

Formaldehyde neurotoxicity: Effects on the mammalian brain, cognitive function, and neurodegenerative risk. A scoping review

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Abstract

Aqueous formaldehyde (FA) solution, known as formalin, is currently the primary agent used for preserving tissue samples and anatomical specimens. Formaldehyde is widely used in laboratories and the chemical industry; it also occurs as an air pollutant and endogenous cellular metabolite. The potential carcinogenic effects of formalin on the respiratory tract are well documented. A less recognized consequence of occupational exposure to FA is its detrimental effect on the central nervous system (CNS) and brain function. A literature review was conducted to investigate the effects of FA on the brain. Five databases were searched: PubMed, Web of Science (WoS), Embase, ScienceDirect, and Google Scholar. To describe the effects of FA exposure and endogenous FA generation, 35 relevant publications were collected and analyzed. The literature review demonstrated that inhalation is the most common route of FA exposure. Several studies have shown that FA may cause hippocampal damage, disrupt melatonin secretion, and induce a wide range of cognitive disorders with varying characteristics and severity. These disorders include memory impairment, disturbances in balance and spatial orientation, learning difficulties, sleep disturbances, impaired judgment, and prolonged reaction times to stimuli. Increased endogenous FA concentration has also been associated with a higher risk of neurodegenerative diseases, such as Alzheimer's disease (AD) and amyotrophic lateral sclerosis. The literature analysis demonstrated the high neurotoxicity of FA, which may lead to numerous neuropsychiatric disorders. We aim to draw attention to the risks associated with the routine use of formalin, particularly among anatomists and pathologists, and to encourage consideration of less harmful alternative preservation agents.

Key words: formaldehyde, occupational exposure, cognitive impairment, neurotoxicity, neurodegenerative diseases

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Highlights

- Formaldehyde exposure may contribute to deterioration in mental health.
- Research suggests that formaldehyde exposure may affect mood, cognitive function, and sleep quality.
- Formaldehyde contributes to oxidative stress and apoptosis in neural cells, potentially leading to cognitive decline.
- Reducing or eliminating formaldehyde use in research, particularly in medical settings, should be a priority for occupational safety and health.

Introduction

Formaldehyde (FA) has been known for more than 150 years. It was first synthesized in gaseous form in 1859 by Alexandr Butlerov. Nearly a decade later, in 1868, German scientist August Wilhelm von Hofmann described its chemical structure.¹ Since then, numerous applications of this substance have been identified. Formaldehyde is commonly used in the textile industry and carpentry as a substrate for the production of resins and glues and, in the form of an aqueous solution known as formalin, is widely recognized as the main ingredient of body-preserving solutions used for anatomical and funeral purposes. The use of FA in anatomy began at the end of the 19th century,² and since then it has continued to be used as a fixative for tissue preservation by pathologists and histologists.³

Formaldehyde is also present in the air we breathe as an environmental pollutant,^{4,5} and is a component of cigarette smoke and vehicle exhaust fumes.^{6–8} It is widely used in industrial production as a substrate in the chemical industry⁹ and can also be found in cosmetic products.^{10,11} A lesser-known fact is that FA is one of the products of biochemical pathways in the human body.¹² These examples demonstrate that the human population is constantly exposed to FA. The level of exposure may vary depending on occupation or place of residence, but exposure is unavoidable.

In 2004, FA was classified as a carcinogen by the International Agency for Research on Cancer (IARC).¹³ There is sufficient evidence suggesting that it increases the risk of nasopharyngeal cancer and leukemia.¹⁴ Several studies have also investigated whether FA exposure may increase the risk of brain tumor development.¹⁵ Formaldehyde has been identified as a neurotoxic substance in numerous *in vivo* and *ex vivo* studies. Although the carcinogenic properties of FA are widely recognized, it continues to be extensively used. Its low cost and ease of use contribute to its popularity in pathology, histology, and education (e.g., gross anatomy courses). In contrast to other fixatives, FA penetrates tissue easily, acts rapidly, and does not require unusual storage conditions. However, relatively few studies have examined the neurotoxicity of FA and its potential effects on cognition and behavior.

Objectives

In this study, we examined the relationship between neuronal damage and death and reduced brain function associated with exposure to FA and endogenous FA production. In particular, we focused on cognitive impairment, including FA-induced alterations in memory and attention span. We also investigated whether FA may contribute to the development of mood disorders.

Furthermore, we investigated the molecular mechanisms of FA action, its biological and psychological implications, and its potential contribution to the development of neurodegenerative diseases. Considering the contribution of FA to carcinogenesis, we hypothesized that FA may also adversely affect neuronal health and neuropsychological functioning. Our investigation aimed to provide an objective and comprehensive evaluation of the available scientific evidence regarding FA and nervous system health.

Materials and methods

Eligibility criteria

To explore the influence of FA on the central nervous system (CNS), we reviewed the available literature. Only original full-text articles written in English were included. Review articles were excluded. No restrictions regarding publication date were applied. We included studies conducted in humans, animal models, and cell cultures. We searched for information regarding changes in cognitive function, cognitive decline, and behavioral alterations following FA exposure. Additional selected articles described FA metabolism and biochemical pathways in organisms, particularly mechanisms underlying neuronal damage and alterations in neuronal physiology. Finally, we also included articles addressing the influence of exogenous and endogenous FA on neurodegenerative diseases.

Information sources and search strategy

Our search was conducted in 5 databases: PubMed, Web of Science (WoS), Embase, ScienceDirect, and Google Scholar. The search began on November 27, 2023, and ended on December 7, 2023.

