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The expanding cocktail of harmful ingredients in human papillomavirus vaccines

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Vaccination-induced disorders are a genuine reality that continue to generate intense controversy. Although the majority of immunization recipients have little or no safety issues, that does not detract from the occurrences of multiple systemic diseases initiated by a wide variety of parenteral vaccine exposures. Over the past four decades case reports of chronic vaccination-induced disorders have generally segregated into two main categories: (a) autoimmune and autoinflammatory diseases; and (b) neuro-psychiatric diseases, characterized by overlapping clinical features of the various neurologic fatiguing syndromes [1-5]. Afflicted individuals in category "b" are typically Gardasil vaccine recipients. They manifest widespread generalized pain, fatigue, muscle weakness, and small fiber neuropathy, along with mood and sleep disturbances, lethargy, headaches, dizziness, vertigo, reduced alertness, tinnitus, hearing loss, motor neuron dysfunction, abnormal gait, adverse cardiovascular events (e.g., orthostatic fainting, postural tachycardia, other arrhythmias, heart block), gastrointestinal complaints (e.g., cramps, nausea, vomiting, diarrhoea), cognitive dysfunction (e.g., memory lapses, learning impairment), tremors, seizures, metabolic disturbances (e.g., menstrual irregularities), and even sudden death [3-9]. The published reports of category "b" phenomena begin after either Gardasil 4 and/or Gardasil 9 immunizations, regardless of whether any single individual had received one, two, or three separate parenteral doses designed to protect against human papillomavirus induced cancers [10-12]. Within category "b" there also exists considerable diversity regarding the types of clinical features manifested by any single patient, as well as considerable heterogeneity in their time to onset, severity and persistence. Complicating all of this is the lack of specific nomenclature for category "b" events, in part because multiple investigators have identified a variety of autoantibodies and cytokines in ailing Gardasil recipients, and others have grossly oversimplified disease features to resemble patterns seen in fibromyalgia, chronic fatigue syndrome, neuroinflammation, dysautonomia, postural orthostatic tachycardia syndrome, Gulf war illness, macrophage myofasciitis, small fiber neuropathy, and complex regional pain syndrome [9,13-18]. In essence, mechanisms of disease causation put forth by these researchers to account for category "b" events are superficial, overly simplistic, disjointed, and at times inherently contradictory [19,20]. All of these confounding factors have added considerable fuel to the Gardasil controversy, and questions continue to persist regarding definitive identification of those at risk for this bizarre syndrome.

How then can one implicate Gardasil 4 and 9 vaccines as the cause of such a profound multisystem illness? First and foremost, it is becoming increasingly apparent that Gardasil vaccines contain a cocktail of harmful chemicals capable of producing dozens of biochemical disruptions in the body [4,21]. Several of these chemicals are organosiloxanes (commonly known as silicones), silicon dioxide (commonly known as silica), and sorbitol. All three have recently been implicated as participants causing systemic toxicity in Gardasil recipients. Any autoimmune features in these scenarios have been relegated to secondary amplification loops that circuitously enhance the disorder once it is already underway [4,5]. As the list of known harmful substances present in Gardasil expands, multiple overlapping pathophysiologic disruptions of the body's biochemistry become more and more plausible. Perhaps the most glaring new revelation is the Identification of volatile organic compounds in the toluene and benzene families that persist in the finished Gardasil products [22]. Official chemical designations are phenylmethylsulfonyl fluoride (PMSF) and aminoethylbenzenesulfonyl fluoride (AEBSF) respectively. A synonym for PMSF is toluenesulfonyl fluoride. These two chemicals are used in the extraction process of the protein peptides that serve as the antigenic stimuli in Gardasil 4 and 9 vaccines. However, volatile organic compounds like toluene and benzene readily diffuse into organosiloxane polymers [23], and silicones are hidden toxic ingredients in Gardasil vaccines [4,5,21]. This, in turn, implies that purification of the protein peptides via inactivation of PMSF and AEBSF is incomplete, because these two compounds can be shielded by their absorption into silicones. Indeed, a recent independent chemical analysis of two Gardasil 9 vaccine vials confirms the presence of toluene and benzene compounds.

