

# The Toxic Effects of Formaldehyde on the Nervous System

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## 1 Introduction

### 1.1 Physical and Chemical Features

Formaldehyde (FA) (formula: HCHO; IUPAC name: metanal) is a member of the aldehyde family and is one of the simplest organic molecules. FA is an irritating, colorless gas that has a pungent smell (Franklin et al. 2000; Smith 1992; Songur et al. 2003; Yamato et al. 2005). It is rarely found in its original state because it has a short half-life in air and decomposes in light to form a toxic substance. FA is highly soluble in water, as well as in most organic solvents, and is a highly reactive molecule that can be irritating to tissues through direct contact. Furthermore, FA causes cytotoxicity through the formation of strong DNA–protein cross-links, as well as cross-links with other molecules, e.g., amino acids (Cheng et al. 2003; Gurel et al. 2005; Metz et al. 2004).

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FA is easily absorbed through the respiratory and gastrointestinal tracts, is metabolized to formic acid (formate) in the nasal mucosa, liver, and erythrocytes of living organisms, and is then excreted in the urine and feces, or is converted into carbon dioxide and exhaled. There are at least seven enzymes that catalyze the oxidation of FA in animal tissues, namely aldehyde dehydrogenase, xanthine oxidase, catalase, peroxidase, aldehyde oxidase, glyceraldehyde-3-phosphate dehydrogenase, and a specific NAD-dependent formaldehyde dehydrogenase (FDH) (Cooper and Kini 1962; Gurel et al. 2005; Solomons and Cochrane 1984). During this latter reaction, the FDH enzyme requires glutathione as a cofactor. Therefore, inhaled FA certainly affects liver metabolism. FA is a naturally occurring metabolite that is found in varying degrees within cells; however, FA cannot be stored in cells (Barber and Donohue 1998; Sogut et al. 2004).

The binding of FA to proteins and nucleic acids, subsequent to being metabolized, is known as *metabolic binding*. Inhaled FA rapidly forms covalent bonds, through several metabolic pathways, with intracellular DNA, RNA, and protein pools, and these interactions underlay the toxic effects of FA. The direct binding reaction without metabolic breakdown, generally in nasal mucosa, is called *irreversible binding* and results in necrosis, allergy, and mutagenicity in living organisms (Upreti et al. 1987). The gaseous form of FA, at concentrations greater than 6 ppm (part per million), causes injuries and cellular denaturation in the nasal mucosa. For this reason, FA concentrations of 6 ppm or greater have been accepted as the *cytotoxic concentration* for nasal mucosa in rats (Morgan 1997).

## 1.2 Sources and Uses

FA is produced and used worldwide on a large scale, predominately in industry, for the production of resins, manufacturing of building materials, and as a component of numerous household products. FA is found in nature, domestic air (e.g., sourced from paint, insulating materials, chipboard and plywood, fabrics, furniture, paper), cosmetics, cigarette smoke, and in the polluted atmosphere of cities from the incomplete combustion of organics, photochemical smog, and off-gassing of products containing FA (Aslan et al. 2006; Franklin et al. 2000; Smith 1992; Songur et al. 2008; Usanmaz et al. 2002).

FA is widely found in workplaces. Occupational exposure to FA mainly results from its presence in amino and phenolic resins used in several products, such as plastics, varnishes, and glues. FA is also used as a component in sanitizing products, histological fixative products, and embalming fluids, and serves as an intermediate in chemical synthesis. Occupational exposure databanks (OEDBs) have been described previously as potential sources of FA data for exposure surveillance or occupational epidemiology (Goldman et al. 1992; LaMontagne et al. 2002). From the foregoing, one can observe that nearly all humans, including susceptible children, may be affected by FA exposure.

FA is also an important public health problem, because cigarette smoke contains FA (Tox Probe 2002). In a study conducted in the US, six different brands

of cigarettes were examined and the presence of FA was found at rates of 45.2–73.1 mg/cigarette and 5.1–8.9 mg/puff (Mansfield et al. 1977). In another study, it was reported that the level of FA in side-stream cigarette smoke is 50 times higher than exists in mainstream smoke (Triebig and Zober 1984). The National Research Council (1986) estimates that there is 5–8 times more formaldehyde in side-stream smoke than in mainstream cigarette smoke (Tox Probe 2002). Smoking is common worldwide, and thus, cigarette smoking can be considered as an important factor for both indoor and outdoor FA release.