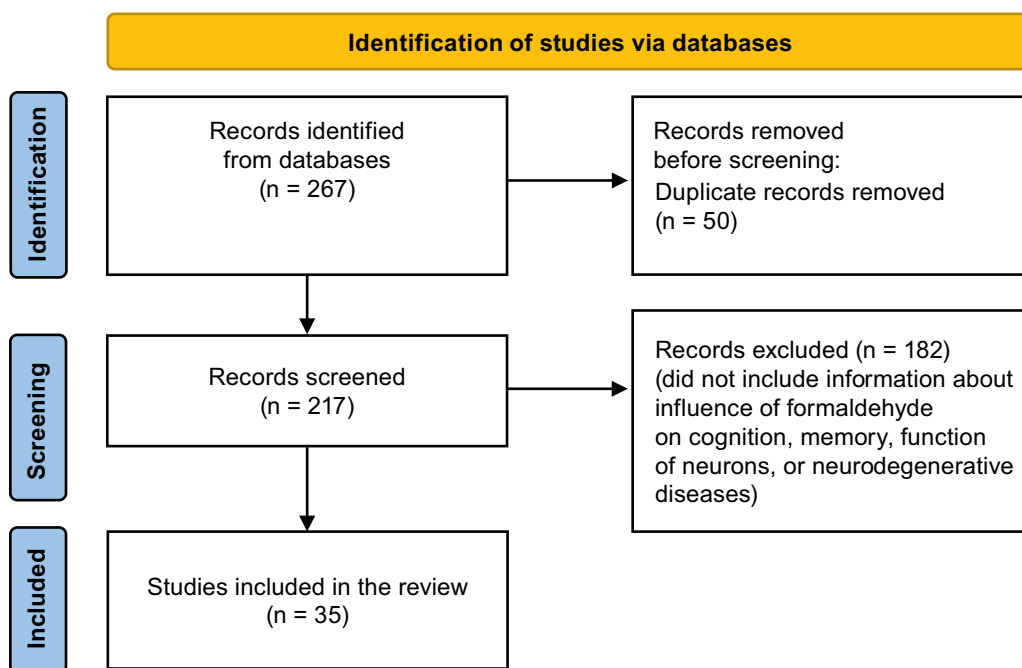


Fig. 1. Flow diagram depicting the study selection process

We defined search phrases that were subsequently used to identify articles describing FA and the CNS. The search phrases consisted of the constant term “formaldehyde exposure”, combined with the following additional terms: “human”, “brain damage”, “cognition”, “cognitive functions”, “dementia”, “intelligence”, “memory”, “memory loss”, “neurobehavioral impairment”, “neurological disorders”, “neuropsychiatric disorders”, “neurotoxicity”, and “induced neuron apoptosis”.

Data collection and outcomes

In the initial search, based on title screening conducted in the above-mentioned databases, we identified 267 articles. After removing duplicates, 217 papers remained. Subsequently, abstracts of these articles were screened, which reduced the number of eligible studies to 35. Studies conducted on animal models comprised 18 of the 35 articles included in the final pool of selected studies (Fig. 1).

In the next step, data were extracted from the selected articles, which were subsequently reviewed and summarized. Using an extraction form created in Microsoft Word 365 (Microsoft Corp., Redmond, USA), we collected all data related to the above-mentioned terms. We searched for information regarding the effects of FA on neuronal function and the CNS. The collected data also addressed the neurotoxicity of FA. We then examined the impact of neuronal damage or death on cognitive functions, including memory, learning processes, spatial orientation, reaction time, abstract thinking, and judgment, as well as prolonged reaction times to stimuli. We were also interested in attention span, behavioral changes, and affective disorders following exposure. Although the focus was mainly on acute and chronic FA exposure, we also

considered endogenous FA formation in the context of cognitive decline and neurodegenerative diseases.

The collected data were subsequently organized into 4 main subject areas: neurotoxicity, the influence of FA on memory, the influence of FA on other cognitive functions, and the development of FA-related neurodegenerative diseases. The summarized data from all studies included in this review are presented in Table 1,^{16–24} Table 2,^{24–43} and Table 3.^{4,5,44–52}

Results and discussion

Neurotoxicity of formaldehyde

Formaldehyde readily crosses the blood–brain barrier (BBB).⁵³ Once in the brain, it may damage neurons. For example, the methyl donor *S*-adenosylmethionine (SAM) in PC12 cell cultures derived from patients with Parkinson’s disease induces a cascade of methanol-derived reactions leading to the formation of endogenous FA. Formaldehyde, produced through oxidation of methanol during SAM-induced reactions, showed marked toxicity toward neuron-like PC12 model cells, which are catecholaminergic pheochromocytoma cells. Under the same conditions, methanol and formic acid did not exhibit comparable toxicity. Furthermore, FA induced a considerably weaker toxic effect in C6 glial cell cultures – mainly excessive protein carboxymethylation and inhibition of tyrosine hydroxylase expression – indicating that neurons may be more susceptible to FA toxicity than glial cells. However, prolonged incubation resulted in decreased viability of both PC12 and C6 cells, suggesting that exposure duration plays a crucial role in the toxic effects of FA on human neuronal and glial cells.¹⁹

Table 1. Formaldehyde-induced mechanisms of neurotoxicity

Reference	Model (human/ animal/cell line)	Size – control group	Size – experimental group(s)	Type and duration of exposure	Mechanism of neurotoxicity	Results
Askar and Halloull (2018) ¹⁶	rat	10 – group 1	10 (group 2), 10 (group 3)	Airborne FA exposure; Group 2: FA exposure for 6 h/day, 5 days/week for 12 weeks, Group 3: FA exposure for 6 h/day 5 days/week + omega-3-wheat germ oil supplement, for 12 weeks	Increased production of ROS; upregulation of BAX	Damage to neurons; Intensified OS, apoptosis
Ciftci et al. (2015) ¹⁷	rat	10	10 (group 2), 10 (group 3)	Group 2: 37% FA injection, 9 mg/kg for 15 days; Group 3: 37% FA injection, 9 mg/kg paired with 100 mg/kg curcumin every day, for 15 days	Increased levels of 8-OHdG in the brain tissue and urine of rats from group 2	Oxidative stress in rats' brains
Gurel et al. (2005) ¹⁸	rat	13	18 – FA, 18 – FA + vitamin E	Intraperitoneal injection 10 mg/kg of FA for 10 days	Lipid and protein peroxidation; formation of ROS; Decreased SOD and cat activity in brain tissue	Increased OS; Degenerative changes in neurons
Lee et al. (2008) ¹⁹	PC12 and C6 cell lines	untreated cells	cells treated with FA, methanol and formic acid	Incubation of cells in increasing concentrations of FA for 24 h	Excessive protein carboxymethylation; Inhibition of tyrosine hydroxylase expression	Death of neurons
Li et al. (2020) ²⁰	rat	11	11 FA-treated (group 1) 11 FA-NHS-treated (group 2)	Intracerebroventricular injection 10 µmol/day FA for 7 days	Significant increase in MDA level and decrease in SOS activity in hippocampal cells; Reduction of expression of BDNF protein; Significant increase in number of apoptotic neurons	Promotion of OS and apoptosis in hippocampal neurons
Li et al. (2021) ²¹	mouse HT22 cell line	untreated cells	cells treated with FA, concentration of 0.1, 0.5, or 1.0 mM	Cells cultured with FA for 6 h	Induction of changes leading to ferroptosis; Upregulation of Warburg effect	Reduced cell viability and increased mortality; Iron-dependent apoptosis in neurons; Increase in oxidative stress
Tang et al. (2013) ²²	PC12 cell line	untreated cells	cells treated with FA	FA present in the phosphate-buffered saline (PBS), 5–15 min incubation	Decrease in anti-apoptotic BCL2 protein; Release of CYT-C leading to apoptosis; Increase in ROS levels; concentration dependent inhibition of paroxonase-1 expression and activity	Induction of apoptosis in PC12 cells; Increase in oxidative stress
Tang et al. (2013) ²²	PC12 cell line	untreated cells	cells treated with FA	120 and 240 mmol/L FA concentrations, incubation for 24 h	Significantly decreased NO and H ₂ S production and CBS expression in cells	Reduced cells' viability; neurotoxicity of FA; Increased ROS accumulation in treated cells
Umansky et al. (2022) ²³	NALM6 and HCT116 cell line	untreated cells	cells treated with FA	Incubation of cell cultures in FA	FA blocks GSH antioxidant capability	Impairment of antioxidant defense; Accumulation of ROS
Zendejdel et al. (2016) ²⁴	human	32	35	Occupational exposure to FA vapors, exposure predates beginning of the study	Higher levels of ache activity in erythrocytes of experimental group	Possible connection with cognitive decline

FA – formaldehyde; ROS – reactive oxygen species; OS – oxidative stress; 8-OHdG – 8-hydroxy-2'-deoxyguanosine; SOD – superoxide dismutase; CAT – catalase; PC12 – pheochromocytoma cell line; C6 – rat glial tumor cell line; MDA – malondialdehyde; BDNF – brain-derived neurotrophic factor; HT22 – mouse hippocampal neuronal cell line; Cyt-C – cytochrome C; NO – nitric oxide; H₂S – hydrogen sulfide; CBS – cystathionine β-synthase; GSH – glutathione; AChE – acetylcholinesterase; NHS – N-hydroxysuccinimide.