The side effects of toluene and benzene are numerous and include virtually all the adverse phenomena noted in category "b", as well as acidosis, chest tightness, and shortness of breath [24-26]. The reasons for these phenomena are multifactorial. Firstly, toluene compounds have been shown to cause dysfunction of cardiac voltage-gated sodium and calcium channels that are responsible for membrane depolarization and action potential conduction [27]. Since voltage-gated sodium channels are also abundant throughout the nervous system, channelopathies caused by toluene, in concert with previously described organosiloxane-induced channelopathies [5], provide a nasty adverse synergistic amplification loop. In addition, both toluene and benzene compounds have been shown to cause dysfunction of potassium channels in neurons and ovaries [28,29]. Consideration also needs to be given to any inherited channelopathies that are clinically innocuous under ordinary everyday conditions. These can become symptomatic following even small amounts of volatile organic compound exposures. Secondly, PMSF and AEBSF are serine protease inhibitors, and both inhibit the enzyme activity of acetylcholinesterase

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[30,31]. As such, they cause overactivity of acetylcholine in any cells, tissues and organs where muscarinic, nicotinic and central neurotransmitter activities are necessary for normal physiologic functioning. Digestive enzymes originating from the pancreas are also serine proteases, and their enzymatic activities are equally negatively affected by these volatile organic compounds [30]. The protein precursor to brain derived neurotropic factor (BDNF) is cleaved by a serine protease to form mature BDNF. BDNF supports memory formation and maintenance, and mitigates against mood swings, stress, and fear [32]. When PMSF and AEBSF interfere with the formation of mature BDNF, neuro-psychiatric dysfunction is the expected result. Thirdly, PMSF is also a serine esterase inhibitor and can have a direct negative effects on the central nervous system by causing pathologic persistence of neuropeptides such as endorphins, enkephalins and substance P. Fourthly, toluene can cause dysfunction of central muscarinic receptors as well as adrenergic arrestin receptor complexes in every autonomic nervous system arena [33-35]. The peptide molecular structures of these receptors incorporates the matrix macromolecule chondroitin sulfate [36], and since organosiloxane degradation molecules can biointegrate into (and disrupt the function of) matrix macromolecules [4], receptor dysfunction caused by PMSF is another example of an adverse synergistic amplification loop. From the above discussion it is obvious that the side effects of PMSF and AEBSF can paradoxically be in competition with each other, creating conflicting havoc at any point in time via simultaneous biochemical blockades and biochemical excesses of many physiologic, neurologic and psychologic mediators and neurotransmitters. This paradoxical competition enhances all the other multifaceted biochemical disruptions attributable to previously described hidden Gardasil ingredients, in particular organosiloxane induced side effects of cholinergic receptor blockade, mitochondrial dysfunction, ion channel malfunction, chelation of dopamine in the brain, alteration of enzyme activities, and inappropriate mast cell degranulation [4,5,21].

PMSF can create additional biochemical and physiological havoc by virtue of its ability to inhibit protein phosphatases, enzymes that remove a phosphate group from a previously phosphorylated amino acid residue of a protein [37]. Phosphatases act in opposition to protein kinases and protein phosphorylases, the latter two being enzymes that catalyze the transfer of a phosphate group from ATP to amino acids on proteins. Phosphate addition and phosphate removal do not necessarily correspond to enzyme activation or enzyme inhibition. This sphere of metabolism is highly dynamic and plays crucial roles in an extraordinary range of nuclear and cytoplasmic functions, including (but not limited to): intracellular trafficking, control of telomere length, apoptosis, cell cycling, cell movement, gene transcription and translation, learning and memory, signal transduction, blood glucose levels, and neuronal activity.

