

**Studies examining toxic agents as potential risk factors for Multiple Sclerosis
Accelerated Cure Project for Multiple Sclerosis
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Category	Description	Author, Date	Pubmed ID	Conclusions	Type of Study	#case/controls	Region
CIGARETTE SMOKE		Flodin U, 1988	3369968	The risk of MS for subjects exposed to cigarette smoke was insignificant when compared to the control group, with a Mantel-Haenszel rate ratio of 1.6 (95% CI: 0.8-3.4).	case-control study	17/85	Sweden
		Hernan MA, 2001	11427406	Researchers reported a 60% greater incidence rate of MS among current smokers compared with never smokers. The incidence of MS increased w/ cumulative exposure to smoking. The odds ratio for ever smokers to never smokers is 1.6	prospective cohort study of women	315/121700	USA
		Hernan MA, 2005	15758034	The odds ratio for ever smokers compared with never smokers is 1.3. The incidence ratio of secondary progression of MS was 3.6 for MS subjects compared with non-MS subjects.	case-control study	201/1913	Britain
		Landtblom AM, 1993	8153592	There was no correlation between smoking and frequency of multiple sclerosis in either men or women. The Mantel-Haenszel rate-ratios were .8 (95% CI .2-2.4) and 1.4 (95% CI .7-2.7), respectively.	epidemiological study	91/348	Sweden
		Riise T, 2003	14581676	The rate ratio of smokers among never-smokers was 1.81.	case-control study	87/22312	Norway
		Bangsi D, 1998	8449016	There was an observed correlation between amount of cigarettes smoked and risk of MS.	prospective cohort study of women	63/17032	Britain
		Pekmezovic, 2006	17095875	Cigarette smoking was associated with risk of MS, with risk increasing with number of cigarettes smoked and duration of smoking in years. Consumption of coffee and hard liquor were also associated with MS, although not independently from the smoking association.	case-control study	210/210	Serbia
	unspecified	Karvonen M, 1994	7721536	Cigarette smoke significantly increases the risk for C. pneumoniae, a pathogen associated with an increased risk for developing MS	blood analysis of C. pneumoniae IgG antibody	1070 smokers, 536 ex-smokers, 1881 non smokers	Finland
	cyanide	Gardner MJ, 1984	6502741	Serum thiocyanate correlated strongly and approximately equally with the number of cigarettes/kg of ideal body weight (r=0.748).	serum sample tested for thiocyanate concentration	60/130	USA
		Lundquist P, 1987	3594853	For smokers who abstained from smoking for >2 hours and then smoked, cyanide concentrations peaked around 4 mins, but rapidly decreased. Also, the cyanide concentration in the blood of smokers was much higher than that of nonsmokers.	analysis of blood cyanide level after smoking	5	Sweden
		Matthews DM, 1965	5838476	There was a positive correlation between tobacco consumption, plasma thiocyanate concentration and urinary thiocyanate excretion.	analysis of plasma thiocyanate levels	6/7	Britain
		Philbrick DJ, 1979	490674	There was evidence of myelin degeneration in the spinal cord of rats fed cyanide and thiocyanate.	rat tissue analysis	10/10	-
		Van Houten WH, 1961	13924587	Cyanide causes experimental demyelination of white matter of rat brains	brain tissue analysis of rats treated with cyanide	-	-
	nicotine	Geng Y, 1995	8545837	Nicotine has immunosuppressive effects and inhibits the stimulation of lymphocytes.	rat study	-	-

		Hans FJ, 1993	8285254	Nicotine increased the amount of microvascular blood flow in three areas of the brain.	local cerebral blood flow measurement in rats	-	-
		Miller VM, 1998	9597555	Researchers found a positive correlation between cotinine (a metabolite of nicotine) and plasma NOx levels. Also, the plasma NOx levels in cigarette smokers was significantly higher than in nonsmokers.	blood analysis of cotinine and NOx activity	32/13	USA
		Smith DA, 1998		The administration of nicotine resulted in an overflow of NO in the rat hippocampal brain slice. Injecting the rats with NOS inhibitor prior to removal of the brain resulted in decreased production of NO.	analysis of rat brain slices when administered w/ nicotine	-	-
		Suemaru K, 1997	9369366	Adding more NOS inhibitor significantly decreased the severity of the tail tremor, suggesting that nicotine induces NO production.	analysis of rat tail tremor after nicotine injection	-	-
		Tonnessen BH, 2000	11046094	Nicotine stimulated eNOS and nNOS activity.	analysis of NOS extracted from adult male mongrel dogs	-	-
