

Methanol: A chemical Trojan Horse as the root of the Inscrutable U

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**Key Words:**

food epidemiology; diseases of civilization; methanol; formaldehyde; aspartame; autism; multiple sclerosis; Alzheimer's; U-shaped curve.

**Abstract:**

Until 200 years ago, methanol was an extremely rare component of the human diet and is still rarely consumed in contemporary hunter and gatherer cultures. With the invention of canning in the 1800s, canned and bottled fruits and vegetables, whose methanol content greatly exceeds that of their fresh counterparts, became far more prevalent. The recent dietary introduction of aspartame, an artificial sweetener 11% methanol by weight, has also greatly increased methanol consumption. Moreover, methanol is a major component of cigarette smoke, known to be a causative agent of many diseases of civilization (DOC). Conversion to formaldehyde in organs other than the liver is the principal means by which methanol may cause disease. The known sites of class I alcohol dehydrogenase (ADH I), the only human enzyme capable of metabolizing methanol to formaldehyde, correspond to the sites of origin for many DOC. Variability in sensitivity to exogenous methanol consumption may be accounted for in part by the presence of aldehyde dehydrogenase sufficient to reduce the toxic effect of formaldehyde production in tissue through its conversion to the much less toxic formic acid. The consumption or endogenous production of small amounts of ethanol, which acts as a competitive inhibitor of methanol's conversion to formaldehyde by ADH I, may afford some individuals protection from DOC.

## **Introduction:**

The quest for a small molecule as an etiological cause of the diseases of civilization has always ignored one of its smallest and most stealthy agents: methanol---a molecule capable of effortless perivascular access. A rare component of unprocessed food, methanol has increased incrementally in the human diet since the advent of commercialized canning in the 1800s and most recently due to the popularity of products sweetened with aspartame. Although the extreme sensitivity of humans to methanol is well established, its conversion to formaldehyde in situ within the vessels of the brain and elsewhere is undetectable, making methanol-placed formaldehyde a paradigm of toxicity that is as compelling in theory as it is difficult in practice to study.

The methanol toxicity literature of the last forty years has been overwhelmingly in favor of a benign role for environmental dosages of methanol. Drawing on scant evidence from arguably inadequate animal models, this research denies any significant link to formaldehyde, pointing instead to a considerably less toxic and considerably more detectable secondary metabolite---formate. Not insignificantly, much of the funding for such studies comes from sources with a vested interest in maintaining public confidence in the dietary safety of methanol. The fact remains, however, that environmental methanol in humans allows formaldehyde greater access to regions of the body prone to disease, exposing vulnerable protein and DNA to methylation and other modifications capable of inducing carcinogenicity, mutagenicity, teratogenicity, and direct macrophage phagocytosis. Given its many harmful effects, the potentially critical role of dietary methanol in the increasing incidence of diseases of civilization needs to be reexamined.

## **The Hypothesis:**

Formaldehyde produced from dietary and environmental methanol metabolized in situ at the non-hepatic sites of class I alcohol dehydrogenase (ADH I) may play a role in many diseases of civilization (DOC). Ethanol may in turn act as a competitive inhibitor of methanol's conversion to formaldehyde by ADH I, as reflected in the U-shaped curve of alcohol consumption.

## Discussion:

July 24, 1981, should be a significant date for scientists investigating worldwide epidemics of Alzheimer's disease (AD),<sup>[#540],[#533]</sup> multiple sclerosis (MS),<sup>[#77],[#214]</sup> atherosclerotic cardiovascular disease (ACD),<sup>[#532]</sup> lupus,<sup>[#536]</sup> skin<sup>[#95]</sup> and breast cancer,<sup>[#250],[#193]</sup> autism,<sup>[#525]</sup> and other diseases of civilization (DOC). On this date the U.S. Food and Drug Administration approved the use of aspartame,<sup>[#472]</sup> a new artificial sweetener.<sup>[#473]</sup> As aspartame eventually became a major source of methanol in the civilized human diet,<sup>[#1]</sup> the incidence of DOC gradually began to rise. Rarely found in nature and an insignificant component of the diets of Pleistocene man and present-day foragers, methanol has been increasing incrementally in the diet of civilized humanity since 1806 when Nicolas Appert commercialized canning, a process that traps methanol derived from the heating and storage of plant materials containing pectin.<sup>[#1]</sup> In addition to aspartame, and canned vegetables, fruits, and their juices,<sup>[#28],[#29]</sup> a major source of the methanol entering the modern civilized human body is cigarette smoke,<sup>[#62]</sup> causatively linked to atherosclerosis, multiple sclerosis,<sup>[#68]</sup> lupus,<sup>[#73]</sup> Alzheimer's disease,<sup>[#535]</sup> rheumatoid arthritis,<sup>[#332]</sup> and other DOC.<sup>[#345]</sup>

