachlorobiphenyl; PCB 138 =2,2',3',4,4',5-hexachlorobiphenyl; PCB-28 =2,4,4'-trichlorobiphenyl; PCB-95 =2,2',3,5',6-pentachlorobiphenyl; PCB 104 =2,2',4,6,6'-pentachlorobiphenyl; 4-OH-PeCB1 =2',3,3',4',5-pentachloro-4-hydroxybiphenyl; PCB 101 =2,4,5,2',5'-pentachlorobiphenyl; PCB-126 =3,4,5,3',4'-pentachlorobiphenyl; PCB 180 =2,2',3,4,4',5,5'-heptachlorobiphenyl; PCB 52 =2,5,2',5'-tetrachlorobiphenyl; PCB-77 =3,4,3',4'-tetrachlorobiphenyl; DGEBA =bisphenol A diglycidyl ether ; TBBPA =tetrabromobisphenol A; DEHP =Diethylhexyl Phthalate; MEHP =mono-(2-ethylhexyl|phthalate; DBP =Dibutyl Phthalate

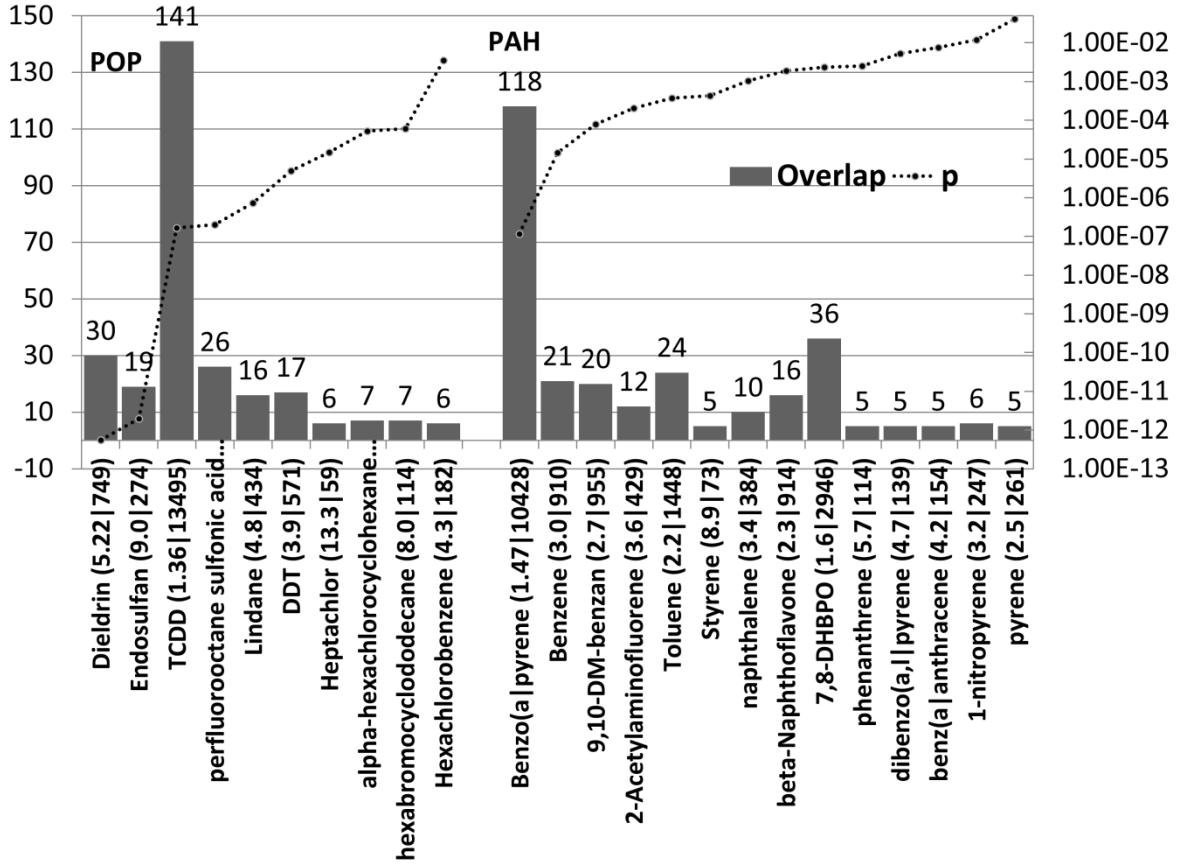


Persistent organic pollutants (POP) and Polycyclic aromatic hydrocarbons (PAH).

Several of these compounds, already recognised for their toxicity in many domains significantly targeted the ASG's (Fig 5). A large number of genes were targeted by 2,3,7,8-Tetrachlorodibenzodioxin and Benzo(a)pyrene**.**

Figure 5. The number of ASG's affected by diverse Persistent organic pollutants (POP) and Polycyclic aromatic hydrocarbons (PAH). (left axis), and p values (right axis). The enrichment ratio and the total number of genes affected by each compound are shown after each compound name. DDT =dichlorodiphenyltrichloroethane; TCDD = 2,3,7,8-

Tetrachlorodibenzodioxin; 9,10-DM-benzan = 9,10-Dimethyl-1,2-benzanthracene; 7,8-DHBPO = 7,8-Dihydro-7,8-dihydroxybenzo(a)pyrene 9,10-oxide.



Endocrine disruptors

138 compounds within this class significantly oriented their effects towards 5 or more autism genes, 79 > 10 genes, 39 >20 genes, 16 > 30 genes ($P<0.05$). Many of these compounds are