PMSF and AEBSF are capable of modifying human proteins by changing their isoform profiles [38,39]. An isoform is two or more functionally comparable proteins that have similar but not identical amino acid sequences. Their amino acid sequences can be encoded by different RNA transcripts from the same gene, a process that can be generated by these two volatile organic compounds because they have been shown to alter transcription regulators [40]. In the case where isoform proteins function as enzymes, these companions generate biologic diversity in their tasks and often perform their functions at different speeds. This, in turn, can alter (and even reduce) metabolic and enzyme efficiency. The field of metabolomics encompasses a comprehensive analysis of molecular compounds, and essentially analyses changes in the body's metabolism by looking at changes in substrates and metabolic products. In several of the neurologic fatiguing syndromes, especially chronic fatigue syndrome/myalgic encephalomyelitis, metabolomic alterations are legion [41,42]. Similar metabolic alterations can result from adverse isoform effects of PMSF and AEBSF. In addition, isoform enhancement caused by volatile organic compounds is capable of augmenting virtually any of the toxic side effects previously discussed, particularly disturbances of ion channel protein function.

Isoforms are also capable of triggering the production of autoantibodies by nature of their varied antigenic amino acid sequences and altered configurations. As previously mentioned, autoantibodies of various types have been identified in ailing recipients following human papillomavirus immunization, including antibodies to adrenergic and muscarinic receptors. These complement the varied mechanisms of autoantibody production caused by the hidden organosiloxanes [2,4,5]. But do these autoantibodies account for the wide variety of clinical phenomena manifested by Gardasil victims? Such diverse phenomena imply that multiple physiologic processes encompassing afferent fibres, efferent fibres, dorsal root ganglia, autonomic tissues, ion channels, and central nervous system are being rapidly compromised. When combined with all the other heterogeneous clinical features that, in the aggregate, are also often of rapid onset in these patients, it seems unlikely that Gardasil-induced systemic disease states are initiated by autoimmune and autoinflammatory events. Although the production of autoantibodies are indeed plausible occurrences after Gardasil immunization, they most likely arise as delayed overlapping secondary amplification loops that then augment and perpetuate any clinical features once the disease process is already underway. Autoreactive and autoantibody presence would not be unique to Gardasil-induced illness, because individuals suffering from chemical exposure, other serious conditions and infections, including SARS-Cov-2, have been noted to develop a variety of autoantibodies [5,43-48].

Why doesn't everyone vaccinated with Gardasil become ill? Part of the answer appears to be rooted in one's liver, which is the primary site of biotransformation of endogenous substrates, drugs and chemicals via the cytochrome P450 superfamily system of enzymes. The genes that code for these enzymes exhibit a high number of polymorphisms. As an example, the cytochrome P450-2D6 (CYP2D6) gene is responsible for the metabolism of many drugs and xenobiotics (chemical substances foreign to animal life). There are more than 130 inherited single nucleotide polymorphisms identified in one or both alleles of the CYP2D6 gene, some of which can even create missense mutations in either allele [49,50]. Thus, different versions of the same gene can confer various levels of functional enzyme status in different patients, ranging from ultra-rapid to poor to absent. Benzene is primarily metabolized by CYP2D6 and CYP2E1. As for toluene, the initial primary route of metabolism is by hydroxylation to benzyl alcohol by five members of the P450 family: CYP2E1, CYP1A2, CYP2B6, CYP1A1, and CYP2C8. A researcher has recently investigated two dozen Gardasil recipients with category "b" features, and allelic missense is present in at least three of these six genes in 100 percent of the cohort (unpublished data). The sickest patients manifest allelic missense in four or more of these six genes. This implies that the metabolism of PMSF and AEBSF in these patients is either significantly compromised or absent altogether. However, it should be noted that the entire family of P450 genes responsible for the metabolism of endogenous and exogenous compounds are not strictly separated from each other. It is therefore no surprise that multiple other P450 genes can code for enzymes that