Table 2. Influence of FA on cognitive functions

Reference	Model (human/animal/cell line)	Size (control group)	Size – experimental group(s)	Type and duration of exposure	Results
Bach et al. (1990) ²⁵	human	not disclosed	61: 32 – workers occupationally exposed to FA 29 – unexposed occupationally	FA concentrations: 0.0, 0.15, 0.4, or 1.2 mg/m ³ climate chamber for 5.5 h for 16 days	possible distractive sensory irritation due to FA exposure
Dou et al. (2012) ²⁶	mouse	12	12 – 1 mg/m ³ FA concentration, 12 – 3 mg/m ³ FA concentration, 12 – 5 mg/m ³ FA concentration	airborne FA exposure	impaired memory and learning ability in mice exposed to FA, increasing with FA concentration
Kilburn et al. (1987) ²⁷	human	not disclosed	305	airborne FA exposure, exposure predated beginning of the study, total duration of exposure varying between individuals	reduced performance on story memory, visual memory, digit span, and sharpened-Romberg
Kilburn et al. (1983) ²⁸	human	not disclosed	420 – FA concentration ranging from 0.4 ppm to 5 ppm	airborne FA exposure, exposure predated beginning of the study, total duration of exposure varying between individuals	impaired short-term memory impaired ability to concentrate
Kilburn et al. (1985) ²⁹	human	26	45 – exposed to FA during fiberglass batt-making, 18 – exposed to FA during fixation of the tissue in histology laboratories	airborne FA exposure, exposure predated beginning of the study, total duration of exposure varying between individuals	impaired memory, loss of concentration, sleep disturbances, dizziness, mood swings
Kilburn et al. (1985) ³⁰	human	56 – only women	76 – only women	airborne FA exposure, exposure predated beginning of the study, total duration of exposure varying between individuals	impaired memory, mainly short-term; loss of concentration, sleep disturbances, mood swings, dizziness and headaches, loss of balance
Letellier et al. (2022) ³¹	human	~69,296	~6,026	occupational exposure, exposure predated the beginning of the study, total duration of exposure varying between individuals	higher risk of global cognitive impairment in exposed population; the severity of cognitive impairment increasing in correlation with level of exposure to FA
Li et al. (2020) ³²	mouse	10	10–0.5 mg/m ³ FA concentration, 10–3.0 mg/m ³ FA concentration	airborne FA exposure	impaired memory and learning ability in mice exposed to FA
Li et al. (2016) ³³	mouse	15	15–1 ppm FA concentration, 15–2 ppm FA concentration	airborne FA exposure, 2 h a day for 7 days	impaired memory and novel objects recognition in mice exposed to higher (5 ppm) doses of FA, depression- and anxiety-like behavior
Lu et al. (2008) ³⁴	mouse	5	5–1 mg/m ³ FA concentration, 5–3 mg/m ³ FA concentration	airborne FA exposure, 6 h a day for 7 days	impaired memory, impaired ability to learn
Malek et al. (2003) ³⁵	rat	not disclosed, total number of rats in both groups was 120	not disclosed, total number of rats in both groups was 120, animals in experimental group were divided to smaller assemblies with different levels of FA exposure	airborne FA ingestion, 10 h a day for 7 days	impaired memory, impaired ability to learn
Marceaux et al. (2008) ³⁶	human	15	5	airborne FA ingestion through smoking marijuana cigarettes, laced with PCP; exposure predated the beginning of the study, total duration of exposure varying between individuals	vocabulary decline, impairment of abstract thinking

Table 2. Influence of formaldehyde on cognitive functions – cont.

Reference	Model (human/animal/cell line)	Size (control group)	Size – experimental group(s)	Type and duration of exposure	Results
Mei et al. (2016) ³⁷	mouse	8	3 groups of n = 8 group 2 – gaseous FA 3.0 mg/m ³ , group 3 – melatonin injection, group 4 – FA + melatonin	airborne FA ingestion, 8 h for 7 days (groups 2 and 4)	lower spatial learning ability, impaired memory retrieval ability
Perna et al. (2001) ³⁸	human	not disclosed	1	acute occupational exposure	impaired general memory, impaired ability to acquire new information
Pitten et al. (2000) ³⁹	rat	14	13–2.6 ppm FA concentration, 13–4.6 ppm FA concentration	airborne FA ingestion, 10 min a day for 90 days	increasing with level of FA exposure: impaired memory formation, impaired learning ability
Schenker et al. (1982) ⁴⁰	human	not disclosed	24	airborne FA ingestion, exposure predates beginning of the study, exposure duration ranging from 6 months up to 3 years	impaired memory, impaired attention span
Tang et al. (2013) ⁴¹	rat	not disclosed	not disclosed; FA concentration: 0.1, 1, or 10 µmol/2.5 µL	FA injection, 7 days	impaired ability to learn
Tong et al. (2013) ⁴²	rat, rat hippocampal neurons and astrocytes culture, human brain samples (healthy and from those who suffered from AD)	not disclosed not applicable not applicable	not disclosed not applicable not applicable	rats: intraperitoneally injected solution 60 mg/kg acute for 7 days chronic for 30 days	suppression of long-term potentiation; NMDA receptor inhibition, resulting in memory loss or memory formation disturbance
Tong et al. (2013) ⁴³	rat, human SY5Y cell culture, rat hippocampal neuron cell line	not disclosed not applicable not applicable	not disclosed not applicable not applicable	FA injection	impaired memory in rats exposed to FA, decreased methylation, re-methylation of the DNA in cells from cell cultures
Zendehdel, et al. (2016) ²⁴	human	32	35	airborne FA ingestion during preparation of melanin tableware, exposure predates the beginning of the study, total duration of exposure varying between individuals	concentration of active AChE particles in the blood increased

FA – formaldehyde; ROS – reactive oxygen species; OS – oxidative stress; 8-OHdG – 8-hydroxy-2'-deoxyguanosine; SOD – superoxide dismutase; CAT – catalase; PC12 – pheochromocytoma cell line; C6 – rat glial tumor cell line; MDA – malondialdehyde; BDNF – brain-derived neurotrophic factor; HT22 – mouse hippocampal neuronal cell line; Cyt-C – cytochrome C; NO – nitric oxide; H₂S – hydrogen sulfide; CBS – cystathionine β-synthase; GSH – glutathione; AChE – acetylcholinesterase; NHS – N-hydroxysuccinimide; NMDA – N-methyl-D-aspartate; SH-SY5Y – human neuroblastoma cell line; AD – Alzheimer's disease.