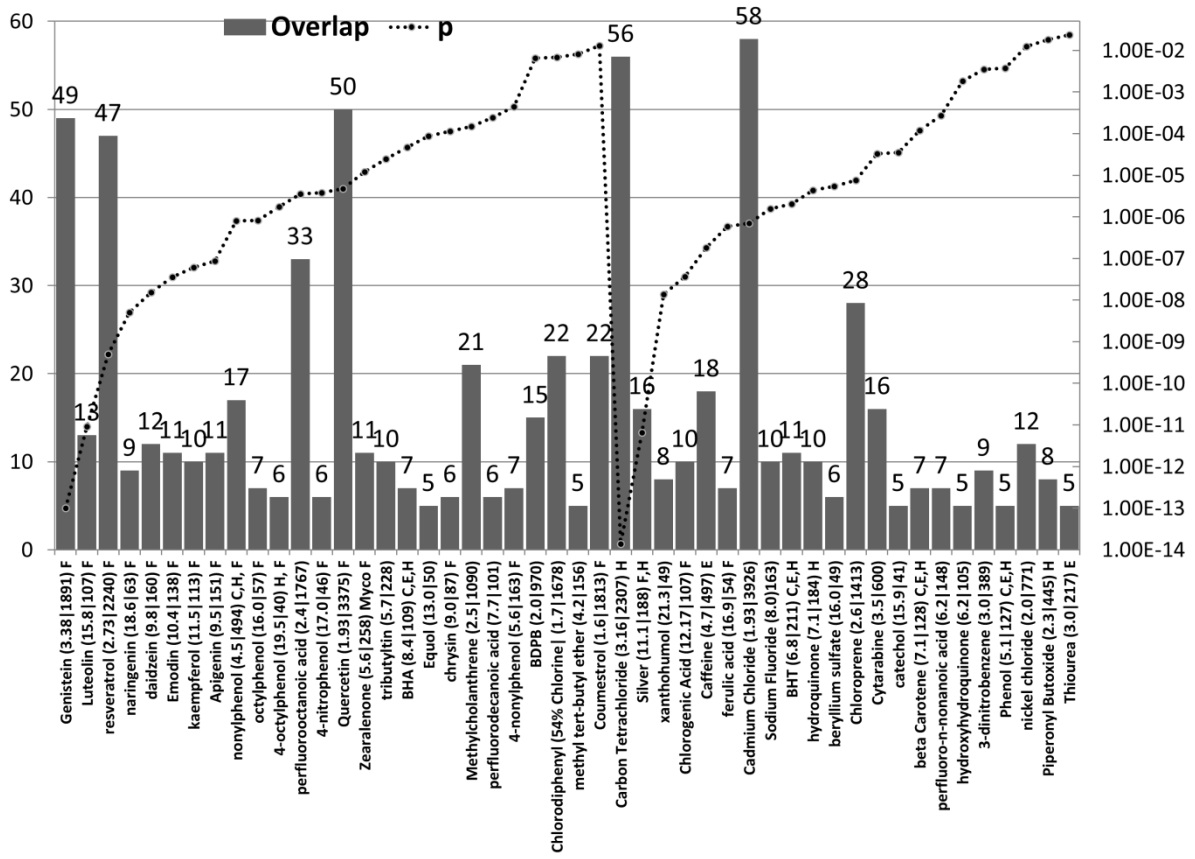
in the EAFUS list or in food, as plant constituents (e.g. phytoestrogens) or contaminants (e.g. alkylphenols). Many are also found in cosmetics or household products and these classes are coded for in Fig 6. Several of these compounds, for example pesticides, heavy metals, bisphenols and phthalates, have already been treated above and are not included in Fig 6. The highly significant endocrine disruptors also include several used in cosmetics including bisphenol A, nonylphenol, Butylated Hydroxytoluene, Butylated Hydroxyanisole, beta Carotene, 4-propylphenol, Styrene, acetyl methyl tetramethyl tetralin, 4-cresol, 4-ethylphenol, Resorcinol, Phenol, Ethylene Glycol, Propylparaben and n-hexane. Several plant-derived phytoestrogens, flavones/flavonoids, selectively target these genes (Apigenin, daidzein, Genistein, kaempferol, Luteolin, naringenin, resveratrol and quercetin). They are common components of food supplements, including baby milk, follow-ons, and soy formula [157-159]. They are generally regarded as potentially beneficial in a number of conditions including cancer, type 2 diabetes, obesity, coronary heart disease, metabolic syndrome, and neurodegenerative diseases. (e.g. resveratrol [160]). Phytoestrogens stimulate estrogen receptors, alpha and beta and many are endowed with antioxidant, and pro-apoptotic effects [161], while some may also have pro- or anti-angiogenic effects [162]. Certain isoflavones inhibit thyroperoxidase activity and may thus influence the thyroid receptor. These processes are important in relation to placental physiology and/or to neurodevelopment [163,164,164] . Endocrine disruptors, including Bisphenol A and polychlorinated biphenyls , but also dietary phytoestrogens are known to affect neurodevelopment in rodents [163,165] Luteolin and quercetin have been reported to reduce autism symptoms in a small clinical trial [166]. However, such compounds are not bereft of toxicological effects. For example neonatally administered genistein in mice later reduces female fertility and embryo implantation [167]. It is also embryotoxic in rats and synergises with Bisphenol A in this respect [168,169]. Pre- or perinatally administered phytoestrogens can also have deleterious effects on animal

behaviour. For example adult male mice perinatally exposed to daidzein show significantly less exploration and higher levels of anxiety and aggression [170]. Genestein given to rat dams during late pregnancy and early lactation affects the differentiation of brain structures as well as changes in anxiety and aggressive behaviour in the male offspring [171].Phytoestrogens can be found in pregnant women's serum and amniotic fluid during pregnancy and soy ingestion increases amniotic fluid phytoestrogen concentrations in female and male foetuses [172] . The use of Soy infant formula has indeed been linked to Autistic behaviour in one study [113].

These endocrine disruptors also include Sodium Fluoride, which is added to domestic water supplies for dental health in many countries. NaF decreases fertility in female rats, via decreases in serum estradiol and progesterone levels and the uterine expression of the follicle stimulating hormone receptor. It also increases uterine estrogen receptor alpha (*ESR1*) and progesterone receptor and luteinising hormone receptor protein expression levels (400;401). In mouse Leydig tumor cells NaF decrease the mRNA expression of steroidogenic acute regulatory protein (*STAR*) and a cytochrome P450 (*CYP11A1*) which catalyses the conversion of cholesterol to pregnenolone, the first rate-limiting step in the synthesis of steroid hormones (402). When given to pregnant rats, NaF decreases the activity levels of testicular steroidogenic marker enzymes (3beta hydroxysteroid dehydrogenase and 17beta hydroxysteroid dehydrogenase) in the 90 day old male offspring (403). Dietary NaF also decreases the serum levels of free and bound triodothronine and thyroxine in rats (404)

NaF also decreases the expression of *CYP1A2* in mouse spermatozoa (405). *CYP1A2* metabolises polycyclic aromatic hydrocarbons, dioxins, polychlorinated dibenzofurans, polychlorinated biphenyls, and acetaminophen (406). NaF thus possesses endocrine disrupting properties and an ability to affect the metabolism of a number of environmental agents implicated in autism.

Figure 6. The number of ASG's affected by diverse known (first batch) and potential (second batch) endocrine disruptors. N ASG's =left axis, p values =right axis). The enrichment ratio and the total number of genes affected by each compound are shown after each compound name. Also appended are compounds found in Food (plant constituents or contaminants (F), the EAFUS list of food additive (E), Cosmetics (C) and household objects (H). Myco = mycotoxin; BDPB = 1,4-bis(2-(3,5-dichloropyridyloxy))benzene; BHA = Butylated Hydroxyanisole; BHT= Butylated Hydroxytoluene;