In addition, FA is widely used in both industrial and medical settings, and as a sterilizing agent, disinfectant, and preservative. Therefore, employees in these settings may be at risk for high levels of exposure to FA. In particular, anatomists, histologists, pathologists, and medical students are the individuals most frequently exposed to FA gas in dissection lectures and laboratories (Cohen et al. 1998; Sarnak et al. 1999). Epidemiological studies of industrial workers, embalmers and pathology anatomists have associated FA exposure with elevated risks for cancers at various sites, including the brain (Coggon et al. 2003; Hayes et al. 1990), nasal cavities (Blair et al. 1990; Coggon et al. 2003), lung (Coggon et al. 2003; Gardner et al. 1993), pancreas (Stone et al. 2001), and lymphohematopoietic system (Hauptmann et al. 2003; Pinkerton et al. 2004). However, these positive findings may have been confused by concomitant exposures and remain controversial.

### ***1.3 Harmful Effects***

It is accepted that FA is toxic and slightly carcinogenic over certain concentrations, and the harmful effects of FA increase under room temperature conditions, because the molecule easily evaporates (Feron et al. 1991; Franklin et al. 2000; Gurel et al. 2005; Ozen et al. 2002; Smith 1992; Songur et al. 2003). FA is thought to have weak carcinogenic effects through the formation of protein cross-links and the promotion of cell proliferation in the human respiratory tract. According to the United States National Toxicology Program (US-NTP), European Union (EU), and International Agency for Research on Cancer (IARC), FA is classified as a weak genotoxic, probable carcinogenic agent for humans (category 3). Exposure to FA is a predisposing factor for the occurrence of cancer in the nasal cavity, paranasal sinuses, and leukemia. According to the World Health Organization (WHO), FA does not have a high carcinogenic potential in humans, but inhalation of FA may be linked to nasal or nasopharyngeal cancers (Binetti et al. 2006).

In our studies, FA inhalation was observed to cause a reversible decrease in food and water consumption, and in body weight (and body weight gain) in rats (Ozen et al. 2002, 2003; Songur et al. 2003; Zararsiz et al. 2006). Furthermore, Martin (1990) and Saillenfait et al. (1989) found that inhalation of FA (10–40 ppm) during the gestation period caused a reduction in maternal food consumption, a decrease in body weight gain, and lower birth weight of pups. These toxic effects may occur by central inhibition or most likely from inhibition of nucleic acid and protein synthesis (Ozen et al. 2003).

After administration, FA rapidly diffuses to many tissues, including the brain. In a postmortem study, FA and the metabolites, methanol and formic acid, were found at similar concentrations in the brain (Nishi et al. 1988). The inhaled FA gas had negative effects on the central nervous system (CNS), which appeared acutely in the form of headache, malaise, insomnia, anorexia, and dizziness (Harris et al. 1981; Solomons and Cochrane 1984). There is a relationship between indoor FA concentrations and the sick building syndrome, which is a form of multiple chemical sensitivities (Kim et al. 2002; Sari et al. 2004, 2005). Long-term exposure (e.g., 14–30 year) to FA may cause irreversible neurotoxicity (Kilburn 1994), and is related to neurodegenerative disorders and brain cancer (astrocytoma) (Stroup et al. 1986). In addition, inhaled FA has been shown to cause behavioral and memory disorders in rats and has been classified as “probably neurotoxic” (Pitten et al. 2000).

FA may be found in the cerebrospinal fluid (CSF), since this compound easily passes through the blood–brain barrier, and would thus affect neuroglial and nerve cells (Malek et al. 2003). A recent study indicated that concentrations of FA exceeding 1 ppm may occur in anatomy dissection laboratories, which is a potential problem for medical and dental students (Kawamata and Kodera 2004; Kunugita et al. 2004). Past regulatory amendments lowered the permissible exposure level of 1 ppm for FA to 0.75 ppm as an 8-hr time-weighted average (U.S. Department of Labor Occupational Safety & Health Administration 1992).

In this review, we compile the literature that concerns the neurotoxic effect of FA on neuronal morphology, behavior, and biochemical parameters.