A poison to which humans are particularly sensitive,<sup>[#3]</sup> methanol was responsible for the loss of hundreds of lives at the beginning of the twentieth century<sup>[#17]</sup> when extensive animal testing determined it was safer than ethanol, allowing its first use in foods and drugs.<sup>[#165]</sup> Because the toxicity of methanol in the human system cannot be properly tested in animals, the results of this research were specious. Searching for the cause of the metabolic anomaly that makes the human relationship to methanol distinct from all laboratory animal models, including primates,<sup>[#116]</sup> has always been muddied by industrial agendas<sup>[#39]</sup> with a vested interest in proving that the formaldehyde produced from methanol in the human body does no harm.<sup>[#40],[#121]</sup>

The prevalence of compromised literature and the lack of an applicable animal model may explain why methanol, which fits many of the criteria of availability and stealth that one would expect of a usual suspect, has not yet caught the attention of scientists searching for the elusive etiologic agent of DOC. The single article that posits methanol as the possible direct cause of multiple sclerosis<sup>[#8]</sup> is never cited in the MS literature. A recent series of comprehensive in-vitro studies has also convincingly linked Alzheimer's disease to very low

concentrations of formaldehyde. This research mentions methanol as a possible in-vivo source,<sup>[#234],[#235]</sup> but significantly, it neglects to stress the fact that there is no simpler way for formaldehyde to get past the blood brain barrier than in the form of this smallest of alcohols.<sup>[#367]</sup> Methanol is itself harmless but is a Trojan horse for formaldehyde, a chemical that can pose a severe risk to humans,<sup>[#7]</sup> who appear to be the only mammal exclusively endowed with a hepatic catalase enzyme incapable of removing dietary methanol before it can enter the general circulation.<sup>[#52]</sup>

Once methanol runs the gauntlet of first-pass metabolism, its detoxification is no longer exclusive to the liver. Formaldehyde, the first metabolite of methanol, can then be produced within the arteries and veins,<sup>[#220]</sup> heart,<sup>[#503]</sup> brain,<sup>[#218]</sup> lungs,<sup>[#221]</sup> breast,<sup>[#358]</sup> bone,<sup>[#503]</sup> and skin.<sup>[#221]</sup> These major organs harbor extra hepatic sites of the only remaining human enzyme capable of metabolizing methanol, class I alcohol dehydrogenase (ADH I).<sup>[#112]</sup> Methanol transports its potential to become formaldehyde past normal biological barriers in the brain and elsewhere that environmental formaldehyde itself cannot usually penetrate.<sup>[#122]</sup> That formaldehyde produced in these organs from methanol has not been detected directly in humans should not be surprising since formaldehyde vanishes within minutes, binding to macromolecules<sup>[#114]</sup> even when a solution of it is injected directly into tissue<sup>[#122]</sup> or spiked into cell-free human serum.<sup>[#236]</sup> Although methylation caused by this toxic process could be functionally destructive to the macromolecule so modified, the addition of methyl groups to large molecules renders the modification and its source invisible to any clinical or histological testing procedure.<sup>[#122],[#236]</sup>

However, in a study by Trocho et al., a portion of the C<sup>14</sup> labeled methanol moiety of aspartame was shown to bind to such macromolecules via formaldehyde and not pass directly into the one-carbon cycle via formate as predicted by the generally accepted model of methanol toxicity,<sup>[#40]</sup> a model developed from studying the severe methanol poisoning of monkeys, not the chronic environmental exposure of humans. Formate derived from methanol metabolism is never measurable in human blood when small environmentally reflective doses of methanol are administered.<sup>[#42]</sup> During acute methanol poisoning, where the methanol concentration of the portal vein far exceeds that of ethanol, liver ADH I would be saturated with methanol. The liver's ample supply of aldehyde dehydrogenase would assure production of formic acid, which is metabolized very

slowly, causing leakage of formate into the general circulation. Formate is not, however, a significant poison to humans and has, in fact, been used therapeutically and as a food additive.<sup>[#365]</sup> It certainly would be more convenient to have a stable, measurable entity such as formate to predict the danger of exposure to methanol, but an iron-clad case for the toxicological significance of this much less toxic, secondary metabolite has not yet been made.<sup>[#55]</sup> Moreover, the results of Trocho's elegant study should give one pause before accepting the widely held premise that formate and not formaldehyde is the toxic component of methanol poisoning.