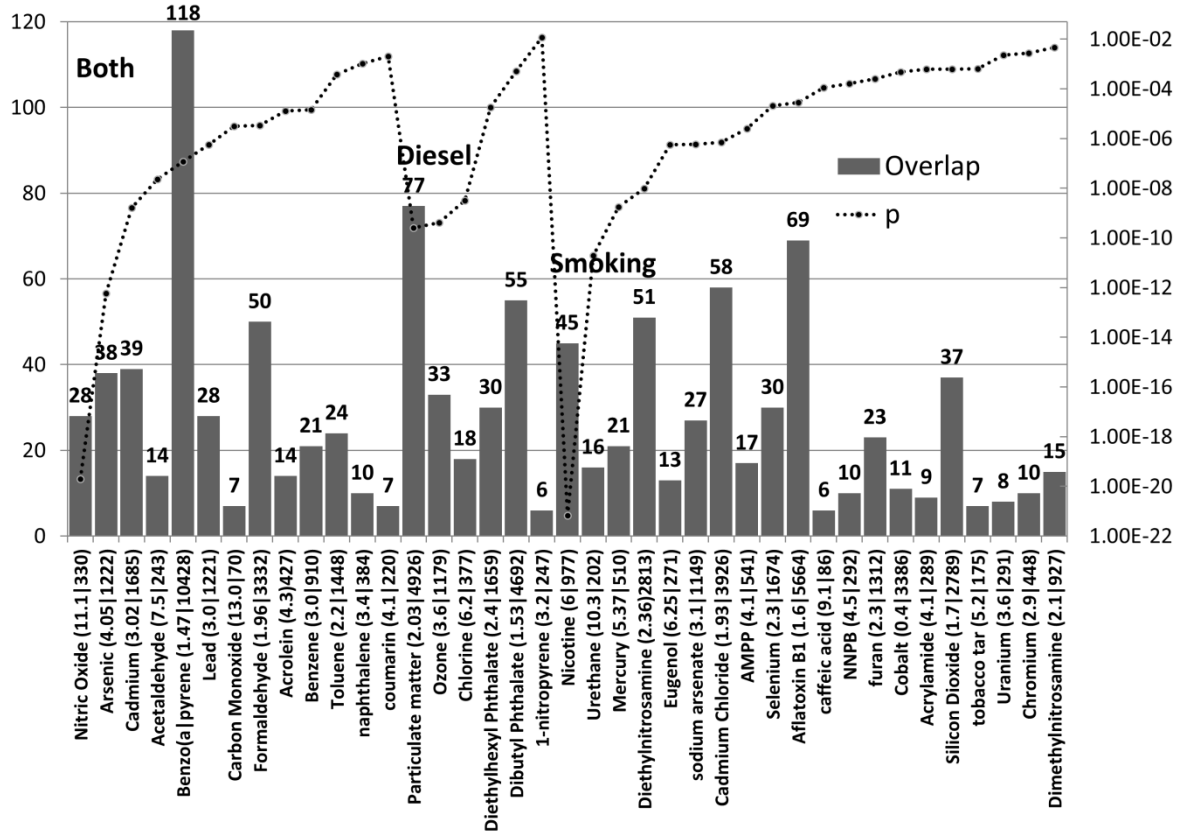


Components of cigarette smoke or diesel exhaust.

Many chemicals found in diesel and/or cigarette smoke significantly targeted a number of ASG's (Fig 7). Their effects must be considered as cumulative.

These data suggest a relationship between the cumulative effects of smoking or diesel toxicants and ASG's. In relation to diesel and traffic pollution, a recent review has highlighted air pollution as a contributory factor to both neurodevelopmental and adult neurodegenerative disorders [69].

Figure 7: The number of ASG's affected by compounds found in cigarette smoke or diesel exhaust or in both. N ASG's =left axis, p values =right axis). The enrichment ratio and the total number of genes affected by each compound are shown after each compound name.



Endogenous compounds targeting the autism genes.

Neurotransmitters, hormones and key endogenous signalling and other metabolites are the agents through which genes and environmental factors act to influence pathology and behaviour. By inference, pollutants that target the same genes/proteins as those related to endogenous messengers must interfere with their function. As shown below, many of the endogenous agents that target autism genes clearly relate to autism pathology and behaviour.

Autism genes are targeted by relevant hormones and transmitters (Fig 8).

Compounds with the most significant enrichment scores (tretinoin (=all-trans retinoic acid), melatonin, progesterone and estradiol) demonstrate a key influence of retinoids and sex hormones that is relevant to the suspected role of environmental endocrine disruptors in autism [173] and to the important role of melatonin in autism [174,175] Many other hormones (thyroxine, triiodothyronine, corticosteroids, calcitriol (1,25-dihydroxyvitamin D3, the hormonally active metabolite of vitamin D, and testosterone)) also showed significant enrichment scores. Low vitamin D status during pregnancy or childhood has also been associated with autism [176]. Severe maternal hypothyroxinaemia during early pregnancy has also been linked to an increased incidence of autism in the offspring [177].

The highest scoring neurotransmitters were serotonin , dopamine and noradrenaline, which is generally consistent with current views on the import of these agents in autism pathology and symptomatology [174,178,179]. Sphingosine-1-phosphate (S1P) plays an important role in oligodendrocytes and in myelination [180]. Aberrant myelination, greater than expected for their age in left and right medial frontal cortex and less than expected in the left temporo-

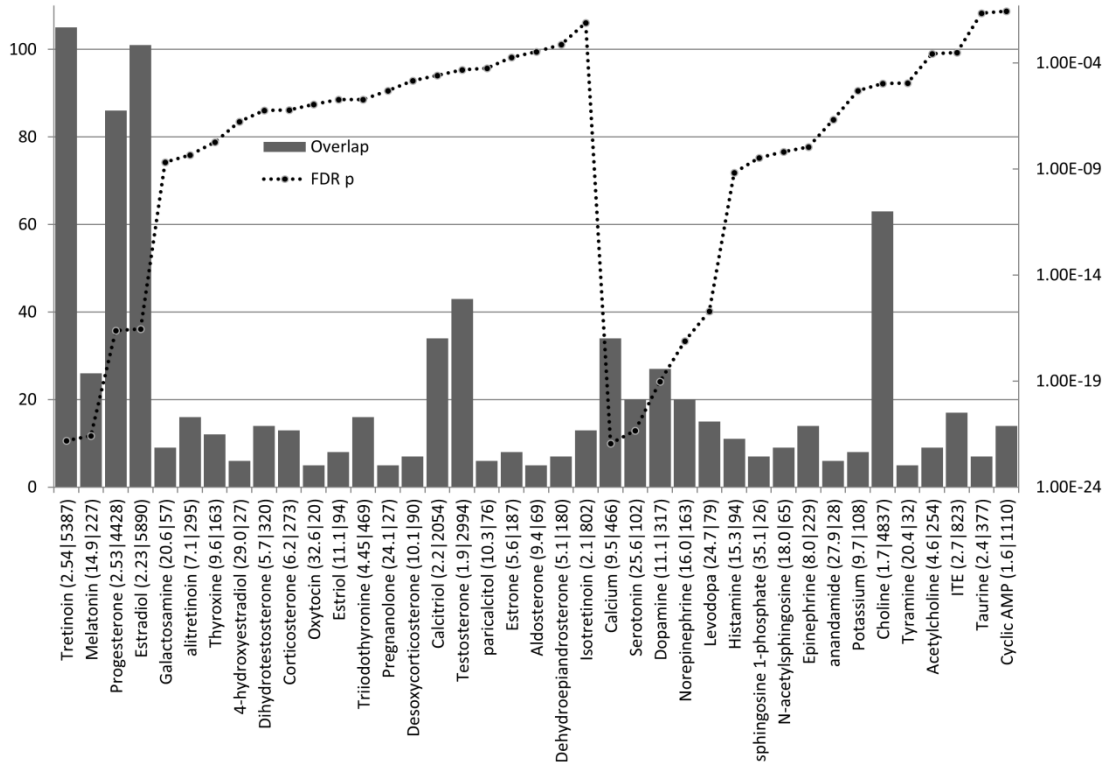
parietal junction has been noted in autistic children and high serum levels of S1P have been reported in a metabolomics study of autistic subjects [181].As recently reviewed, oxytocin has both beneficial and deleterious effects in autism. While its use to induce labour has been linked to the subsequent development of autism in the children, it can also help in relation to the social skills in autistic patients [182] .