use xenobiotics as substrates, including CYP2A6, CYP2A13, CYP2C9, CYP2C18, CYP2C19, CYP2F1, CYP3A4, CYP3A5, CYP3A7, and CYP3A43. It seems plausible that Gardasil recipients who are at risk for systemic toxicity lack the ability to properly confront the presence of parenterally administered PMSF and AEBSF in a timely manner. When such events are coupled with all the other hidden toxic Gardasil vaccine ingredients, a pathophysiologic mission impossible is initiated. This simultaneously clarifies the multiple confounding factors inherent to the Gardasil controversy, including the vulnerable population at risk and the subsequent evolution of autoantibodies. Other confounding factors for P450 enzyme suppression, such as alcohol consumption, cannabinoid use, estrogen use, and prescription drugs have been properly evaluated and excluded in the compromised Gardasil cohort. On a final note, it should be recognized that the antigenic portions of the Gardasil vaccine itself, via cytokine induction, can suppress P450 enzyme activities against a variety of chemicals and drugs [51]. Thus, in the presence of multiple defective P450 genes, even the beneficial portions of the Gardasil vaccine can circuitously enhance its own toxicity.

In conclusion, human papillomavirus vaccine-induced systemic illness is a genuinely novel disorder that likely encompasses dozens of biochemical and physiological disruptions orchestrated by the presence of multiple hidden toxic vaccine ingredients. The populations at risk for Gardasil-induced adverse events are not likely to exhibit autoimmune diatheses, but they probably exhibit overlapping indigenous risk factors that markedly facilitate acute chemical poisoning. These risk factors, in conjunction with all the hidden toxic vaccine ingredients in Gardasil, also elicit delayed secondary autoreactive amplification loops which, in turn, become capable of augmenting and sustaining the initial biochemical and physiological disruptions once they are already underway. Researchers investigating Gardasil-induced disease states should consider focusing their primary investigations towards identifying indigenous risk factors that logically correlate with chemically related adverse events.

