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Dietary methanol and autism

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ABSTRACT

The authors sought to establish whether maternal dietary methanol during pregnancy was a factor in the etiology of autism spectrum disorders.

A seven item questionnaire was given to women who had given birth to at least one child after 1984. The subjects were solicited from a large primary care practice and several internet sites and separated into two groups – mothers who had given birth to a child with autism and those who had not. Average weekly methanol consumption was calculated based on questionnaire responses.

550 questionnaires were completed by women who gave birth to a non-autistic child. On average these women consumed 66.71 mg. of methanol weekly. 161 questionnaires were completed by women who had given birth to an autistic child. The average estimated weekly methanol consumption for this group was 142.31 mg. Based on the results of the Wilcoxon rank sum-test, we see a significant difference between the reported methanol consumption rates of the two groups. This study suggests that women who have given birth to an autistic child are likely to have had higher intake of dietary sources of methanol than women who have not. Further investigation of a possible link of dietary methanol to autism is clearly warranted.

Although there is some controversy with regard to the relative contribution of enhanced diagnostic awareness, there is nevertheless widespread consensus that there has been a very significant, and real, increase in the worldwide prevalence of autism spectrum disorders [1]. This increase probably began in the mid 1980s, when the prevalence was estimated at 4–5 per 10,000, compared to the current estimate of 147 per 10,000 [2]. Although autism's etiology is currently unknown, recent evidence suggests a prenatal origin [3] caused by a yet unidentified teratological agent [1]. It is our hypothesis that maternal dietary methanol during pregnancy acts as a major autistic teratogen.

There is good reason to suspect methanol might be the cause of neurological complications of human pregnancy. The Centers for Disease Control and Prevention (CDC) warns that "methanol may cause birth defects of the central nervous system in humans" and further that "chronic or repeated exposure to methanol is suspected to be a developmental toxicity risk" [4]. Every species of laboratory animal fed methanol during early pregnancy at sufficient concentration shows methanol as a neurological teratogen [5,6]. Methanol has been linked to congenital malformations in the children of women exposed to it in the workplace [7]. Methanol is known to induce behavioral abnormalities in rat pups whose mothers consumed methanol during gestation [8] and aspartame (a methanol-producing sweetener) was shown to be neurologically teratogenic in several studies done on rabbits during early testing of its safety [9].

Surprisingly little is currently known of the cause of the harm to the developing human fetus from methanol. This is particularly unusual in light of the monograph on this very subject published in 2003 by the CDC Center for the Evaluation of Risks to Human Reproduction [10]. The final report of an expert panel composed of industry and government representatives, after 5 years of debate, warned that "methanol is a potential cause of human birth defects." However the strength of the warning was insufficient for two senior EPA staff scientists, both members of the industry-heavy 12-person panel, who refused to sign the final report. Letters explaining their notable objections can only be found in the complete monograph [11].

Methanol was a rare component of the average western diet before the epidemic of autism began, with average consumption estimated to be less than 8 mg. per day [12]. Daily consumption associated with a typical American diet was estimated to be even less [13]. However, due to changes in the dietary habits of the U.S. population, which included increased consumption of aseptically processed juice drinks (in which methanol develops from pectin over time) and the introduction of the artificial sweetener

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aspartame, the average daily consumption of methanol began to increase [14]. At present in the United States the largest single contributor to dietary methanol is aspartame. Aspartame is a weak methyl ester which quickly releases 11% of its weight as methanol in the gut after consumption. Its dietary burden has been steadily increasing as it is now being used as a low cost replacement for sugar. Aspartame was first introduced into the American food supply in 1981. Consumption expanded dramatically with its allowance in carbonated beverages (diet sodas) in the summer of 1983, shortly before the beginning of the meteoric rise in prevalence of autism [15] (Table 1). Autism has continued to rise as aspartames consumption in the diet of the United States has increased each year from its introduction [14]. Obese women [16] and those with diabetes have a significantly higher incidence of autistic pregnancy outcomes [17]. Both groups are much more likely to be heavy consumers of aspartame-containing foods. The very strong protection from autism (almost 50%) afforded to mothers supplementing with folic acid around the time of conception [18] is a compelling link to methanol, which is detoxified via a folic acid-dependent pathway. Identical protection from developmental toxicity due to methanol poisoning has been shown by early folate supplementation in the pregnant CS-1 mouse which is considered to be closer to humans in its reaction to methanol poisoning [19] (see Figs. 1 and 2).