Also of interest is an endogenous aryl hydrocarbon receptor (*AHR*) ligand (2-(1'H-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE). [183] . *AHR* is a xenobiotic sensor and the target of dioxins, persistent organic pollutants, polycyclic aromatic hydrocarbons, polychlorinated biphenyls, organochlorine pesticides and endocrine disruptors [184,185], many of which are the top chemicals targeting the autism genes [186-188]. There appear to have been no studies relating *AHR* to autism.

Calcium is directly relevant to 3 calcium channels ***CACNA1C, CACNA1G, CACNA1H*** in the autism gene set. Voltage sensitive calcium channels play an important role in neural function. They are also expressed in the placenta and trophoblast and play an important role in the delivery of calcium to the foetus [189,190].Heavy metal cations, particularly lead and mercury, are potent calcium channel blockers but can also permeate these channels, gaining access to the cell [191].

Figure 8: The number of ASG's affected by Hormones (first batch) and transmitters (second batch: including cations and second messengers). (N ASG's =left axis, p values =right axis). The enrichment ratio and the total number of genes affected by each compound are shown after each compound name.

(ITE = 2-(1'H-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester. Galactosamine is included as it is a constituent of some glycoprotein hormones (follicle-stimulating hormone and luteinizing hormone).



Other endogenous compounds targeting autism genes

These are grouped by general function in Fig 9. They include compounds related to oxidative stress and folate/methionine/homocysteine metabolism which play key roles in autism [192-195] as do cholesterol and fatty acid metabolism [196-199] or inflammation [200-203]..

Several bile related compounds appear in this figure. Bile acids act as nutrient signalling hormones and activate a number of nuclear receptors and G-protein coupled receptors including a specific bile acid receptor *GPBAR1* which regulates intestinal barrier structure via modification of epithelial tight junctions [204]. Many of the ASG's are implicated in barrier function and intestinal permeability increases (leaky gut) have been reported in autism [11,205]. No studies relating bile acids to autism were found in Pubmed, but this area appears to be of interest.

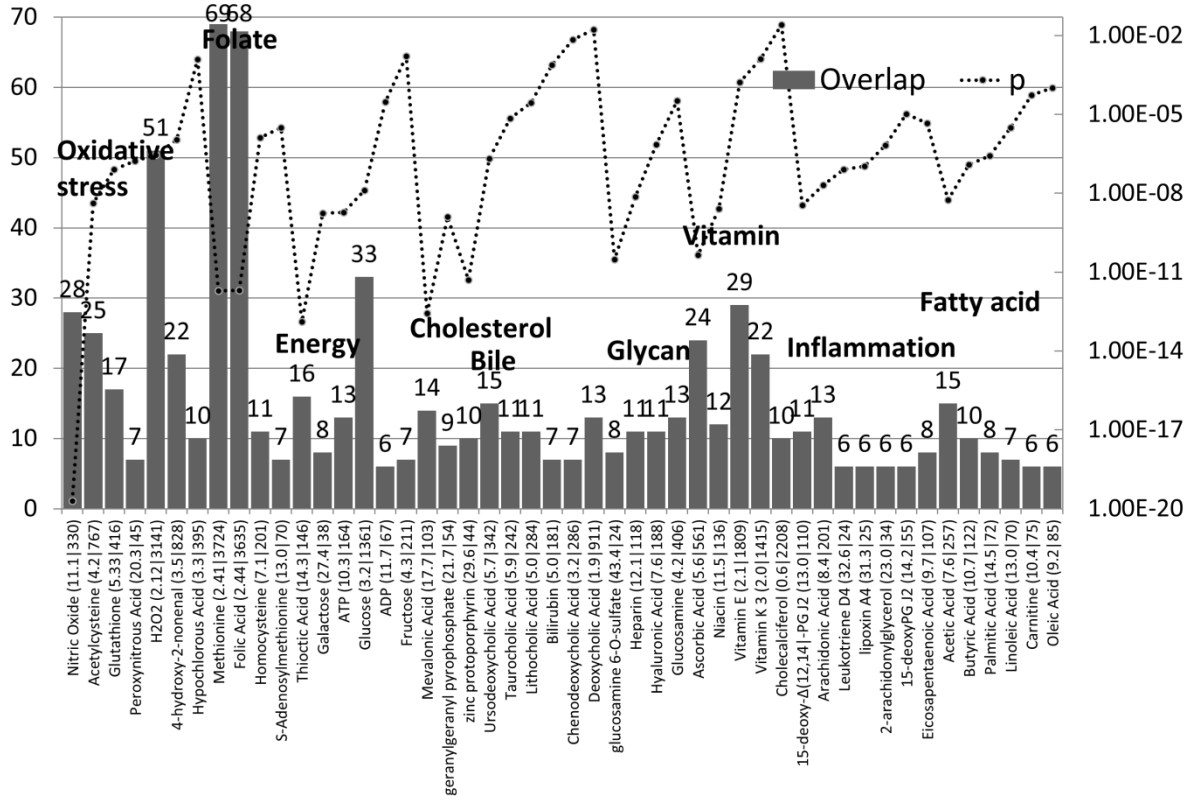
It is important to note that compounds generally considered as beneficial in relation to autism also target autism genes (see discussion caveats). These include folic acid (see above) , glutathione and its precursor acetylcysteine which has reported benefits in the treatment of autism and related psychiatric disorders [206] as might vitamins [207,208] .

Thioctic acid or alpha-lipoic acid is an essential coenzyme for α-ketoglutarate and pyruvate dehydrogenase and thus an obligate requirement for energy production[209]. Lipoic acid protects against the effects of Bisphenol A or Bi-n-butyl phthalate on testicular mitochondrial toxicity [210,211]. In various other models it also protects against the toxic effects of acetaminophen [212], acrolein [213], cyclosporine [214], indomethacin [215], paraquat [216] and rotenone [217] as well as cypermethrin [218], dimethoate, glyphosate and zineb [219],chrysene [220] lindane [221] and Tetrachlorodibenzodioxin [222]. Lipoic acid and other antioxidants have also been used in the clinical management and prevention of heavy metal intoxication [223]. The targeting of autism genes by this product may thus reflect beneficial rather than deleterious effects and, in particular, lipoic acid protects against a large number of toxicants that target autism genes and which have been implicated in the disorder. It has not been analysed in epidemiological studies or tested in the clinic, and blood or tissue levels do not appear to have been measured in pregnancy, neonates or autistic children.