Moreover, numerous studies conducted in laboratory animals have demonstrated visible alterations in brain neuronal tissue following FA exposure. Detected abnormalities included increased reactive oxygen species (ROS) formation,^{16,18} other manifestations of oxidative stress (OS),¹⁷ neuronal apoptosis,^{16,20} and neuronal degeneration (Fig. 2,3).¹⁸

Oxidative damage induced by FA

Following FA exposure, numerous biochemical changes indicative of redox imbalance have been observed across different studies. Levels of malondialdehyde (MDA)

in the frontal cortex and hippocampus increased after FA exposure.^{16,18,21} Malondialdehyde is a product of lipid peroxidation and is considered one of the most important markers of OS.⁵⁴ Increased MDA levels have also been observed under controlled conditions simulating occupational exposure.¹⁶ In the frontal cortex and hippocampus, catalase and superoxide dismutase (SOD) activity decreased following FA exposure.^{16,18} Both enzymes are involved in defense against OS – catalase through decomposition of hydrogen peroxide (H₂O₂)⁵⁵ and SOD through dismutation of superoxide anion radicals into H₂O₂.⁵⁶ Rats exposed to FA also exhibited elevated

Table 3. Influence of FA on the development of neurodegenerative diseases

Reference	Model (human/animal/cell line)	Size – control group	Size – experimental group(s)	Type and duration of exposure	Symptoms, results of study
Calderon-Garciduenas et al. (2015) ⁴	human	44 – from group 2	95 67 (group 2) 28 (group 1)	airborne FA ingestion correlated with air pollution, exposure predates beginning of the study	brain imbalance impacting levels of oxidative stress, immune response and inflammation in neural tissue; higher prevalence of tight junction antibodies and neural antibodies; autoimmune response and higher risk of neuroinflammation, development of AD and Parkinson's disease
Hanna et al. (1999) ⁴⁴	human	not included in the study	100 with multiple system atrophy, 100 with Parkinson's disease	airborne FA exposure, contact with FA during work-related activities, exposure predates beginning of the study	advanced glial changes, cell loss and depigmentation in substantia nigra, development of multiple system atrophy; possible development of Parkinson's disease
He et al. (2017) ⁴⁵	N2a cell line	cells without any treatment, cells with DMSO pre-treatment and FA treatment	Cells with FA treatment, Cells with resveratrol treatment, Cells with FA and resveratrol treatment	incubation in FA	smaller and atrophied cells treated with FA, cell borders were irregular and cellular processes were reduced, FA induced neuronal cell death and tau hyperphosphorylation
Lee et al. (2020) ⁴⁶	human	40	50 with ALS	endogenous FA	significantly higher levels of FA detected in plasma of people affected with ALS
Liu et al. (2018) ⁴⁷	mouse	10	30 10 – FA exposure: 0.155 mg/kg/day, 10 – FA exposure: 1.55 mg/kg/day, 10 – FA exposure: 15.5 mg/kg/day	formalin intranasal instillation, daily for 7 days	impaired spatial memory in mice exposed to FA concentration 1.55 and 15.5 mg/kg/day, blood–brain barrier (BBB) damage, swollen and deformed hippocampal cells, with loose and disordered cell arrangement, disappearing apical dendrites, decrease in Nissl substance. damaged circular structure of the synaptic glomerulus in the olfactory bulb, FA-induced decrease in the number of cells in cerebral and prefrontal cortex, markedly increased expression of Tau-P in cerebral cortex, increased activation of glia and astrocytes, increased OS level and inflammation
Lu et al. (2013) ⁴⁸	mouse, N2a cell, rat hippocampal neuron culture	untreated cells	not disclosed	mice injected with FA solution, cells cultured with 0.5 mM FA solution; hippocampal neuron cultures treated with 0.2 mM FA at the indicated intervals	shrunken cells and atrophied largely processes, hyperphosphorylation and polymerization of tau protein in cytoplasm and nuclei of observed cells and in mice brains, possible role in AD development and other tauopathies
Nie et al. (2007) ⁴⁹	SH-SY5Y cell line, rat hippocampal cells	not applicable not applicable	not applicable not applicable	incubation with increasing concentrations of FA from 0.01% to 0.5%	induction of aggregation of human tau protein, possible role in development of tauopathies
Tong et al. (2011) ⁵⁰	human	38 patients, autopsy hippocampus tissues from 4 healthy patients, mice	141 patients with dementia, 49 hypertension or diabetes patients, autopsy hippocampus tissues from 4 patients with AD, age-related AD-like animal models – mice	not disclosed	in dementia patients and patients with mild cognitive impairment: higher levels of FA in urine, in the hippocampal tissues from patients with AD and in brains from AD-like mice models: higher levels of FA detected, in mice treated with FA for 30 days: impaired spatial reference memory function
Tong et al. (2015) ⁵¹	human	not disclosed	236 – clinical participants 139 – healthy volunteers	aging related-endogenous FA	increased FA levels in urine of clinical patients, formaldehyde levels showed positive correlation with age and levels of cognitive decline in individuals

Table 3. Influence of formaldehyde on the development of neurodegenerative diseases – cont.

Reference	Model (human/animal/cell line)	Size – control group	Size – experimental group(s)	Type and duration of exposure	Symptoms, results of study
Tong et al. (2015) ⁵¹	human hippocampal tissue	8 from healthy patients	9 patients with AD	endogenous FA	increased formaldehyde levels and reduced global methylation in hippocampus of people affected with AD, significant decrease of DNMT1 and DNMT3a in the samples from older advanced age group; 1000% increase of levels of hippocampal formaldehyde in AD patients
Tong et al. (2015) ⁵¹	rat	8	8 – recent spatial memory training, 8 – remote spatial memory training	FA injection, once a day for 7 days	deficits in spatial memory of formaldehyde-injected rats, decline in DNMT expression, significant decrease of DNMT1 and DNMT3a in the samples from 30-month-old rats compared to 3-month-old rats
Tong et al. (2015) ⁵¹	SH-SY5Y cell line	not applicable	not applicable	incubation in FA	reduction in DNMT1 and DNMT3a expression levels
Weisskopf et al. (2009) ⁵²	human	not disclosed	1,156 patients passed due to ALS	unspecified environmental exposure, including FA	doubled mortality rate for ALS for individuals with documented duration of formaldehyde exposure strong dose-response relationship with number of years of exposure
Yuan et al. (2023) ⁵	human	not included in the study	not disclosed	tropospheric FA exposure, indoor FA pollution	higher levels of tropospheric and indoor formaldehyde are linked to a higher occurrence of AD

FA – formaldehyde; ROS – reactive oxygen species; OS – oxidative stress; 8-OHdG – 8-hydroxy-2'-deoxyguanosine; SOD – superoxide dismutase; CAT – catalase; PC12 – pheochromocytoma cell line; C6 – rat glial tumor cell line; MDA – malondialdehyde; BDNF – brain-derived neurotrophic factor; HT22 – mouse hippocampal neuronal cell line; Cyt-C – cytochrome C; NO – nitric oxide; H₂S – hydrogen sulfide; CBS – cystathionine β-synthase; GSH – glutathione; AChE – acetylcholinesterase; NMDA – N-methyl-D-aspartate; SH-SY5Y – human neuroblastoma cell line; ALS – amyotrophic lateral sclerosis; Tau-P – hyperphosphorylated tau protein; DNMT1 – DNA (cytosine-5)-methyltransferase 1; DNMT3a – DNA (cytosine-5)-methyltransferase 3 alpha; DMSO – dimethyl sulfoxide; N2a – mouse neuroblastoma cell line; AD – Alzheimer's disease.

levels of 8-hydroxy-deoxyguanosine (8-OHdG), another important marker of OS,⁵⁷ in both brain tissue and urine.¹⁷

Exposure to FA decreases glutathione levels while increasing concentrations of 4-hydroxynonenal.²¹ Concentrations of lipid peroxides and oxidized proteins also increased,^{16,18,21} as did total ROS levels.^{21,22} Increased ROS levels reduced the viability of PC12 cells.²² This overall increase in OS marker levels following exposure suggests substantial intensification of OS induced by FA.