	nitric oxide	Encinas JM, 2005	15865889	This article discusses endogenously produced NO and the overproduction of NO by iNOS. Possible roles of NO with regard to MS include <ul style="list-style-type: none"> • the damaging effects of peroxynitrite (a derivative of NO) on oligodendrocytes • decompaction of myelin due to exposure to NO • elevated glutamate release and uptake due to effects of NO, resulting in damage to 	review	-	-
		Hooper DC, 1997	9122229	Brain tissue of MS patients had a increased concentration of monocytes expressing iNOS. EAE was virtually prevented with high levels of uric acid, and severity of EAE decreased significantly with other iNOS inhibitors or NO scavengers.	Brain tissue analysis of post-mortem MS subjects	-	USA
		Node K, 1997	9185651	The mean plasma NO concentration for heavy smokers was much lower than that of nonsmokers. The results were reversible after smoking was ceased.	blood analysis of NO concentrations	219 current smokers/93 former smokers	Japan
		Smith KJ, 2001	11310624	Small quantities of NO caused axonal degeneration when coupled with an electrical pulse.	in vivo study of rat dorsal roots	-	-
		Zhou JF, 2000	10853840	Cigarette smoking significantly increased the level of plasma nitric oxide. There was a positive correlation between duration of smoking and plasma NO levels.	blood analysis of cigarette and non-cigarette smokers	1255 smokers/524 non smokers	China
	tobacco glycoprotein	Francus T, 1988	3257988	TGP stimulated the production of human peripheral blood T cells and the differentiation of B cells. This overstimulation of the immune system may contribute to the onset of MS.	analysis of human cell culture	-	-
MERCURY							
		Bangsi D, 1998	9758123	There was no significant correlation between either duration or exposure of dental fillings and the risk of MS. Those with >15 fillings had an odds ratio of 2.57 (95% CI: 0.78-8.54) compared to those with no fillings.	case-control study	143/128	Montreal, Canada
		Bates MN, 2004	15155698	There was a positive correlation between dental amalgams and MS, with a hazard ratio of 1.24 (95% CI: 0.99-1.53)	retrospective cohort study	7/20000	New Zealand

	Casetta I, 2001	11359082	There was a positive association between number of dental fillings and risk of MS, but this was not statistically significant.	case-control study	132/423	Ferrara, Italy
	Craelius W, 1978	711974	A geographical comparison of incidence of MS and dental caries supports the hypothesis that dental amalgams may be a risk factor for MS. Positive correlations of $r=0.97$ and $r=0.55$ were reported in Australia and the USA, respectively.	geographical comparison	-	various locations
	Ingalls TH, 1986	3728417	In several clusters of multiple sclerosis, the researcher identified mercury exposure as a common link between the cases.	epidemiological	-	USA
	McGrother CW, 1999	10520544	Researchers found a 21% increased risk of MS for subjects who had dental caries (odds ratio=1.213), and risk increases with number of caries. However, there was no association found between MS and the number of mercury fillings.	matched case-control study	39/62	Leicestershire, Britain
	Clausen J, 1993	8356875	Researchers found no significant difference between brain mercury levels of MS subjects and controls. There was a significantly lower amount of lipid-soluble mercury in MS subjects. This evidence does not support the hypothesis that mercury is a risk factor for MS.	case-control study/brain tissue analysis	8/8	Denmark
	Eley BM, 1988	3290302	Researchers review past studies on the mercurial toxicity of dental amalgams. They concluded that there is insufficient evidence to implicate dental amalgams as a source of mercury poisoning.	review	-	-
	Huggins, 1998	9727079	Removal of dental amalgams in MS subjects resulted in a change of photolabeling characteristics of the CSF fluid. No conclusions on how the changes occurred were made.	CSF analysis	4	USA
	Mackert JR Jr, 1991	2019689	The T lymphocyte levels of patients with dental amalgams and those without were not significantly different.	blood analysis	21/16	USA
	Moreau T, 1999	10506871	After a review of data available on dental amalgams and the risk of MS, researchers concluded that there was not enough evidence to require the removal of dental amalgams because of health concerns.	review	-	-