References

1. Vadala M, Poddighe D, Laurino C, Palmieri B (2017) Vaccination and autoimmune diseases: is prevention of adverse health effects on the horizon? *EPMA J* 8: 295-311. [Crossref]
2. Brawer AE (2020) Why are vaccination induced rheumatologic disorders so diverse? *J Med Clin Res Rev* 4: 1-3.
3. Ozawa K, Hineno A, Kinoshita T, Ishihara S, Ikeda SI (2017) Suspected adverse effects after human papillomavirus vaccination: a temporal relationship between vaccine administration and the appearance of symptoms in Japan. *Drug Saf* 40: 1219-1229. [Crossref]
4. Brawer AE (2019) Hidden toxicity of human papillomavirus vaccine ingredients. *J Rheum Dis Treat* 5: 1-4.
5. Brawer AE (2020) Vaccination induced diseases and their relationship to neurologic fatiguing syndromes, channelopathies, breast implant illness, and autoimmunity via molecular mimicry. *Int J Vaccines and Immunization* 4: 1-5.
6. Blitshteyn S, Brinth L, Hendrickson JE, Martinez-Lavin M (2018) Autonomic dysfunction and HPV immunization: an overview. *Immunologic Res* 66: 744-754. [Crossref]
7. Holland M, Rosenberg KM, Iono E (2018) The HPV vaccine on trial. Skyhorse Publishing, USA.
8. Palmieri B, Poddighe D, Vadalà M, Laurino C, Carnovale C, et al. (2017) Severe somatoform and dysautonomic syndromes after HPV vaccination: case series and review of literature. *Immunol Res* 65: 106-116. [Crossref]
9. Dahan S, Segal Y, Dagan A, Shoenfeld Y, Eldar M, et al. (2019) Cardiac arrest following HPV vaccination. *Clin Res Trials* 5: 1-7.
10. Jorgensen L, Gotzsche PC, Jefferson T (2020) Benefits and harms of the human papillomavirus (HPV) vaccines: systematic review with met-analyses of trial data from clinical study reports. *Syst Rev s* 9: 1-23. [Crossref]
11. Cervantes JL, Doan AH (2018) Discrepancies in the evaluation of the safety of the human papillomavirus vaccine. *Mem Inst Oswaldo Cruz* 113: e180063. [Crossref]
12. Ikeda SI, Hineno A, Ozawa K, Kinoshita T (2019) Suspected adverse effects after human papillomavirus vaccination: a temporal relationship. *Immunol Res* 66: 723-725. [Crossref]
13. Schofield J, Hendrickson J (2018) Autoimmunity, autonomic neuropathy, and the HPV vaccination: a vulnerable subpopulation. *Clin Pediatr* 57: 603-606. [Crossref]
14. Martinez-Lavin M, Tejada-Ruiz M (2020) Gulf war illness, post-HPV vaccination syndrome, and macrophage myofasciitis: similar disabling conditions possible linked to vaccine-induced autoimmune dysautonomia. *Autoimmunity Rev* 19: 102603.
15. Hineno A, Ikeda SI, Scheibenbogen C, Heidecke H, Schulze- Forster K, et al. (2019) Autoantibodies against autonomic nerve receptors in adolescent Japanese girls after immunization with human papillomavirus vaccine. *Ann Arth Clin Rheumatol* 2: 1-6.
16. Ryabkova VA, Churilov LP, Shoenfeld Y (2019) Neuroimmunology: what role for autoimmunity, neuroinflammation, and small fiber neuropathy in fibromyalgia, chronic fatigue syndrome, and adverse events after human papillomavirus vaccination? *Int J Molecular Sciences* 20: 1-14. [Crossref]
17. Giannotta G, Giannotta N (2018) Vaccines and neuroinflammation. *Int J Public Health Safety* 3: 163.
18. Bizjak M, Bruck O, Kanduc D, Praprotnik S, Shoenfeld Y (2016) Vaccinations and secondary immune thrombocytopenia with antiphospholipid antibodies by human papillomavirus vaccine. *Semin Hematol* 53: 48-50. [Crossref]
19. VanElzakker MB, Brumfield SA, Mejia PSL (2019) Neuroinflammation and cytokines in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): a critical review of research methods. *Front Neurol* 9: 1033. [Crossref]
20. Miglis MG, Muppidi S (2020) Is postural tachycardia syndrome an autoimmune disorder? And other updates on recent autonomic research. *Clin Autonomic Res* 30: 3-5. [Crossref]
21. Brawer AE (2020) The continuing saga of hidden vaccine toxicity. *J Med Clin Res Rev* 4: 1-3.
22. The Corvelva Team. The Corvelva Report. 2018.
23. Saunders JE, Chen H, Brauer C, Clayton M, Loock HP (2018) Two distinct mechanisms upon absorption of volatile organic compounds into siloxane polymers. *Soft Matter* 14: 2206-2218.
24. (1985) Topics in Emergency Medicine. Advanced Emergency Nursing J: 7.
25. Case Studies in Environmental Medicine: Toluene Toxicity. Agency for Toxic Substances and Disease Registry. U.S. Dept. of Health & Human Services. 1993.
26. Toxicological Profile for Benzene. Agency for Toxic Substances and Disease Registry. U.S. Dept. of Health & Human Services. 2007.
27. Carreon-Garciduenas M, Godinez-Hernandez D, Alvarado-Gómez N, Ortega-Varela LF, Cervantes-Durán C, et al. (2018) Participation of voltage-gated sodium and calcium channels in the acute cardiac effects of toluene. *J Toxicol Mechanisms Methods* 28: 670-677. [Crossref]
28. Bassetto CAZ, Passianoto LVG, González ERP, Varanda WA (2019) Benzenesulfonamides act as open-channel blockers on Kv3.1 potassium channel. *Amino Acids* 51: 355-364. [Crossref]
29. DelRe AM, Dopico AM, Woodward JJ (2006) Effects of the abused inhalant toluene on ethanol-sensitive potassium channels expressed in oocytes. *Brain Res* 1087: 75-82.
30. Ritchie C (2013) Protease inhibitors. *Mater Methods* 3: 169.
31. Skau KA, Shipley MT (1999) Phenylmethylsulfonyl fluoride inhibitory effects on acetylcholinesterase of brain and muscle. *Neuropharmacol* 38: 691-698.
32. Papolos D, Mattis S, Lachman HM, Teicher MH (2019) Thermoregulatory fear of harm mood disorder: in depth exploration of a unique juvenile onset phenotype that provides a parsimonious clinical disruption of certain youths with highly comorbid treatment refractory psychiatric disorders. *J Psychiat Brain Sci* 4: e190004.
33. McKay RT, Brooks SM (1983) Effect of toluene diisocyanate on beta adrenergic receptor function: biochemical and physiologic studies. *Am Rev Respir Dis* 128: 50-53.
34. Fuxe K, Martire M, von Euler G, Agnati LF, Hansson T, et al. (1987) Effects of

subacute treatment with toluene on cerebrocortical alpha and beta adrenergic receptors in the rat. *Acta Physiol Scand* 130: 307-311. [Crossref]