The intensification of OS may result from multiple pathways. Incubation of PC12 cells with FA leads to a significant decrease in the concentration and production of the antioxidant molecule H₂S. Exposed cells also displayed a significant increase in inducible nitric oxide synthase (iNOS)¹⁶ and neuronal nitric oxide synthase (nNOS) levels and over-produced nitric oxide (NO), which is a major mechanism inhibiting cystathionine β-synthase, the H₂S-producing enzyme in PC12 cells.²² Formaldehyde also interacts with glutathione (GSH), thereby depleting the organism's antioxidant defenses.²³ Intensification of OS may additionally result from inhibition of paraoxonase-1, an antioxidant enzyme.⁵⁸

It is well established that neurons are highly susceptible to damage caused by OS, especially those located in the hippocampus and amygdala.⁵⁹ Given the information presented above, OS may be considered one of the major mechanisms of cellular damage associated with FA exposure.

Apoptosis induced by formaldehyde

Cells exposed to FA showed changes typical of apoptosis.^{16,22} Following exposure, neurons in the frontal cortex and hippocampus of rats exhibited extensive degenerative changes, dark pyknotic nuclei, and shrunken cytoplasm.^{18,21} Moreover, their axons retracted, and the cells became separated from one another.²¹ The cerebellum is also affected by FA exposure, leading to neuronal damage in all its layers, with Purkinje cells being the most severely affected.¹⁶ Formaldehyde exposure also results in altered expression of proteins involved in apoptosis and cellular protection. In capillaries supplying Purkinje cells, Bax protein levels increased. Bax is a pro-apoptotic protein and a member of the *Bcl-2* gene family involved in p53-mediated apoptosis activation.¹⁶

In PC12 cells, FA exposure induced cytotoxic and apoptotic effects, including decreased levels of Bcl-2 protein and increased release of cytochrome C.⁵⁸ Bcl-2 is a protein responsible for inhibiting apoptosis,⁶⁰ whereas increased release of cytochrome C into the cytoplasm leads to apoptosome formation and activation of caspase-9, thereby initiating the caspase cascade and inducing apoptosis.⁶¹

Formaldehyde may also induce ferroptosis – an iron-dependent form of programmed cell death – in HT22 cells (a mouse hippocampal cell line) by increasing expression of genes involved in the ferroptosis pathway. A possible

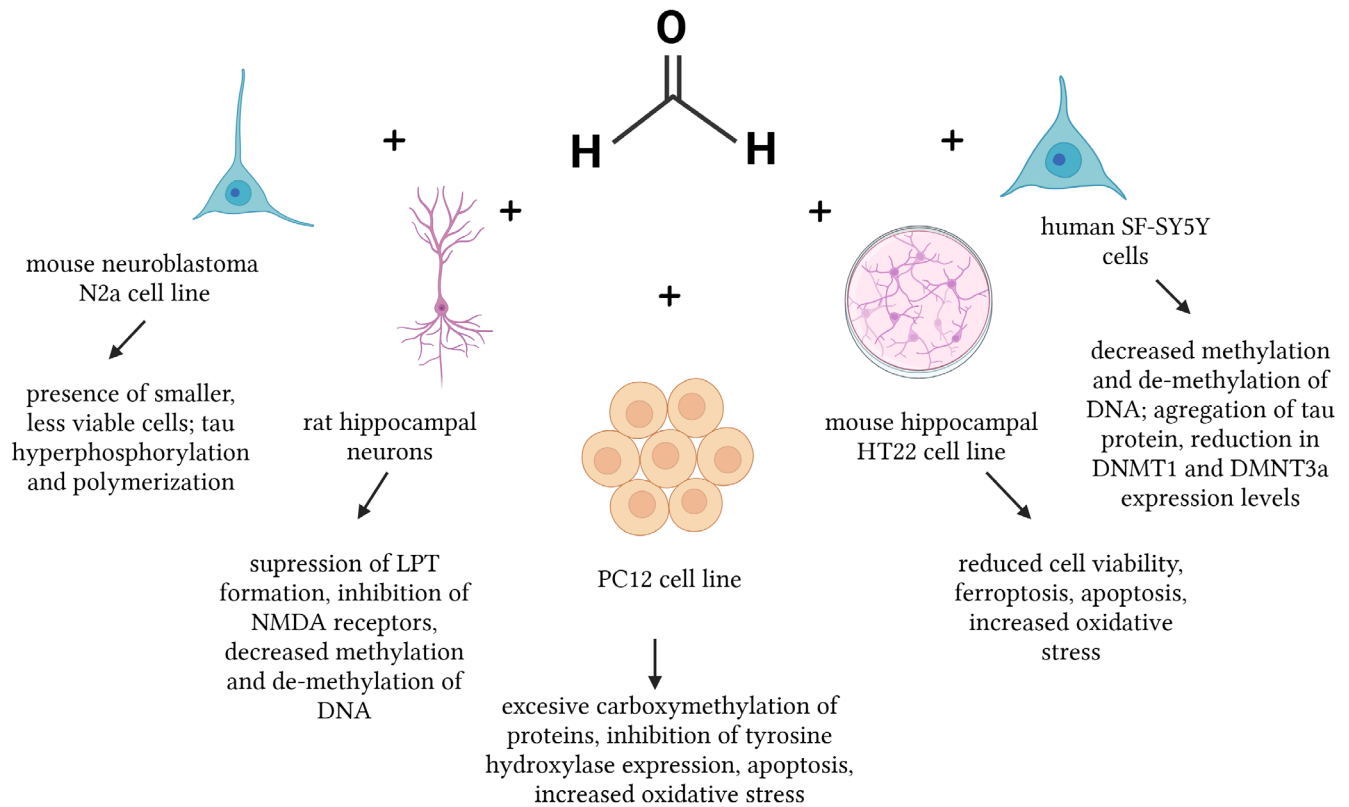


Fig. 2. The range of responses of human and rat/mouse neuronal cell lines to formaldehyde (FA) exposure (created using BioRender.com)