	Prochazkova J, 2004	15349088	6 MS subjects who had dental amalgams removed displayed long term health improvement, both subjectively and objectively.	case study	6	Prague, Czech Republic
	Siblerud RL, 1992	1496084	MS subjects who had dental amalgams removed reported improvement in mental health in a self-administered survey when compared to MS subjects who still had dental amalgams in place.	case-control study	50/47	Colorado, USA
	Siblerud RL, 1994	8191275	MS subjects who had dental amalgams removed had significantly lower hair mercury levels and significantly higher immune factors (IgG and T lymphocytes) and red blood cell counts compared with MS subjects with amalgams.	case-control study/blood analysis	50/47	Colorado, USA
	Ware RA, 1974	4446967	Rats administered methyl mercuric chloride showed blood-brain barrier dysfunction.	rat study	-	-
	Forte G, 2005	16244395	Mercury levels were lower in blood samples from MS cases than controls	case-control study/blood analysis	60/60	Italy
	Visconti A, 2005	16244396	Mercury levels in serum were equivalent in MS cases compared with controls	case-control study/blood analysis	12/12	Italy

LEAD		Campbell AM, 1950	15420314	Areas of high multiple sclerosis incidents correlated with high lead content of the soil and water in areas of Britain.	epidemiological	-	Britain
		Ingalls TH, 1986	3728417	A cluster of MS subjects in Key West, Florida may have been caused by mercury and lead contamination, stemming from a city dump. Paper also reviewed several other cluster studies that may be a result of mercury/lead poisoning.	cluster study	38	Key West, Florida USA
		Irvine DG, 1988		The lead content of soils in Henribourg, an area with an unusually high number of MS cases, was higher than control areas.	ecological study	-	Henribourg, Saskatchewan
		Millar JH, 1966	5979333	The soil content in two areas of Northern Ireland with high incidences of multiple sclerosis revealed a higher lead to copper ratio than normal.	ecological study	-	Northern Ireland
		Sutherland JM, 1956	13396068	A comparison of lead levels in the drinking water of areas with high incidences of multiple sclerosis in Northern Scotland showed no significant differences from control areas.	ecological study	-	Northern Scotland
		Warren HV, 1963	14073676	Lead concentration in soil of different geographical regions is correlated to the risk of multiple sclerosis.	ecological study	-	-
		Levine S, 1978	690668	Lead implanted in the brains of rats did not cause significant necrosis.	rat study	-	-
		Pentschew, 1966	4164205	Lead caused blood-brain barrier damage as well as other neurological problems in suckling rats. The brain damage was much more pronounced in the younger rats than had been previously shown in adult rats.	rat study	-	-
		Perry TL, 1965	14306331	There was no significant difference between urinary excretions of 15 metals (including lead, tin, nickel, silver, copper, iron molybdenum and zinc) of MS subjects and controls.	case-control study/urine analysis	12/12	Canada
		Sauer RM, 1970	5449319	Lead poisoning in primates caused demyelination in the white matter of their brains.	primate case study	4	-
		Waterman SJ, 1994	7536156	Lead may enhance the immunogenicity of MBP and GFAP, two neural proteins, providing evidence that lead may be involved in immunologically mediated neurological diseases.	mouse study	-	-
		Westerman MP, 1974	4429404	Results displayed no correlation between lead poisoning and the risk of MS. Researchers analyzed urine, bone, and blood content.	analysis of lead levels	5	USA
		Forte G, 2005	16244395	Lead levels were lower in blood samples from MS cases than controls	case-control study/blood analysis	60/60	Italy
		Visconti A, 2005	16244396	Lead levels in serum were equivalent in MS cases compared with controls	case-control study/blood analysis	12/12	Italy
ORGANIC SOLVENTS	n-pentane, isopentane, cyclopentane, n-hexane, 2-methylpentane, 3-methylpentane, cyclohexane, methylcyclopentane, n-heptane, isoheptane, 2,4-dimethylpentane	Amaducci L, 1982	7072486	The risk of MS in workers in the shoe and leather industry was 4.87 times greater than the risk for the general population living in Florence.	epidemiological/cluster study	5/4703	Florence, Italy
	not specified	Casetta I, 1994	8015665	The odds ratio of risk of MS in workers exposed to organic solvents was 4 (95% CI 1.48-11.11) when compared to those unexposed.	case-control study	104/150	Ferrara, Italy