## **2 Formaldehyde Neurotoxicity**

### ***2.1 The Effect on Various Biochemical Parameters***

The first response to a toxic agent is at the chemical level, and morphological changes are observed as damage continues. In our studies on FA neurotoxicity, FA was observed to affect cerebral oxidant/antioxidant systems and cause oxidative damage. Although reactive oxygen species (ROS), including singlet oxygen, hydrogen peroxide, superoxide anion, and hydroxyl radical, are essential for many normal biological processes and are produced physiologically, the excessive production and accumulation of ROS can become hazardous to cells and tissues (Bas et al. 2007; Gurel et al. 2005; Sarsilmaz et al. 2003; Tian et al. 2005). ROS are important mediators of cellular injury, play a role in oxidative stress, and can contribute to a variety of diseases, or be present in situations where toxicity is produced. ROS-initiated oxidative stress can be regulated by cellular defense mechanisms, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) (Halliwell 1997). The brain has a high content of easily peroxidizable unsaturated fatty acids and requires very high amounts of oxygen per unit weight. Additionally, the rates of oxidative metabolic activities in the brain are relatively high and antioxidant enzymes activities are low in the brain. Therefore, the neurons

are more vulnerable to toxic or ischemic occurrences in the CNS (Irmak et al. 2003; Tian et al. 2005).

We performed a study in this topic area and observed that exposure to FA during the adult period (10 mg/kg, 10 days, intra peritoneal (ip)) caused an increase in oxidant substances, such as malondialdehyde(MDA) and protein carbonyl (PC), but resulted in a decrease in the activity of antioxidant enzymes, such as SOD and CAT, in the rat frontal cortex and hippocampus (Gurel et al. 2005). In another study, we found that exposure to FA under similar conditions (10 mg/kg, 14 days, ip) led to an increase in the MDA level and a decrease in the activity of SOD and GSH-Px in the rat prefrontal cortex (Zararsiz et al. 2006, 2007). Inhalation of FA during the early postnatal period was also found to cause an increase in the activity of GSH-Px and levels of MDA and NO, and a decrease in t-SOD activity at postnatal day (PND) 30, in the rat cerebellum. In general, the results of FA exposure to rats at PND 90 were similar to those at PND 30. Additionally, we observed that the effect of FA on cerebellar oxidant/antioxidant systems increased in a dose-related manner and continued for a long time (Songur et al. 2008). An increase in MDA levels, which is one of the common findings of our three studies, is an indication of lipid peroxidation and neuronal membrane injury. Thus, fluidity of cell membranes and cell compartmentation is disrupted, and eventually the cell is lysed, if injury is not prevented (Datta and Namasivayam 2003). Exposure to FA has also been demonstrated to lead to an increase in lipid peroxidation products in different tissues (Tang et al. 2003; Teng et al. 2001), and our studies confirm these results. Decreases in GSH-Px and SOD activities provide evidence that these enzymes have acted to protect cells from increased oxidative events. Furthermore, these activities provide evidence for the involvement of glutathione, since FA is metabolized by FDH and this enzyme is dependent on glutathione. Therefore, we postulate that FA causes oxidative damage as a general toxic effect. Also, FA neurotoxicity may be mediated by the activation of free radical producing enzymes and by the inhibition or expenditure of free radical scavenger systems, thereby enhancing the production of ROS.

We have also investigated the effect of FA on certain cerebral trace elements. Subacute (4 week) or subchronic (13 week) inhalation of FA (6 and 12 ppm) was discovered to lead to a time- and concentration-dependent increase in zinc (Zn) and copper (Cu) levels, and also resulted in a decrease in iron (Fe) levels in the rat cerebral cortex. Zn, Cu, and Fe are involved in important chemical processes in the brain, and levels of these elements in the cerebral tissue reveal the condition of cerebral functions (Ozen et al. 2003). As Zn and Cu are the prosthetic groups of SOD, which is an antioxidant enzyme, elevated levels of these elements in tissue may portend the action of SOD. Therefore, we may regard these elevated levels as an indicator, which confirms the decrease of SOD that was detected in the aforementioned studies (Gurel et al. 2005; Zararsiz et al. 2006, 2007). FDH is utilized in the detoxification of FA in the cerebral cortex. Since FDH requires glutathione and NAD<sup>+</sup> as cofactors, the excessive use of FDH results in the utilization of glutathione, which indirectly results in oxidative damage. Oxidative stress coupled to elevated Fe levels may cause negative effects on cerebral cortex (Ozen et al. 2003).