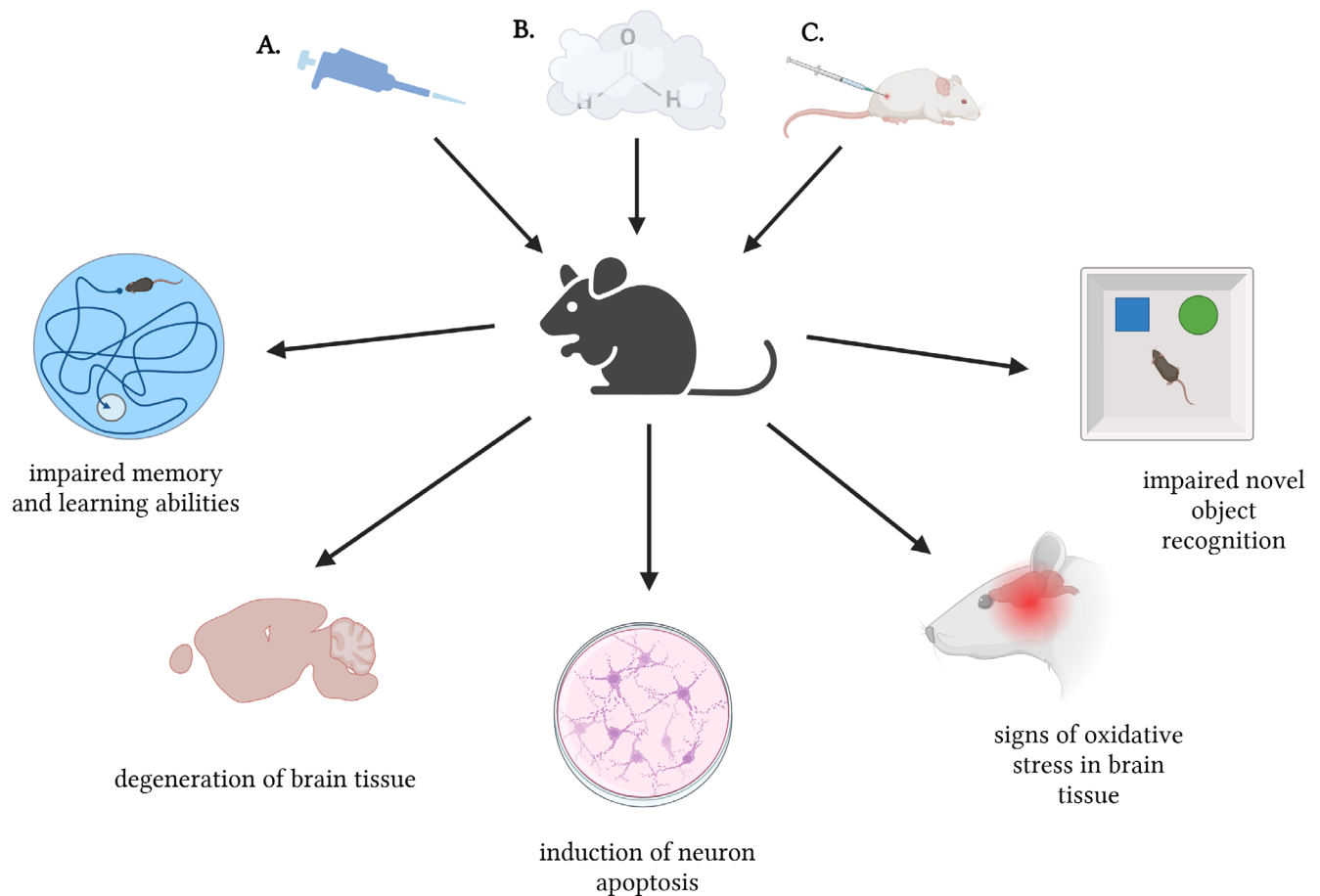


Fig. 3. The effects of formaldehyde (FA) on the function and condition of nervous tissue in mice and rats. Letter labels indicate the studied routes of FA exposure in animals. A. Intranasal instillation of FA; B. Inhalation of FA vapors; C. Intravenous administration of FA solution (created using BioRender.com)

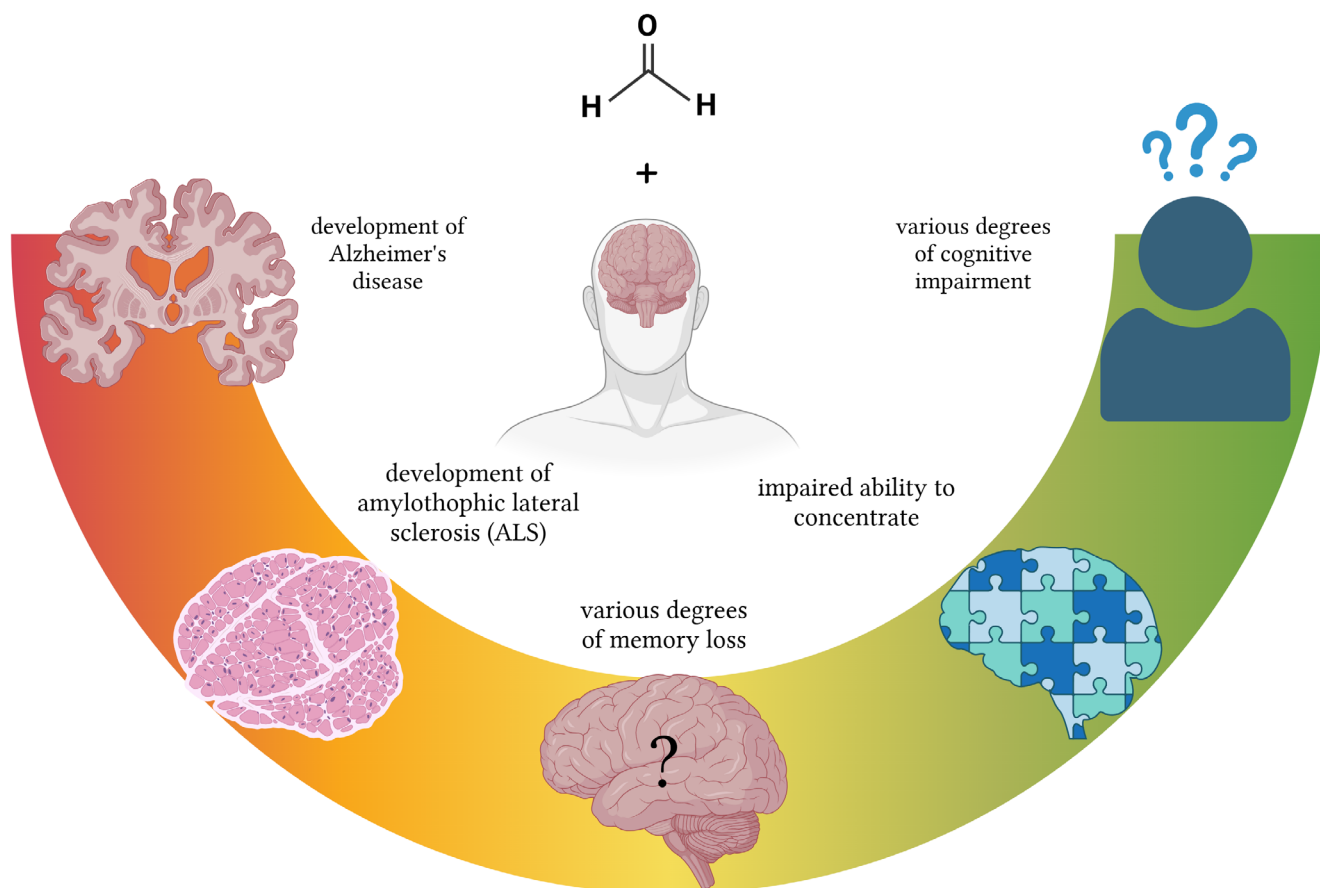


Fig. 4. Potential effects of formaldehyde (FA) on human brain function (created using BioRender.com)

mechanism underlying ferroptosis in this cell line may involve upregulation of the Warburg effect following FA exposure.²¹