	mostly aliphatic hydrocarbons	Flodin U, 1988	3369968	There was a 2.3 (90% CI 1.1-4.9) Mantel-Haenszel rate ratio of MS subjects with solvent exposure as compared with unexposed subjects.	case-control study	83/467	Sweden

volatile anaesthetics	Flodin U, 2003	12499460	Researchers found a significant increased risk of multiple sclerosis for nurse anaesthetists (SIR=2.9, 95% CI: 1.3-5.3), who are exposed to volatile anaesthetics, which chemically resemble organic solvents.	case-control study	11/13	Sweden
glue solvents	Giuliani G, 1988	-	There was a significant correlation between organic solvents and multiple sclerosis, with an odds ratio of 3.1 (95% CI: 2.0-4.8).	epidemiological study	108	Italy
alkanes, alkenes, white spirit, trichloroethylene, aromatic hydrocarbons, alcohols, ketones	Gronning M, 1993	8256566	A study on the incidence of multiple sclerosis in western Norway did not support the hypothesis that organic solvents cause MS. The odds ratio found was 1.55 (95% CI: 0.83-2.90)	case-control study	150/195	Hordaland, Norway
not specified	Hopkins RS, 1991	1745329	There was no association between MS and exposure to various chemicals, radiation or potentially toxic gases. No odds ratios were available	case-control study	16/61	Galion, Ohio
not specified	Juntunen J, 1989	2818977	6 subjects had been exposed to solvents and 1 had been exposed to lead. Two monozygotic twins had MS while 5 were healthy co-twins. The authors concluded that this study does not support the association of organic solvent exposure to the development of MS.	twin study	27/27100 twin pairs	Finland
not specified	Koch-Henriksen, 1989	2683558	Researchers correlating organic solvent exposure to risk of MS found an odds ratio of 2.0 (95% CI: 0.8-4.7	case-control study	187	Denmark
solvent mixtures, kerosene	Landtblom AM, 1993	8153592	There was a 2.8 odds ratio of solvent exposure and risk of MS for women and men combined (3.3 for men and 1.9 for women).	case-referent study	91/540000	Sweden
not specified	Lauer K, 1989	2911392	The r_s value for association of work in the chemical industry and risk of MS was 0.4. Other regions (Norway, Switzerland, and Sweden) showed no correlation between the two.	epidemiological study	84	Europe
not specified	Lauer K, 1990	2402320	The correlation between a chemical industry occupation and the risk of multiple sclerosis was weak ($r_s=0.4624$, $p<0.05$).	epidemiological study	-	France
not specified	Milham S, 1983.	-	The proportional mortality ratio for automobile mechanics was 233.	mortality study	-	USA
not specified	Mortensen JT, 1998	9504285	The study found no correlation between solvent exposure and the risk of MS.	case-control study	93/212267	Denmark
not specified	Nelson NA, 1994	8199679	There was a 2.7 odds ratio (95% CI: 0.6-13.0) between solvent exposure in automobile workers and risk of MS.	case-control	20/944	USA
toluene, xylene, white spirit, other solvent mixtures	Riise T, 2002	12410015	The relative risk for MS for painters exposed to organic solvents compared with workers not exposed was 2.0.	epidemiological study	27/57755	Norway
not specified	Souberbielle BE, 1990	2281747	No correlation was found between organic solvent exposure due to occupation and the risk of MS.	case-control study	230/230	France
not specified	Cooper GS, 2002	11811933	Evidence strongly suggests a correlation between occupational exposure and autoimmune disease, but there is a lack of experimental data and linkage between models and epidemiological studies.	review of past studies	-	-

	toluene, n-hexane	Davies MB, 2000	10911827	The patient suffered from MS-like syndromes, including relapses in incoordination, lower limb weakness, paraesthesia in the hands, and upper limb ataxia due to glue sniffing. Brain scans showed diffuse white matter changes, unlike MS patients.	case study	1	Britain
	toluene	Filley CM, 1990	2314597	MRI scans revealed increased white matter abnormality in the brains of patients who had abused toluene. There was a positive relationship between intensity of abuse and level of abnormality.	MRI scan analysis	14	USA
	methanol	Henzi H, 1984	6708848	Researcher reported two subjects diagnosed with MS who had well documented occupational exposure to methanol.	case study	2	Switzerland
	aliphatic hydrocarbons, aromatic hydrocarbons, carbon disulphide, trichloroethylene, xylene, hexane	Juntunen J, 1982	7097311	There was a correlation between exposure to organic solvents and stimulation of lymphocytes in the CNS, as well as slight blood-brain barrier damage in patients exposed to the solvents at the time of the study.	cerebrospinal fluid analysis	33	Finland