According to the literature, FA is a highly reactive compound and easily reacts with the amino acid residues of proteins. A postulated mechanism for FA neurotoxicity is the production of epoxides, which bind to axonal neuro(micro)filaments, rendering these filaments nonfunctional. Axons then swell, and as axonal neurofilaments are implicated in rapid axonal transport of proteins, axonal transport becomes progressively abnormal (Kilburn 1994). The resulting hydroxymethyl derivatives react with nucleophilic groups and form methylene bridges, resulting in the formation of intramolecular and intermolecular bonds. These bonds not only result in changes in protein function, but also cause changes in polypeptide structure and physiochemical features (Kilburn et al. 1987). The previously mentioned studies by Kilburn are highly significant, since these are among the first studies to explore FA neurotoxicity.

## 2.2 *The Effect on Neuronal Morphology*

In a previous study that addressed FA neurotoxicity, inhalation of FA at concentrations of 6 and 12 ppm, during the early postnatal period (PND30), resulted in an increase in pyknotic neuron counts in the rat hippocampus pyramidal cell layer. These increases, in the tested rats, were most significant in the CA3 area and continued throughout the PND60 period. However, there were no significant changes in the PND90 group of rats (Songur et al. 2003). In this same study, FA inhalation also resulted in an increase in immunostaining of heat shock protein 70 kDa (*Hsp70*) in the rat hippocampus, particularly at the exposure concentration of 12 ppm, and for the PND30 group rats. In contrast, *Hsp70* immunostaining decreased in the PND60 and PND90 rat groups (Songur et al. 2003). *Hsp70* is an intracytoplasmic molecular chaperone that helps repair, connect, and transport proteins. *Hsp70* is a component of the cytoprotectant system, which protects the cell in response to cellular damage and stressful perturbations. The increase in *Hsp70* production indicates that the cells were exposed to a toxic agent and cellular defense mechanisms were activated (Gilby et al. 1997).

It was observed, in a stereological study performed to confirm the aforementioned investigation, that FA inhalation at 12 ppm concentration during the early postnatal period caused a reversible decrease in the volume of cerebral hemispheres and in the hippocampal pyramidal cell layer. Additionally, FA inhalation caused a decrease in the total pyramidal neuron counts in hippocampal CA regions. The decrease was evident in both PND30 and PND90 group rats, and thus, the damage appeared to be permanent (Sarsilmaz et al. 2007). In comparison to these results, the volumes of the dentate gyrus (DG) were observed to significantly increase in the rat brain after inhalation exposure to both 6 and 12 ppm FA for the PND30 group. This increase in DG volume was also observed at the 6 ppm FA inhalation level for the PND90 rat group. Furthermore, exposure to 12 ppm FA inhalation for the PND90 group caused a decrease in the total number of granular cells of the DG, in comparison to the control group and the 6 ppm FA inhaled rat groups (Aslan et al. 2006).

Drawing on the results of these three studies, FA inhalation, during the early postnatal period at cytotoxic concentrations, appears to result in an increase in apoptosis,

a decrease in neuronal development, and damage to the hippocampal formation. Generally, this damage is positively correlated with the dose and is morphologically reversible. The observed increase in DG volume could be a result of the high rate of neuronal generation in the DG during the early weeks of postnatal life. It could also constitute the neurotoxic effects of FA, which might trigger inflammation of the DG, resulting in a volume increase. The reduction in granule cell number (12%) at the 12 ppm FA inhalation level, compared to the 10% increase in neuronal number at the 6 ppm level, in the PND90 groups, may represent neurogenesis stimulation at the 6 ppm dose, whereas the 12 ppm dose might impair generation of new neurons. Some neuroprogenitor cells are found in the DG, as seen in the subventricular zone and in the olfactory bulb. These cells may also contribute to neuronal formation in response to brain damage (Aslan et al. 2006; Gould et al. 1998; Jin et al. 2004; Lie et al. 2004; Lucassen et al. 2004; Ohnuma and Harris 2003). In particular, granular cells of the DG are more sensitive to FA toxicity and may display a latent neurotoxic effect after FA exposure. If so, this would support the hypothesis that exposure to toxic agents during childhood may lead to diseases later in life.