35. Tsuga H, Honma T (2000) Effects of short-term toluene exposure on ligand binding to muscarinic acetylcholine receptors in the rat frontal cortex and hippocampus. *Neurotoxicol Teratol* 22: 603-606. [Crossref]

36. Avram S, Shaposhnikov S, Buiu C, Mernea M (2014) Chondroitin sulfate proteoglycans: structure-function relationship with implications in neural development and brain disorders. *Biomed Res Internat* 2014: 642798.

37. Bollen M, Stalmans W (1988) Fluorine compounds inhibit the conversion of active type-1 protein phosphatases into the ATPMg-dependent form. *Biochem J* 255: 327-333. [Crossref]

38. Narayanan A, Jones LH (2015) Sulfonyl fluorides as privileged warheads in chemical biology. *Chem Sci* 6: 2650-2659. [Crossref]

39. Schuchard MD, Mehigh RJ, Cockril SL, Wildsmith J, Kappel WK, et al. (2004) The protease inhibitor aminoethylbenzenesulfonyl fluoride covalently modifies human plasma proteins and changes protein isoform profiles. HUPO 3rd Annual World Congress, Beijing 2004; poster # MC-010.

40. Nagashima A, Higaki T, Koeduka T, Ishigami K, Hosokawa S, et al. (2019) Transcriptional regulators involved in responses to volatile organic compounds in plants. *J Biol Chem* 294: 2256-2266.

41. Perez M, Jaundoo R, Hilton K, Del Alamo A, Gemayel K, et al. (2019) Genetic predisposition for immune system, hormone, and metabolic dysfunction in myalgic encephalomyelitis/chronic fatigue syndrome: a pilot study. *Front Pediatr* 7: 206. [Crossref]

42. Naviaux RK (2018) Metabolic features and regulation of the healing cycle-a new model for chronic disease pathogenesis and treatment. *Mitochondrion* 46: 278-297.

43. Woodruff MC, Ramonell RP, Lee FEH, Sanz I (2020) Broadly targeted autoreactivity is common in severe SARS-Cov-2 infection. *medRxiv*. [Crossref]

44. Brawer Ae, Korem S (2019) Multiple myeloma presenting with clinical and serological features of systemic lupus erythematosus: a case report. *Clin Rev Cases* 2: 1-2.

45. Bigazzi PE (1997) Autoimmunity caused by xenobiotics. *Toxicology* 119: 1-21. [Crossref]

46. Pollard KM, Hultman P, Kono DH (2010) Toxicology of autoimmune disease. *Chem Res Toxicol* 23: 455-466. [Crossref]

47. Abou-Donia MB, Lieberman A, Curtis L (2018) Neural autoantibodies in patients with neurological symptoms and histories of chemical/mold exposures. *Toxicol Ind Health* 34: 44-53. [Crossref]

48. Brawer AE, Goel N (2016) The onset of rheumatoid arthritis following trauma. *Open Access Rheumatol Res Rev* 8: 77-80. [Crossref]

49. Guengerich FP (2017) Intersection of roles of cytochrome P450 enzymes with xenobiotic and endogenous substrates. Relevance to toxicity and drug interactions. *Chem Res Toxicol* 30: 2-12. [Crossref]

50. Cao X, Durairaj P, Yang F, Bureik M (2019) A comprehensive review of common polymorphic variants that cause missense mutations in human CYP's and UGT's. *Biomed Pharmacotherap* 111: 983-992.

51. Pellegrino P, Carnovale C, Perrone V, Salvati D, Gentili M, et al. (2014) On the possible interaction between vaccines and drugs. *Eur J Clin Pharmacol* 70: 369-371.