	not specified	Landtblom AM, 1996	8793371	Meta-analysis displayed a 2 fold increased risk of MS when exposed to organic solvents	Synthesis of 13 studies done on the correlation between organic solvent exposure and MS. Performed pooled and meta analyses on the data.	-	-
	not specified	Landtblom AM, 2003	14658041	Researchers searched for possible polymorphisms of two enzyme systems that metabolize organic solvents in multiple sclerosis subjects but no link was found. Researchers concluded that the apparent correlation between organic solvents and MS is not due to genetic defects in the respective metabolism system of the body.	genetic analysis	24/26	Sweden
	xylene, n-hexane, styrene, acetone, toluene, trichloroethylene, hexane, other hydrocarbons	Moen BE, 1990	2337535	Increased amounts of protein, albumin, and IgG were found in patients diagnosed with chronic toxic encephalopathy who were exposed to organic solvents. This suggests that organic solvents alter the blood-brain barrier.	cerebrospinal fluid analysis	19/16	Norway
	not specified	Reis J, 2001	11603618	Authors attribute the development of MS in the man to have been triggered by the action of organic solvents. They hypothesize that organic solvents impaired the impermeability of the blood-brain barrier.	case study of a 45 yr old man occupationally exposed to toluene	1	France
	toluene	Rosenberg NL, 1988	3408242	MRI scans of toluene abusers showed brain atrophy and loss of differentiation between gray and white matter, suggesting that toluene either increases the water content of white matter or causes metabolic changes in myelin.	case study	7	USA
	not specified	Wikkelso C, 1984	6592927	Patients heavily exposed to organic solvents had increased albumin ratio in the CSF compared to controls, indicating that the blood-brain barrier became more permeable to macromolecules because of organic solvents.	case-control study /CSF analysis	17/17	Scandinavia
RADIATION							
	ionizing	Axelson O, 2001	11490163	Researchers found an odds ratio of 4.4 (95% CI 1.6-11.6) for radiological work, and 1.8 (95% CI 1.2-2.6) for X-ray examinations for MS subjects when compared with non MS subjects	case-control study	174/814	Sweden

		Flodin U, 1988	3369968	The Mantel-Haenszel rate ratio for MS subjects who had x ray examinations as compared with non-MS subjects was 2.4 (95% CI 1.4-4.0)	case-control study	47/174	Sweden
		Cooper RL, 1997	9352500	Cooper hypothesized that ionizing radiation generated free radicals within the body, which in turn damaged myelin. He theorized that this could be the initiating factor of multiple sclerosis.	-	-	-
		Landtblom AM, 1993	8153592	MS subjects had X ray treatment until 5 years before diagnosis, but no controls had same experience	case study	5	Sweden
		Peterson K, 1993	8413974	Radiation may have a detrimental effect on patients with MS by quickening the rate of demyelination	case study	5	USA
	radon	Gilmore M, 2003	12901091	Researchers found a positive correlation between level of radon exposure and the risk of MS.	epidemiological study	-	Ireland
		Bolviken B, 2003	12566959	Researchers found a positive, statistically significant correlation between level of indoor radon and risk of MS.	epidemiological study	-	Norway
OTHER							
	illegal drugs	Brosseau L, 1993	8327025	There was a positive correlation between drug abuse and the risk of MS. No correlation was found between alcohol and medical abuse and MS.	case-control study	108/108	Canada
	oral contraceptives	Hernan MA, 2000	10994007	Use of oral contraceptives (ever or current) was not correlated to an increased risk of developing MS.	two prospective cohort studies	121,700 and 116,671	USA
		Thorogood, 1998	9883921	Results of a cohort study of women showed no elevated risk of MS due to use of oral contraceptives	cohort study	46,000	USA
		Villard-Mackintosh L, 1993	8449016	Data showed no increased risk of MS due to oral contraceptive use or pregnancy	prospective study	17,032	Britain
	herbicides and pesticides	Casetta I, 1994	8015665	Researchers found no correlation between exposure to herbicides and pesticides and multiple sclerosis (OR=0.95, 95% CI: 0.4-2.21)	case-control study	104/150	Ferrara, Italy
		Landtblom AM, 1993	8153592	There was no correlation between herbicide exposure and risk of MS	case-referent study	91/540000	Sweden