In another study, it was revealed that exposure to FA (10 mg/kg, 10 days, ip) increased pyknosis and decreased neuronal number in the adult rat frontal cortex and hippocampus (Gurel et al. 2005). Furthermore, FA administration under similar conditions increased apoptosis in the rat prefrontal cortex and caused an increase in the immunoreactivity of Bax, which is a pro-apoptotic protein (Zararsiz et al. 2006, 2007). The Bax protein induces cytochrome C release from the mitochondrial membrane to the cytoplasm, which initiates the apoptotic process through activation of caspases in the cytoplasm (Zararsiz et al. 2006, 2007).

Sorg et al. reported the effect of exposure to repeated low-level formaldehyde on the corticosterone level in rats (Sorg et al. 2001). Sari et al. (2004) found that chronic exposure to low levels of formaldehyde in rats caused an increase in the number of CRH-ir neurons in the hypothalamus (PVN) and ACTH-ir cells in the pituitary gland, with an increase in ACTH-mRNA expression in a dose-dependent manner. In view of these results, FA inhalation was suggested to increase activity of the HPA axis so as to mitigate FA neurotoxicity (Sari et al. 2004).

FA forms strong bonds with proteins and nucleic acids, and the neurotoxic effect of FA is postulated to be a result of the formation of epoxide products, as well as molecular binding that renders axonal neurofilaments nonfunctional (Kilburn 1994). The reason for the noted augmentation of gray matter injury, after FA exposure, may be that there is less FA dehydrogenase in the neural gray than white matter, and almost none in the neural perikarya (Keller et al. 1990).

### ***2.3 The Effect on Behavior***

Although FA studies have not focused on the behavioral effects, several symptoms of associated disorders have been observed during studies of FA-exposed rats, such as lethargy, decrease in motor activity, and loss of appetite (Ozen et al. 2003; Songur et al. 2003; Zararsiz et al. 2006, 2007).

There have been reports indicating extensive neurobehavioral impairments, such as malaise, headache, indigestion, balance dysfunctions, sleep disorders, as well as mental and memorial disorders from FA exposure (Kilburn et al. 1987; Kilburn 1994). Moreover, reports of severe fatigue, thirst, convulsion, irritability, lethargy, memory loss, behavioral, and sensory-emotional disorders of people working in industrial areas, who were regularly exposed to FA, are further indicators of FA neurotoxicity (Kilburn 1994; Kilburn et al. 1987). In certain experiments with FA inhalation in rats, FA-exposed animals exhibited a pronounced impairment in open field, maze trail performance, and in CNS function (Kilburn 1994; Malek et al. 2003; Pitten et al. 2000). A labirent test with FA-exposed rats (>2.6 ppm, 10 min/day, 90 days) demonstrated an influence on food-finding abilities, such as a decrease in overall success, increases in food-finding time, and increases in mistakes (Pitten et al. 2000). Inhalation of FA at 11 ppm for 7 days or 1 ppm for 20 days was observed to cause an increase in cocaine-induced locomotor activity and a conditioned fear response to odor (Sorg and Hochstatter 1999), suggesting that FA may cause chemical encephalopathy.

During biochemical and histopathological studies of FA neurotoxicity, disorders linked to FA exposure were related to the duration of exposure and dose, but these disorders were morphologically reversible. However, morphological changes do not correlate with behavioral changes at all times. Therefore, it is not a rule that morphological changes do not necessarily induce behavioral changes, or changes in behavior do not inevitably result in morphological changes. Furthermore, FA exposure during the early postnatal period may lead to disorders and behavioral changes in adults (Ladefoged et al. 1991; Pryor 1991; Slomianka et al. 1992).

### 3 Conclusion

The reviewed studies have indicated that FA induces several characteristics of neurotoxicity, in addition to systemic toxic effects. The neurotoxic effects produced by FA become more pronounced with increases in concentration and exposure duration, though this is not always the case. Additionally, FA-produced neurotoxicity may vary among different species of organisms and exposure concentrations. The neurotoxic effects in FA studies with animals are extremely pronounced and occurred at concentrations exceeding those that would be acceptable for human studies. Notwithstanding, neurotoxic effects in humans from FA exposure occur at lower concentrations than in rodents, because of different nasal structure and respiration characteristics between the species. It is known that the basis for many psychological diseases in adult humans is dependent on factors that occurred prenatally or during the early postnatal period (Lemaire et al. 2000; Schmitz et al. 2002; Slomianka et al. 1992). Therefore, it is hypothesized that inhalation of FA during the early postnatal period may well predispose to certain neurological diseases in adults.