The effects of some fatty acids and carnitine are also oriented towards the ASG's. Faecal levels of acetic, butyric, other short chain fatty acids and ammonia are increased in autistic children, related to microbiome alterations [224,225]. Reduced serum carnitine and linoleic acid levels and modified omega3/omega6 fatty acid ratios have also been noted in autism [226].

Figure 9: The number of ASG's affected by diverse endogenous compounds (N ASG's =left axis, p values =right axis). The enrichment ratio and the total number of genes affected by

each compound are shown after each compound name. The compounds are organised in relation to their general function.



Food additives and compounds in cosmetics targeting the autism genes (Fig 10)

70 compounds in the EAFUS list targeted >5 autism genes (P<0.05) .The interactomes of several compounds which might be considered beneficial (folic acid, methionine, ascorbic acid, niacin and oleic acid) were significantly enriched in autism genes. (Methionine (69/3724: 2.41 fold: P= 2.E-12); Folic Acid (68/3635: 2.44 fold: P=2.03E-12); Ascorbic Acid (24/561: 5.6 fold: p=4.52E-11); Niacin (12/136: 11.5 fold: P=2.58E-09); Oleic Acid (6/85: 9.2 fold: p=0.0001).

Ammonium chloride, the highest scoring compound, derived from burning coal is also used as a flavour enhancer. Ammonium hydroxide in brine solutions is used as a meat tenderiser (363) and is also widely used in food processing to increase pH, while ammonia gas is used to kill bacteria in ground beef (364). NH_4Cl might be considered as a potential by-product of such procedures due to reaction with salt or gastric hydrochloric acid. No reports in relation to autism could be found. However NH_4Cl (Fig 11) increases the permeability of cerebrovascular pial venular capillaries [227] and that of the blood brain barrier to creatine [228] and increases gastric permeability to hydrogen ions [229]. It is also an expectorant used in cough medicines and is able to increase the beat frequency of respiratory cilia [230]. No relationships with autism or neurodevelopment have been reported. Given the barrier and ciliary function of many autism genes [11], it is perhaps this aspect rather than neurodevelopmental criteria that provides such a high score.

It is not practical, given space limitations, to discuss all of these compounds whose relationships with autism or to barrier function remain to be analysed. There are several however that are perhaps of more interest than others due to their extensive use (aspartame, a

constituent of over 6000 food products) or as anticaking agents that are also constituents of widely used sunscreens (Titanium dioxide , silicon dioxide, and zinc oxide).

Aspartame acts via sweet taste receptors *TAS1R2 /TAS1R3* [231] and also activates transient receptor potential heat and inflammation sensitive channels (*TRPV1*). These are involved in metallic taste perception as they are also activated by copper, zinc and iron sulphates [232]. ***TAS2R1***, within the autism gene set, is a bitter taste receptor. Recent evidence suggests that such receptors, also found in areas outside the mouth, may activate defensive mechanisms against noxious chemicals including cytokine and immune systems. In the human lung, TAS2 receptors are expressed in the cilia that sweep harmful chemicals, particles, and microbes from the airways [233]. TAS2 receptor activation in nasal cells results in the secretion of antimicrobial peptides, an effect inhibited by *TAS1R2 /TAS1R3* sweet activation [234]. Thus, aspartame, excessive glucose and other sweet substances activating TAS1 receptors would be expected to inhibit the clearing of pathogens and noxious chemicals stimulated by TAS2 receptor activation.

Microbiome profiling has shown that low-dose aspartame, which has also been implicated in the development of obesity and metabolic disease, increases total bacteria, the abundance of Enterobacteriaceae and Clostridium leptum in diet-induced obese rats. It also increases the serum levels of the short chain fatty acid propionate [235].High levels of faecal enterobacteria and Clostridial families have also been reported in autism [236]. The intracerebroventricular administration of propionate in rats induces behavioural and pathological signs that are relevant to autism [237-240] .

Titanium and silicon dioxide (silicon dioxide (37/2789 : 1.7 fold p=0.0006: not on figure) are used, often in nanoparticle form, in a large number and variety of commercial products including pigment colours, anti-bacterial and other pharmaceutical components, ultraviolet

radiation scavengers (sunscreens), as well as in cosmetics. Both are also food additives used as anticaking agents or colorants [241,242]. Their risks are generally uncharacterised in epidemiological studies although they are manufactured and used worldwide in large quantities [243]. Zinc oxide is also used as a sunscreen.

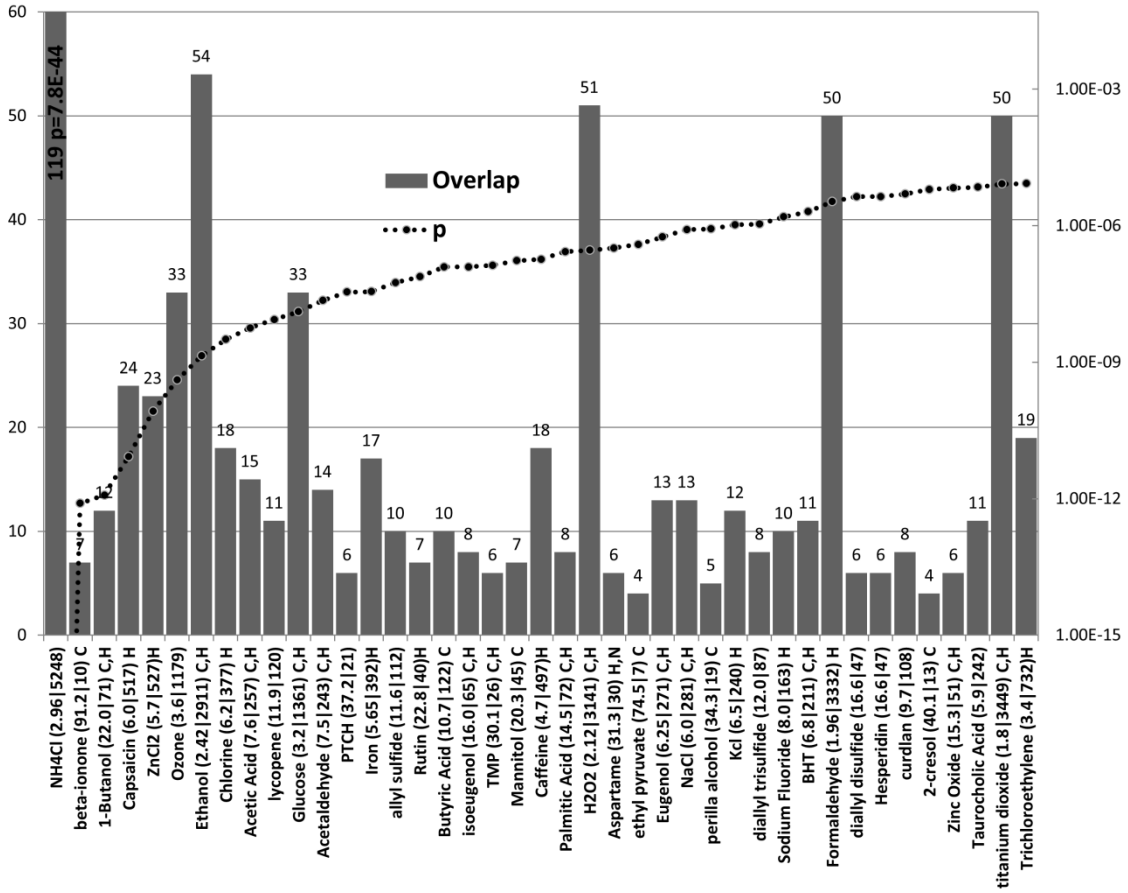
Titanium dioxide nanoparticles are internalised by human neuronal SHSY5Y cells and induce dose-dependent cell cycle alterations, apoptosis, and genotoxic effects that appear to be unrelated to oxidative damage [244]. In contrast, in human epidermal cells, they reduce glutathione and increase lipid hydroperoxide and reactive oxygen species levels, leading to genotoxicity via oxidative DNA damage [245]. Titanium nanoparticles also suppress angiogenesis [246,247].

