

## **Embryo Toxicity and Teratogenicity of Formaldehyde (FA)**

Jack D. Thrasher, Ph.D., Sam-1 Trust, Alto, New Mexico 88312

toxicologist@msn.com

Kaye H. Kilburn, M.D., University of Southern California, Keck School of Medicine  
Environmental Sciences Laboratory, 2025 Zonal Avenue, CSC 201, Los Angeles, California 90033

### **ABSTRACT**

C-14 FA crosses the placenta and enters fetal tissues. The incorporated radioactivity is higher in fetal organs (brain and liver) than in the maternal tissues. The incorporation mechanism has not been fully studied, but FA enters the single carbon cycle, and is incorporated as a methyl group into nucleic acids and proteins. Also, FA chemically reacts with organic compounds (DNA, nucleosides, nucleotides, proteins, amino acids) by addition and condensation reactions, forming adducts and DNA-protein cross links. The following questions need answered: What adducts (e.g. N-methyl amino acids) are formed in the blood following FA inhalation? What role do N-methyl-amino adducts play in alkylation of nuclear and mitochondrial DNA as well as mitochondrial peroxidation? The fact that the free FA pool in the blood is not affected following exposure to the chemical, does not mean that FA is not involved in altering cell and DNA characteristics beyond the nasal cavity.

Teratogenic effect of FA in the English literature has been sought beginning the 6th day of pregnancy (rodents).<sup>79-82</sup> The exposure regimen appears to be critical and may account for the differences in outcomes. Pregnant rats were (1) either exposed prior to mating, mated, and during the entire gestation period or (2) were exposed during the entire gestation period. These regimens increased embryo mortality, fetal anomalies (cryptochordism, aberrant ossification centers), decreased concentrations of ascorbic acid, and abnormalities in enzymes of mitochondria, lysosomes and ER. The alterations in enzymatic activity persisted four months after birth. In addition, FA caused a metabolic acidosis, which was augmented by iron deficiency. Furthermore, newborns exposed to FA in utero had abnormal performances in open-field tests.

Disparities in teratogenic effects of toxic chemicals are not unusual. For example, Chlorpyrifos has been shown to not have teratogenic effects in rats when mothers are exposed on days 6 through 15(16) of gestation.<sup>83,84</sup> However, either changing the end-points for measurement or exposing neonates during periods of neurogenesis (days 1-14 after birth) and later developmental periods, produced adverse effects. These included neuro-apoptosis, decreased DNA and RNA synthesis, abnormalities in adenylyl cyclase cascade, and neurobehavioral effects.<sup>85-92</sup> Furthermore, the terata caused by thalidomide is a graphic human example in which the animal model and timing of exposure were key factors.<sup>93,94</sup> Thus, it appears that more sensitive end-points (e.g. enzyme activity, generation of reactive oxygen species, timing of exposure, etc.) for the measurement of toxic

effects of environmental agents on embryos, fetuses and neonates are more coherent than are gross terata observations.

The perinatal period from the end of organogenesis to the end of the neonatal period in humans approximates the 28th day of gestation to 4 weeks post partum. Therefore, it is of primary concern to investigate similar stages of development, e.g. neurogenesis occurs in the 3rd trimester in humans and neonatal days 1-14 in rats and mice, while guinea pigs are more like humans.

Finally, screening for teratogenic events should also include exposure of females prior to mating or shortly after mating. Such a regimen is fruitful since environmental agents do cause adverse effects on ovarian elements, e.g. thecal cells and ova (nDNA and mitDNA) as well as zygotes and embryos prior to implantation. mtDNA mutations and deletions occur in human oocytes and embryos.<sup>93,94</sup> Thus, it is probable that xenobiotics directly effect nDNA and/or mitDNA in either or both the ovum and zygote/embryo<sup>96</sup> and could account for the increasing appearance of a variety of mitochondrial diseases, including autism.<sup>97-99</sup>

Two cases of human birth defects were reported in FA-contaminated homes. One was anencephalic at 2.76 ppm, and the other defect at 0.54 ppm was not characterized.

## Introduction

Formaldehyde (FA) is widely spread in the environment, used to manufacture a wide variety of products, and its major uses are ureaformaldehyde (UF) resins (25%), phenol-FA (PhF) resins (20%), plastics (15%) and intermediates (22%). It is an intermediate in acetylenic chemicals, and used to produce 4,4'-hexamethylenetetramine, UF concentrates, 4,4'-methylenediphenyl diisocyanate, chelating agents, and trimethylolpropane. UF and PhF resins are used primarily as adhesives in the manufacture of particle board, fiberboard, plywood, molding, paper treating and coating, textile treating, surface coating and fiberglass insulation.<sup>1</sup> OSHA estimates that approximately 2.1 million workers are exposed to formaldehyde (1,2). Domestic exposures occur mainly from consumer products that include textiles (clothing and household furnishings), insulation (fibrous and foams), paper, cosmetics and wood-products (particle board, plywood, medium density fiber board) (3).

The current OSHA permissible exposure limit (PEL) is 0.75 ppm as an 8-hour time weighted average (TWA). This standard includes a 2 ppm short-term 15 minute exposure limit (STEL) with an 'action level' of 0.5 ppm measured over 8 hours.<sup>2</sup> Other exposure levels are: ACGIH TLV of 0.3 ppm (0.37 mg/m<sup>3</sup> ceiling); NIOSH REL of 0.016 ppm (TWA) and 0.1 ppm (15 minute ceiling). FA is classified as a probable human carcinogen: US EPA (Class 2A); IARC (Class 2A), OSHA (Carcinogen); NIOSH (Carcinogen) and NTP (Reasonably anticipated as a carcinogen)<sup>4</sup>.

Acute health effects and doses are: odor threshold (0.05-1.0 ppm); eye irritation (0.01-2.0 ppm); irritation of eyes/nose/throat/upper respiratory system (1.0-3.0 ppm); intolerable; (4.0-5.0 ppm); severe respiratory symptoms/difficulty breathing (10-20 ppm); serious respiratory tract injury (>50 ppm); and death (>100 ppm). The IDLH is 20 ppm for an exposure of 13-30 min. Chronic exposure to FA can lead to dermal and respiratory sensitization, lower airway and chronic pulmonary obstruction and immunologic manifestations.<sup>5,6,7</sup> Evaporation from formalin at 20 °C yields 5 ppm of FA.

Reproductive and developmental effects are believed to be minimal. This conception is based on a few epidemiological studies and the absent of birth defects in animal studies

Following FA exposure,<sup>8</sup> as a result of reviews by EPA<sup>9</sup> and WHO<sup>10</sup> of the scientific/medial literature prior to 1989. More recent epidemiologic investigations have shown exposure to FA is associated with delayed conception,<sup>11</sup> and an increased risk of spontaneous abortion in wood workers,<sup>11</sup> laboratory personnel<sup>12</sup> and cosmetologist.<sup>13</sup> Reports from Japanese and Russian literature on the embryotoxicity of FA in rodents demonstrate that FA crosses the placenta to the fetus, causes birth defects and affects on enzyme function in mitochondria, lysosomes and endoplasmic reticulum. This communication reviews this research with critiques in the perspective of the current scientific knowledge of the biological chemistry of FA.

If you want a copy of this contact Dr. Thrasher at [toxicologist1@msn.com](mailto:toxicologist1@msn.com)