Complete prevention of FA exposure is impossible for anatomists, histologists, pathologists, medical/dental students, and members of industries utilizing FA.

However, the following suggestions may decrease and/or prevent the systemic and neurotoxic effects from FA exposures that do occur:

1. In anatomy and pathology laboratories, the FA exposure concentration must be maintained so that it is beneath the legal limit. To achieve this, periodic measurement of FA concentrations is required, ambient humidity and temperature must be lowered, air conditioners with special filters must be used, and the ventilation of laboratories must be monitored. Moreover, novel mechanisms must be used to eliminate or reduce FA concentrations, care must be taken during the preparation of FA solutions, and dissections should be performed on downdraft ventilated dissection tables that remove or direct FA vapors down and away from the user.
2. Less toxic novel preservative techniques (e.g., plastination) that meet users' requirements must be developed.
3. Formaldehyde-free household products are preferred and should be offered, when possible. Wood, porcelain, marble, and natural fibers should be used instead of chipboard, melamine, synthetic fibers, and plastics. Products that are released into the atmosphere as FA, such as quaternium 15, dimethyloldimethyl (DMDM), hydantoin, imidiazolidinyl urea, diazolidinyl urea, and bronopol, should not be used. The rate of formaldehyde release depends on the type of resin contained in the product. The use of products made from wood that contains phenol resins, instead of urea resins, will result in a decrease in FA inhalation. Interior paints and materials, which are manufactured using nanotechnology and do not contain FA, are preferred.
4. Temperature and humidity (30–50%) inside homes must be kept at low levels through the use of air conditioners and dehumidifiers. Houses must be ventilated, especially when new items that contain FA are placed inside the house.
5. FA is a component of tobacco smoke; therefore, smoking indoors should not be allowed.
6. Liquid petroleum gas (LPG) catalytic heaters should not be used without venting pipes.
7. Clothes are treated with FA to help make them wrinkle-resistant. Such clothing should be laundered prior to use.
8. The intake of antioxidants and/or neuroprotective agents (e.g., melatonin, fish omega-3 fatty acids, vitamins E and C, erdosteine, or caffeic acid phenethyl ester (CAPE)) is recommended for individuals who are exposed to FA in their work environment.

## 4 Summary

Formaldehyde (FA) is found in the polluted atmosphere of cities, domestic air (e.g., paint, insulating materials, chipboard and plywood, fabrics, furniture, paper), and cigarette smoke, etc.; therefore, everyone and particularly susceptible children may

be exposed to FA. FA is also widely used in industrial and medical settings and as a sterilizing agent, disinfectant, and preservative. Therefore, employees may be highly exposed to it in these settings. Of particular concern to the authors are anatomists and medical students, who can be highly exposed to formaldehyde vapor during dissection sessions. Formaldehyde is toxic over a range of doses; chances of exposure and subsequent harmful effects are increased as (room) temperature increases, because of FA's volatility.

Many studies have been conducted to evaluate the effects of FA during systemic and respiratory exposures in rats. This review compiles that literature and emphasizes the neurotoxic effects of FA on neuronal morphology, behavior, and biochemical parameters. The review includes the results of some of the authors' work related to FA neurotoxicity, and such neurotoxic effects from FA exposure were experimentally demonstrated. Moreover, the effectiveness of some antioxidants such as melatonin, fish omega-3, and CAPE was observed in the treatment of the harmful effects of FA.

Despite the harmful effects from FA exposure, it is commonly used in Turkey and elsewhere in dissection laboratories. Consequently, all anatomists must know and understand the effects of this toxic agent on organisms and the environment, and take precautions to avoid unnecessary exposure.

The reviewed studies have indicated that FA has neurotoxic characteristics and systemic toxic effects. It is hypothesized that inhalation of FA, during the early post-natal period, is linked to some neurological diseases that occur in adults. Although complete prevention is impossible for laboratory workers and members of industries utilizing FA, certain precautions can be taken to decrease and/or prevent the toxic effects of FA.

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