Both titanium and silicon dioxide nanoparticles cross the placental barrier in mice and can be found in foetal liver and brain following maternal administration. Such treatment results in smaller uteri and foetuses [248]. Titanium dioxide nanoparticles accessing the nasal or pulmonary route are also translocated to the brain or the systemic circulation and thence to other organs [249]. The prenatal administration of titanium dioxide nanoparticles in rats increases frontal cortical and neostriatal dopamine levels in the offspring [250] and modifies the expression of neurodevelopmental genes in the brains of the young offspring in mice [251] . Both silicon and titanium dioxide nanoparticles activate inflammatory cascades in microglia and the supernatants collected from the treated microglia are cytotoxic to PC12 neuronal cells [252]. Titanium dioxide nanoparticles are also internalised by microglial cells resulting in an inhibition of cell adhesion and an overproduction of superoxide [253].

Beta-ionone (EAFUS/cosmetics) is also formed in animals by beta-carotene oxygenase 2 (*BCO2*) which converts betacarotene to β-10'-apocarotenal and β-ionone, en route to the synthesis of Vitamin A [254]. It does not activate retinoid receptors *RARA* or *RARB* [255] but

binds to a retinol binding protein, beta-lactoglobulin B, involved in the oral delivery of retinol to neonates [256]. It is a potent inhibitor of a mouse retinal dehydrogenase (*raldh4*: human homologene = *ALDH8A1*). These enzymes catalyze the dehydrogenation of retinal into retinoic acids, which are required for embryogenesis and tissue differentiation [257].

Fig 10. Compound on the EAFUS list that target the ASG's The maximum left and minimum Y axes are truncated for clarity (NH_4Cl affected 119 autism genes : p= 7.78E-44). BHT = butylated hydroxytoluene; PTCH = protocatechuic acid (a major metabolite of antioxidant polyphenols found in green tea.) TMP= tetramethylpyrazine. Compounds also found in cosmetics are appended with C and those in household products with H.



Cosmetic ingredients targeting autism genes.

Several of these are also in the EAFUS list (see above) and may be used in both as solvents or fragrances and only those specific to cosmetics or not dealt with above are shown in Fig 11. In relation to cosmetics it has recently been reported that many perfumes are mutagenic at femtomolar concentrations [258]. They also reduce arginine vasopressin receptor and oxytocin receptor positive neurons in male neuroblastoma cells, but not in female cell lines. In both male and female neuroblastoma cells fragrances (1 in 1 million dilutions of the shelf-marketed product, all ingredients included) also induced neuronal proliferation, central chromatolysis, enlargement of the neuronal cell body, shortening or abnormal increase and thinning of axonal length, syncytia formation, or selective neurotoxicity [259].

Tretinoin, (all-trans retinoic acid) is the highest scoring compound. It is used for acne and as an anti-ageing component in face creams [260] and is available, without prescription, on many websites. Tretinoin treatment in pregnant rats results in postnatal mitochondrial complex 1 dysfunction in the cerebellum of the offspring [261] and has also been shown to increase levels of fear and anxiety in offspring [262]. Gestational treatment also results in a delayed appearance of the cerebellar righting reflex and reduces open-field activity in the offspring. In addition the offspring show impaired motor coordination and motor learning ability coupled with a reduction in the cerebellar size and impairment in the cerebellar foliation profile [263,264]. A 3 day exposure to 2.5 mg/kg tretinoin (gestational days 11-13) produces a 10% reduction in weight of cerebellum at 4 weeks of age, not accompanied by other malformations [265]. In rats treated with retinoic acid at gestational day E10, the foetuses show structural changes similar to humans with Arnold-Chiari malformation, including downward displacement of the cerebellum to just above the foramen magnum and compression of the developing medulla into a small posterior fossa [266]. A recent MRI study has commented on the co-existence of Chiari malformation with some paediatric autism patients [267]. The targeting of the cerebellum by tretinoin is particularly relevant

given that cerebellar abnormalities are a consistent feature of autism [268-270]. The transfer of retinoic acid across pig skin is increased by exposure to particulate matter containing polycyclic aromatic hydrocarbons [271].

Brief details of some of the other high-scoring compounds are shown below.

Acetovanillone inhibits the free radical superoxide generator NADPH oxidase [272] . The activity of this enzyme is decreased in granulocytes and lymphocytes of autistic children contributing to a spectrum of mitochondrial malfunction in these cases [273,274].