Other possible mechanisms of formaldehyde neurotoxicity

Formaldehyde can cross-link proteins with nucleic acids⁶² and form covalent bonds with proteins.¹⁹ The presence of covalent bonds between FA and proteins results in accumulation of protein methylation changes typically observed in aging cells.¹⁹ Additionally, cross-linking between proteins and nucleic acids may lead to mutations in the cellular genome.⁶² Reduced dopamine activity has also been observed following FA exposure, possibly as a result of decreased expression of tyrosine hydroxylase, an enzyme involved in dopamine synthesis.³⁸

Workers exposed to FA show a significant correlation between occupational FA exposure and increased blood acetylcholinesterase (AChE) activity,²⁴ which is used as a marker of neurotoxicity.⁶³ Therefore, elevated AChE activity may indicate neuronal damage induced by FA.

Neuronal death in the hippocampus disrupts learning processes and memory.⁶⁴ Damage to cerebellar neurons is associated with impaired motor coordination, imbalance, and loss of spatial orientation.⁶⁵ Finally, damage

to the frontal lobes may lead to personality changes, reduced attention span, impaired concentration, language dysfunction, and impaired decision-making.⁶⁶ These examples demonstrate how FA-induced neuronal damage may contribute to cognitive decline.

Formaldehyde exposure leads to cognitive impairment and behavioral changes

The correlation between FA exposure and the occurrence of numerous types of cognitive impairment in humans suggests that FA may be harmful to human health (Fig. 4).^{7,14} Even moderate but persistent exposure to FA may significantly affect the cognitive functions of exposed individuals.³¹ People occupationally exposed to FA had a statistically higher risk of cognitive decline. The risk of impairment increased with the duration of exposure. Moreover, FA-induced changes persisted even after exposure had ended.³¹

Inhalation of airborne FA in the form of “fry joints” or cigarettes immersed in FA solution and laced with phencyclidine (PCP) was associated with decreased language abilities and vocabulary decline.³⁶ In the case of fry joints, however, it remains unclear whether the observed decline resulted solely from FA exposure or whether other components of “fry” also contributed.³⁶ Studies have also

reported impaired abstract thinking following FA exposure.³⁶ Additional studies demonstrated similar language impairments after occupational exposure.³¹ Another important consequence of FA exposure is reduced attention span and, in some cases, impaired concentration.^{31,40} Some individuals exposed to FA also exhibited reduced affect and psychomotor slowing.^{31,40}

Chemical analyses of workers in melamine tableware factories showed that individuals exposed to airborne FA had significantly elevated blood levels of active AChE. Such alterations are thought to contribute to cognitive impairment through reduction of cholinergic signaling in neurons.²⁴ Cases of acute airborne FA exposure leading to neurobehavioral impairment and cognitive decline have also been described, including confusion, impaired concentration, and deficits in sequential processing. Depression and emotional distress accompanied these symptoms, persisting for up to 3 years after exposure.³⁸

Studies in rat models also demonstrated that animals exposed to FA exhibited depression-like behaviors, such as reduced locomotor activity, decreased food and water intake, and anxiety-like behavior.³³ Rats exposed to FA for short periods (3 h/day for 2 days in 3 groups receiving 5 ppm, 10 ppm, and 20 ppm FA⁶⁷; or 2 h/day for 10 days in 3 groups receiving 0.1 ppm, 0.5 ppm, and 5.4 ppm FA³⁵) exhibited reduced motor activity.³⁵ Prolonged exposure led to enhanced aggressive behavior. This change was associated with disruption of dopaminergic and serotonergic pathways in the frontal cortex. Reduced activity of dopamine and serotonin neurons results in impaired concentration and attention deficits. Moreover, FA has been shown to reduce melatonin levels in rats. Rodents examined in the study conducted by Mei et al. demonstrated memory impairment and abnormal behaviors, including remaining motionless in a huddled position and decreased active exploration.³⁷ Lower melatonin levels may be associated with sleep disorders reported after FA exposure.⁵⁴ Studies have shown that decreased melatonin levels are also associated with depression, anxiety, Alzheimer's disease (AD), and other types of dementia. Melatonin supplementation has been shown to attenuate the effects of FA-induced OS and structural hippocampal damage, thereby reducing cognitive decline.³⁷

Formaldehyde exposure leads to memory loss

Formaldehyde can have a detrimental impact on memory. Several studies have investigated this issue, mostly using animal models, although some also involved humans. Animal studies investigating memory were conducted in rats and mice. These experiments employed various tests specifically designed to assess cognitive function in animals following exposure to specific factors, in this case FA in gaseous form or in solutions of various concentrations. Animals exposed to FA, either in gaseous form

or through intracerebroventricular injection, exhibited memory alterations characterized by impaired learning ability, as demonstrated in the Morris water maze and water labyrinth tests,^{34,35,41} as well as decreased memory performance observed in the step-down test.²⁶ Studies have shown that FA exposure can reduce spatial memory performance, as demonstrated in the Morris water maze and dry food-reward maze tests.^{20,32,39,42} Impaired novel object recognition may also indicate memory dysfunction and has been observed in mice exposed to FA.^{20,32}

Microscopic and biochemical studies have also been performed to investigate the possible mechanisms through which FA induces memory impairment. Formaldehyde may disrupt memory-related processes in the hippocampus by inhibiting alcohol dehydrogenase-3 and aldehyde dehydrogenase-2, thereby suppressing long-term potentiation (LTP) formation, or by nonspecifically inhibiting N-methyl-D-aspartate (NMDA) receptors,⁴³ both of which are believed to be associated with memory formation.⁶⁸ Formaldehyde may also directly impair the brain's ability to acquire new information by inducing hippocampal neuronal death,^{18,37} as demonstrated in rats following intraperitoneal injections of FA at a dose of 10 mg/kg for 10 days.¹⁸

Studies investigating the influence of FA on memory in humans included a total of 944 participants. Most focused on occupational exposure.^{25,27-30} One study was based on full-time residents of houses insulated with urea-formaldehyde foam.⁴⁰ Only 1 study was conducted under experimental conditions, in which participants were placed in a climate chamber and exposed to gaseous FA at concentrations that increased throughout the experiment.³ Individuals exposed to FA appeared to exhibit deficits in short-term²⁵ and long-term memory,^{28,29} as well as visual memory, history memory,²⁷ and episodic verbal memory.³¹ Formaldehyde originating from building materials such as foam insulation may also impair memory processes.⁴⁰ Finally, FA exposure may cause memory loss in affected individuals.³⁰ Acute and severe exposure to FA may impair both general memory and the ability to acquire new information.³⁸