Method

In this retrospective study we assess a possible relationship between maternal dietary sources of methanol during pregnancy and the risk of giving birth to an autistic child. A seven item questionnaire (Table 2) was given to women who had given birth to at least one child after 1984. The subjects were solicited from a large primary care practice and from several internet sites. On the basis of the response to question 1, the subjects were separated into 2 groups – mothers who had given birth to a child with autism and those who had not. Average weekly methanol consumption was then calculated from questions 3–7. Methanol levels per food item are listed in Table 1. Wherever a range was given as an answer, the average of that range was assumed (e.g. for a response of 2–6 per week, 4 was assumed). A Wilcoxon rank sum test was then performed to compare median weekly consumption values between the two groups. At the 5% significance level, the null hypothesis that the groups' data come from distributions with equal medians is rejected ($p = 5.0013e{-}26$). Analysis was performed in MATLAB R2014a Statistics Toolbox.

Results

Five hundred and fifty (550) questionnaires were completed by women who gave birth to a non-autistic child. On average, these women consumed 66.71 mg of methanol weekly.

One hundred and sixty-one (161) questionnaires were completed by women who had given birth to an autistic child. The average estimated weekly consumption for this group was 142.31. Based on the result of the Wilcoxon rank sum test, we see a significant difference between the reported methanol consumption rates of these groups.

Table 1
Methanol content of questionnaire food choices.

Question	Food items	Mg aspartame	Mg methanol
3	12 oz diet soda	225	24.74
4	1 pack sweetener	37	4.07
5	1 stick of gum	12	1.32
6	8 oz lite yogurt	100	11
7	8 oz serving of juice	0	18

Discussion

There is no consensus as to the exact mechanism by which methanol acts as a neurologic poison in humans [20]. Humans metabolize methanol differently than all other animals, including the non-human primates [21]. Elucidation of methanol's toxicity has been impeded by the conundrum that in all non-human animals the first metabolite of methanol, formaldehyde, is produced by catalase safely in the peroxisome where its conversion to formic acid and then carbon dioxide can proceed easily via the same enzyme [22]. Unfortunately the human peroxisome has no such protective mechanism, leaving methanol's conversion to formaldehyde to the free floating alcohol dehydrogenase class 1 (ADH) enzyme in the cytosol of many non-hepatic cells such as the Purkinje in the cerebellum and the lining of the blood vessels of the brain [23]. Further oxidation of formaldehyde is unlikely in the cytosol, which in most cells lacks readily available aldehyde dehydrogenase. This exposes all organelles and the nucleus of these cells to formaldehyde which can readily react with proteins RNA and DNA. The mechanism and strength of this reaction is driven by highly reactive formaldehyde hydrate (always formed as the dominant molecular configuration when formaldehyde dissolves in water) which has two resonating –OH groups on either side of its single carbon atom, both slightly acidic, so each easily bonds to basic proteins in such a way as to potentially elicit unwanted macrophage attention and possible activation. This same acidic hydrate of formaldehyde can act on DNA and RNA and certain basic proteins in the cytosol to not only attach but to cross link and thus inactivate them. All this is consistent with changes found in the autistic brain [14].

Formaldehyde is a much more toxic methanol metabolite than methanol's second metabolite, formic acid. This makes formaldehyde a much greater risk within every compartment of the human cells that contain ADH I. This mechanism, in fact, may be the only natural way to poison the inside of a cell, particularly a brain cell, with the highly reactive and dangerous aldehyde, an aldehyde which is so reactive as to not even be detectable in the blood minutes after massive suicidal consumption [24].

Because of this, the lethal dose of methanol for humans is extraordinarily low when compared to all other laboratory animals, including primates. Man's median lethal dose of methanol is guessed at being 0.3 g per kg [25] (only 5% the lethal dose for monkeys [26]) but individuals have succumbed to doses as little as 0.09 g per kg almost a hundred times less than other mammals [27]. These other mammals succumb to the "organic solvent effect" of the aliphatic alcohol which manifests as an anesthesia leading to narcosis and eventually death [28]. This anesthetic property becomes more manifest with increasing length of the aliphatic chain [29]. For instance, the median lethal dose of ethanol is 7 g per kg body weight for all mammals (including man). Since methanol has only one carbon it takes a larger dose of 8 or 9 g per kg to kill rats, mice and monkeys [26]. To put this into perspective, the median lethal dose of table salt is 6 g per kg. These disarmingly large lethal doses of methanol to most living things is most likely what has discouraged serious consideration of its real danger to humans. Even though the morbidity and mortality rate in human accidental methanol poisonings is high (with 20% of hospital admissions resulting in death and even more to permanent disability [30]) few scientists understand this anomaly which makes methanol so dangerous to humans.

At the turn of the 19th century, due to the outcome of numerous animal safety tests showing methanol less toxic than ethanol, methanol was substituted for ethanol in cough syrup and vanilla