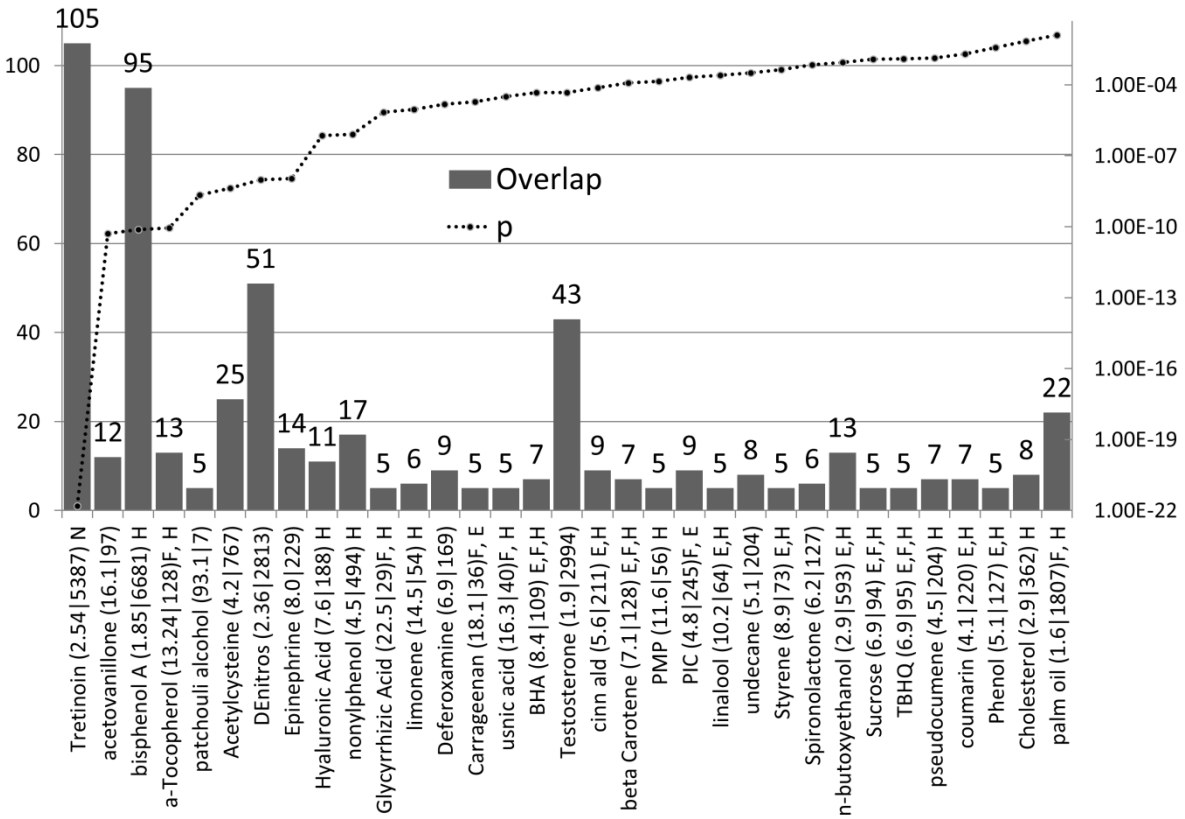
Patchouli alcohol decreases cell growth in MCF7, BxPC3, PC3, and HUVEC cells and downregulates histone deacetylase *HDAC2* in human colorectal cancer cells [275]. *HDAC2* is a valproate target also forming a complex with the Rett syndrome gene ***MECP2*** [276,277].

Limonene is an inhibitor of protein farnesyl transferase (*FNTA FNTB*) and protein geranylgeranyl transferase (*PGGT1B*) [278]. Farnesylation is essential for embryonic development [279] and Farnesyl and geranylphosphate play a role in angiogenesis in human umbilical endothelial cells [280,281]. Limonene is metabolised by cytochrome p5450's *CYP2C9* and *CYP2C19* [282] both of which metabolise progesterone, while testosterone is a substrate for *CYP2C19* [283].

Nonylphenol is a persistent endocrine disruptor used in home maintenance products that is also ubiquitous in foodstuffs for babies and toddlers commercially available in Germany [284] and in many other foods including human breast milk in Europe [285,286]. Nonylphenol and other compounds including dioxins, polychlorinated biphenyls, organochlorine pesticides, bisphenol A, and phytoestrogens have also been detected in umbilical cords and cord sera in Japan [287].

The role of these and many other compounds, alone or as mixtures more relevant to shelf products, in relation to autism remains to be further characterised.

Figure 11. The number of ASG's affected by compounds in cosmetics (N ASG's =left axis, p values =right axis). The enrichment ratio and the total number of genes affected by each compound are shown after each compound name. The presence of these compounds in food (F), the EAFUS list (E), nutraceuticals (N) or household products (H) is also indicated. a-Tocopherol = alpha-Tocopherol; BHA= Butylated hydroxyanisole; DeNitros = Diethylnitrosamine ; PMP= phenylmethylpyrazolone; PIC= phenethyl isothiocyanate; TBHQ = 2-tert-butylhydroquinone.



Compounds affecting barriers or respiratory cilia.

As previously reported [11], many of the autism genes in this set are involved in barrier functions across several different boundaries (blood/brain, skin, intestinal and placental) and also in the control of respiratory cilia that clear the airways of noxious particles. Evidently, environmental chemicals have to traverse such boundaries. In addition, some also have deleterious effects on barrier or cilia function.

Several pesticides (malathion and lead acetate , Chlorpyrifos or a combination of the insect repellent, DEET (N,N-Diethyl-meta-toluamide) and permethrin) are able to disrupt the blood brain barrier in animal models [288] and nicotine and smoking disrupt brain microvasculature and the blood brain barrier[289]. Long-term air pollution in cities relates to neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of beta-amyloid in children and young adults [290]. Air pollution also disrupts epithelial and endothelial barriers and triggers autoimmune responses involving tight junction and neural autoantibodies [291]. Nanoparticles from aluminium, silver or copper increase spinal cord pathology after trauma, an effect correlated with breakdown of the blood-spinal cord barrier [292]. NH_4Cl increases the permeability of pial venular capillaries to Lucifer Yellow, as does histamine .[227]. The transfer of retinoic acid across pig skin is increased by exposure to particulate matter containing polycyclic aromatic hydrocarbons [271].

With regard to respiratory cilia, cigarette smoke decreases beat frequency and cilia length is reduced in healthy smokers. Long-term exposure to cigarette smoke leads to reduced numbers of ciliated cells in mice [293,294]. A combination of cigarette smoke and alcohol also decreases ciliary beat frequency in bovine primary ciliated bronchial epithelial cells [295]. Chlorocresol, a disinfectant, decreases ciliary beat frequency in human nasal epithelial cells [296] , and the insecticide deltamethrin provokes respiratory ciliary damage in rats [297] . The fungicide benomyl and its metabolites, butyl isocyanate and carbendazim, decrease

ciliary beat frequency in canine tracheal epithelial tissue [298] . Progesterone inhibits cilia beat frequency in human lung and cultured primary human airway epithelial cells, an effect inhibited by 17beta-estradiol [299]. No effects could be found in relation to endocrine disruptors, although they might be expected to exert effects in relation to those of these steroid hormones. Ciliary function is also compromised by vanadium, vanadium-rich oil-fired fly ash and cadmium [300,301]. As noted above, bitter taste receptors increase cilia function, and these are inhibited by sweet taste receptors activated by aspartame and glucose.

Such deleterious effects are likely to modify the intake of many other compounds.

Ecological pollution and bioaccumulation.

Many compounds used in cosmetics or as food additives can be directly absorbed or ingested and pesticide sprays and volatile compounds inhaled. While the concentrations of some may well be too low to elicit direct toxicity individually, a further problem relates to the disposal of multiple products down drains or in waste dumps from where they can seep into the air and water tables. For example, a recent study relating to fragrances in the Venice lagoon showed that the total concentrations of multiple ingredients , at different times, varied from ~ 30ng/litre to > 10µg/litre in polluted canals during low tide [302]. Such compounds can be concentrated by the food web (bioaccumulation). and contraceptive ingredients, drugs, pesticides , endocrine disruptors and other pollutants have been found in marine invertebrates or in fish, at levels which have demonstrable effects on endocrine function [303-305]. Compounds in pesticide sprays, such as nonylphenol, can also travel long distances [306]. Such compounds exist in multiple permutations in relation to environmental contamination. The effects of the various compounds, as illustrated in the figures above, apply to individual compounds, but the real life situation involves multiple ingredients in

food or cosmetics and diverse mixtures of environmental pollutants with additive effects. The enrichment of autism genes in the effects of these compounds must therefore be viewed in this context. In an American study in 2011, certain polychlorinated biphenyls, organochlorine pesticides, perfluorinated compounds, phenols, polybrominated diphenyl ethers (flame retardants), phthalates, polycyclic aromatic hydrocarbons, and perchlorate were detected in 99-100% of pregnant women [307].This ecological problem applies to agrochemical and industrial pollutants and likely to hundreds of biologically active compounds in food, cosmetic, drug and household products. Concerns about these products in relation to autism and other neurodevelopmental and cognitive disorders has recently been raised in The TENDR Consensus Statement, a call to action to reduce exposures to toxic chemicals [308].