Neurodegenerative diseases occurrence after formaldehyde exposure

Exposure to FA is not limited to healthcare or laboratory workers; individuals living in large urban areas may also be at risk. In major metropolitan areas, air pollution, including FA, may adversely affect health.⁴ Elevated levels of antibodies targeting FA-bound protein adducts have been detected in children living in urban environments exposed to air pollution. We would like to highlight a possible link between this heightened immune response and an increased risk of neurodegenerative diseases such as AD or Parkinson's disease.⁴ Occupational exposure to FA has also been suggested to influence the development of Parkinson's disease.³⁸

Alzheimer's disease in relation to formaldehyde

High tropospheric and indoor FA levels may be associated with an increased risk of AD in humans.⁵ Mice exposed to high concentrations of FA (1.55 mg/kg/day and 15.5 mg/kg/day) through nasal instillation exhibit brain changes resembling early manifestations of AD. These mice show disruption of the BBB, inflammation, and increased production of ROS, leading to OS. Additionally, degenerative structural changes are observed in the hippocampus, olfactory bulb, cerebral cortex, and prefrontal cortex. Exposed mice also display impaired spatial memory acquisition and retention, as demonstrated in the Morris water maze test.⁴⁷ These findings have been proposed as potential mechanisms underlying AD.⁶⁹

Formaldehyde levels in urine and the hippocampus increase with age and cognitive decline in both rats and humans with AD. In the hippocampus, elevated FA levels correlate with reduced expression of DNA methyltransferase-3 (DNMT3), resulting in suppression of its activity, as well as decreased expression of DNA methyltransferase-1 (DNMT1), as demonstrated in studies of human hippocampal tissue and rats treated with FA injections. These enzymes are responsible for DNA methylation; consequently, DNA methylation was also reduced under these conditions.⁵¹ DNA methylation is crucial for spatial memory formation and maintenance of long-term memory.⁷⁰ Inhibition of DNMT activity and expression by FA may therefore contribute to the pathophysiology of AD.⁵¹

Elevated FA levels in mouse and rat cells have also been associated with the presence of hyperphosphorylated tau protein analogs linked to AD.^{47,48} Formaldehyde particularly affects nuclear tau protein, inducing hyperphosphorylation mediated by glycogen synthase kinase-3 β (GSK-3 β), as demonstrated in studies of neuroblastoma (N2a) cell nuclei and mouse brains.⁴⁸ This hyperphosphorylation is accompanied by aggregation of reversible hyperphosphorylated tau protein polymers within the cytoplasm,⁴⁸ as well as morphological changes in these cells, including shrinkage, disruption of cellular processes,^{45,48} and ultimately cell death.⁴⁵

Formaldehyde also influences tau protein misfolding and aggregation, which may contribute to the development of tauopathies. Tau protein plays a key role in maintaining cytoskeletal structure through its association with microtubules.⁷¹ Formaldehyde induces formation of amyloid-like aggregates in rats and human neuroblastoma cells,⁴⁹ amyloid plaques in mice and rats,⁴⁷ and amyloid- β accumulation in mice.⁵⁰

Alzheimer's disease is the most common cause of dementia.⁷² Formaldehyde levels in the hippocampi of individuals with dementia are significantly elevated. However, the study sample was small ($n = 4$); therefore, further studies are needed to confirm or refute this observation. Urine samples demonstrated significantly increased FA

levels in patients with AD and slightly increased levels in patients with mild cognitive impairment. Studies using transgenic mice have shown that elevated FA levels accompany amyloid- β deposition.⁵⁰ Formaldehyde increases both the number and size of amyloid- β oligomers.⁵² The potential use of urinary FA measurement as a biomarker of dementia cannot be excluded.⁵⁰

Amyotrophic lateral sclerosis and formaldehyde

Among individuals exposed to FA, the mortality rate from amyotrophic lateral sclerosis (ALS) is more than twice as high as that observed in non-exposed individuals, and the duration of FA exposure appears to have a significant impact.⁷³ Elevated plasma FA levels may increase the risk of ALS or exacerbate disease progression. Plasma FA levels in patients with ALS were higher than those observed in healthy individuals, as demonstrated in the study conducted by Lee et al.⁴⁶ Increased FA levels induce abnormal folding and aggregation of tau protein in nerve cells, leading to apoptosis, as shown in the study by Nie et al. conducted on SH-SY5Y human neuroblastoma cells.⁴⁹ Additionally, the presence of FA in cells increases mitochondrial membrane permeability and decreases SOD activity, thereby causing oxidative damage, as observed by Hanna et al.⁴⁴ These are all mechanisms associated with ALS.

Air pollution, including the presence of FA, has also been suggested to influence the development of multiple system atrophy. This was supported by findings of extensive cell loss, glial alterations such as glial cytoplasmic inclusions, and depigmentation in the substantia nigra (SN) and locus coeruleus (LC), identified post mortem in a previously exposed patient.³⁸

Limitations of the study

However precise and thorough we aimed to be, our review is not without limitations. First, the heterogeneity of the studies available on FA exposure-related diseases made any type of meta-analysis impossible. We also acknowledge that our search strategy, although broad, may have lacked certain details, which could have resulted in omission of some relevant studies. Even though the data included in this review were collected using structured tables with predefined variables of interest, some information may still have been overlooked; e.g., certain important details may not have been fully captured.

Conclusions

The purpose of this study was to gather and analyze the available literature describing the influence of FA on the human brain and cognition. We aimed to highlight










potential problems that may result from exposure to this compound. Formaldehyde may negatively affect cognitive function. Reported symptoms include language and vocabulary difficulties, reduced attention span, depression, emotional distress, and anxiety. Sleep disturbances have also been described following FA exposure. Most studies in this area focus on memory and demonstrate substantial impairment of memory function. Formaldehyde also promotes pathological changes associated with neurodegenerative diseases such as AD and ALS. At the cellular level, FA primarily disrupts the function of the frontal cortex, hippocampus, and cerebellum. The main mechanisms underlying neuronal damage and death appear to be OS and apoptosis induction. Based on the available evidence, FA is not neutral to CNS health. However, most studies have been conducted using animal models. Therefore, further research involving human participants is needed and may be feasible due to the widespread use of FA in industry and medicine.

This review provides additional arguments supporting the need to identify safer alternatives to FA for tissue preservation, particularly in medicine. We hope that increasing awareness of the effects of FA on brain function will contribute to the development of improved strategies for minimizing exposure or, where possible, eliminating it entirely. This issue is especially important in anatomy, where FA remains the primary preservative used for cadavers. As a result, students and teachers are routinely exposed to chemical agents that may impair concentration and learning ability, in addition to potentially increasing the risk of serious neurological disorders. It is in our best interest to create an environment in which young people can study safely and develop into highly qualified specialists and physicians.

Use of AI and AI-assisted technologies

Not applicable.

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