Caveats: There are numerous caveats. Firstly, this is a comparison of two lists of gene symbols, with no indication of weight (relative importance in relation to specific genes or processes) or directionality (i.e. does the compound activate or inhibit, or are the effects on binding, transcription or phosphorylation, etc.), although these can be found within CTD and in the literature for any interaction of interest. The question of dosage and timing is also important when comparing human and animal studies. However, the enrichment data and those of certain animal studies (For example the use of mixtures of endocrine disruptors [26,29]see Table 1) suggest that "overall toxicological burden" may be a more relevant comparison. This type of enrichment applies to toxicant chemicals, but also to those that might be beneficial (e.g. folic acid, lipoic acid, or glutathione), or a mixture of both (e.g. Oxytocin, where prenatal use is associated with risk and later use with benefit).In many cases, for example pesticides, heavy metals, bisphenol A, phthalates, valproate, etc.), a link to autism is supported by epidemiology and/or by animal studies in relation to development (see Table 1) . Related compounds not yet studied in autism, particularly atrazine and other

pesticides, blue asbestos or known endocrine disruptors can hardly be considered as benign. Other compounds, for example aspartame, titanium dioxide or sodium fluoride, do possess endocrine disrupting or other toxic effects relevant to neurodevelopment. As stated on the CTD website, such data can be used for hypothesis testing. It is impossible to predict whether any uncharacterised compound plays a causal role in autism, but these data can at least provide a long list worthy of further investigation in epidemiological and animal studies.

For all of the suspect compounds, replication in epidemiological and neurodevelopmental studies is essential to verify any causal effect in relation to autism. Meta-analysis studies support the involvement of particulate matter or ambient air pollution in relation to autism in North American [81,309] but not European studies [87] and for the prenatal uses of SSRI's [310] or Vitamin D deficiency in autistic patients [311] but the diverse methodologies used to measure timing and exposure have rendered clear conclusions difficult for these and others such as phthalate esters [312]. These problems are confounded by the gene/environment interactions raised in this study (i.e. compound X may contribute to autism but only in individuals with gene variants that allow it to do so). Environmental pollution also involves exposure to multiple airborne, ingested or contact toxins whose effects may be cumulative and where individual blame is difficult to dissect.

Discussion

The specific question posed by this type of analysis is not whether any compound affects autism genes/proteins, but whether it affects more autism genes than would be expected from the overall toxicological profile of that compound. If such is the case, one might assume that there is a particular relationship between genes and environment that suggests that the genetic polymorphisms, as well as disrupting key autism pathways related to pathology, also affect the ability of certain toxicants to exert their effects via the same genes or proteins. One might

therefore expect that many of these genes, also related to barrier function, modify the absorption, metabolism, excretion or physiological effects of the toxicants. In several cases, this has been shown to be the case, and certain autism polymorphisms do affect these parameters[3,11], although this has not been tested for all of the many genes or chemicals involved.

In relation to these questions, several hundred compounds selectively target multiple members of this particular group of 206 genes. 6338 unidentified compounds in CTD did not affect any autism gene, while the effects of many others were not significant, showing a degree of specificity. Within this group of significant compounds are the majority of the compounds suspected to be implicated in autism including pesticides, heavy metals, and industrial pollutants, Bisphenol A and phthalates , flame retardants, and several drugs , fluoxetine and other SSRI's, as well as acetaminophen, valproate and certain drugs used in labour. This exercise also returned all of the general classes of compounds suspected to be implicated in autism, including particulate matter and other components of diesel exhaust, polyhalogenated biphenyls, polycyclic aromatic hydrocarbons, persistent organic pollutants and endocrine disruptors. The endogenous hormones and transmitters targeting these genes are also highly relevant to endocrine disruption and to the key transmitters related to autism (retinoids, sex steroids, thyroxine, melatonin, folate, dopamine, and serotonin) and to the processes implicated in pathology (compounds related to oxidative stress, folate/methionine/homocysteine, inflammation or myelination). Many more compounds were identified, which due to the cumulative nature of many of these exposures, might also play a role. Overall, these data show that this type of enrichment analysis can identify key compounds reported to be involved in autism. Some of the other compounds also targeting the autism genes clearly possess relevant toxic effects, (e.g. other pesticides, titanium dioxide, tretinoin or aspartame). However, overall enrichment may reflect beneficial and

deleterious effects and such a list can really only suggest compounds worthy of consideration in epidemiological and toxicological studies, particularly during pregnancy and in relation to neurodevelopment and autism. Given the multiplicity of compounds potentially involved, many with different solvent requirements and diverse assay techniques and sensitivities, it might also be useful to establish autism blood and tissue banks and research consortia along the lines now used in genome-wide studies, to adequately quantify such a large variety of chemicals.

Many of these compounds are considered safe by government authorities, but no regulatory toxicological studies could have taken into account the possibility that toxicity might be determined by the same genes that govern susceptibility to autism. This problem could perhaps be addressed using a range of compounds and banked stem cells or tissues from autistic patients or their parents to analyse whether toxicant properties differ in autism cells. A large number of chemicals relate to many autism genes suggesting that the two act in concert and that the rise in the incidence of autism is likely to be chemically driven, in a gene-dependent manner. In this study relating chemicals or environment to genes, it seems that genes and environment are indissociable and that the susceptibility genes themselves may constitute one of the strongest arguments for a causal effect of the environment, as it is towards their products that multiple environmental influences are selectively directed, and via the agency of the gene products that the pathology must be induced, or the toxic products allowed to pass or act.

There appears to be no known reason to suppose that the same genetic variants did not exist in the population prior to the autism epidemic, but a modified environment might have rendered them more relevant to autism. This is akin to the classical population genetics example of the peppered moth. The genes controlling its mottled colouring originally conferred protection from birds, due to camouflage on similarly marked tree bark. Such trees

were blackened by industrial soot pollution, and the same genes now conferred a high risk of predation [313], a situation reversed by clean air acts in the UK and USA [314].

The solution to autism prevention may thus similarly reside in the detection, avoidance and removal of the pollutants, a task involving the development of stricter and more appropriate toxicological and environmental controls at governmental level worldwide, as already proposed in the recent TENDR Consensus Statement (Targeting Environmental Neuro-Developmental Risks) [308].

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