Laboratories that publish the most cited works are often financially supported by industries with much to lose were the safety of methanol disproved. This research must be carefully reconsidered before we can dismiss the potential threat posed by formaldehyde strategically placed by dietary methanol. Formaldehyde produced within the cell immediately reacts with water to produce formaldehyde hydrate,<sup>[#27]</sup> an acid<sup>[#114]</sup> with twice the number of available hydrogen ions as the next methanol metabolite, formic acid. Formal hydrate produced from methanol by the ADH I sites found in the intima, media, and adventitia lining of the circulatory system of the heart and brain<sup>[#220]</sup> would be expected to diffuse into the localized tissue, quickly methylating basic molecules such as myelin basic protein (MS)<sup>[#224]</sup> and tau protein (Alzheimer's).<sup>[#234]</sup> Such changes have been shown in these disease states. Formaldehyde, also known to uncouple oxidative phosphorylation and inhibit phosphorylation within cells,<sup>[#113]</sup> could contribute to these changes reported in MS<sup>[#224]</sup> and Alzheimer's.<sup>[#506]</sup> The immune system reacts swiftly to methylation of protein by formaldehyde---a phenomenon put to good use by the vaccine industry for the last hundred years.<sup>[#26]</sup> Macrophages have activation sites specifically for formaldehyde modified protein<sup>[#23]</sup> and are well known to have a ravenous appetite for LDLs reacted with small aldehydes.<sup>[#507]</sup> This induces the esterification of phagocytized LDL cholesterol and the subsequent transformation of the macrophages to foam cells,<sup>[#508]</sup> similar to the sequence of events leading to atheroma production adjacent to the intima layer of the human aorta, rich in ADH I.<sup>[#220]</sup> The potential for antibody production against methylated self-protein phagocytized by macrophages has never been investigated.

Ethanol in low concentrations acts as a powerful competitive inhibitor<sup>[#439]</sup> with a 16:1 preference for ethanol to acetaldehyde over the conversion of methanol to formaldehyde by ADH I.<sup>[#389]</sup> For this reason, ethanol is used, without FDA approval, as the preferred antidote for accidental methanol poisoning in emergency

rooms throughout the world.<sup>[#253]</sup> Very low levels of ethanol in the bloodstream would substantively prevent all formaldehyde production from dietary methanol anywhere in the body. Protection from formaldehyde production may account for the yet unexplained dose region of apparent improvement in the U-shaped curve of alcohol consumption. Epidemiologic studies show moderate consumption of alcohol is associated with a reduced risk of myocardial infarction,<sup>[#485]</sup> dementia,<sup>[#534]</sup> lupus,<sup>[#73]</sup> and other DOC. Low doses of ethanol appear to provide a preventative measure against the causes of DOC.<sup>[#279]</sup> Recent studies of individuals who consumed at least one alcoholic drink per day show subjects had an additional 86 percent reduction in risk of myocardial infarction if they were genetically endowed with a genotype of ADH I that was 2.5 times slower to metabolize ethanol than the control. These findings were "consistent with the hypothesis that a slower rate of clearance of alcohol enhances the beneficial effect of moderate alcohol consumption on the risk of cardiovascular disease."<sup>[#483]</sup>

A compelling explanation of the dose region of adverse effects of the U-shaped curve with high ethanol consumption, which shows increased risk of these same diseases, could be the mechanism by which humans habituate to high consumption of ethanol. The induction of the P450 hepatic microsomal ethanol-oxidizing system<sup>[#175]</sup> results in a considerably higher clearance rate of ethanol from the bloodstream for an extended period of time, thus accounting for more consumption leading to statistically less time of protection. Small amounts of supplemental alcohol not sufficient to induce P450 might be expected to prolong the residence time and avoid gaps in the protection afforded by ethanol in preventing methanol placed formaldehyde. It appears that the average person, whether or not an imbiber, may typically have endogenous ethanol in the blood<sup>[#174]</sup> produced by gut fermentation.<sup>[#363]</sup> This ethanol must pass through the liver via the hepatic portal vein coincidentally with dietary methanol absorbed from the gut contents. The liver has the highest concentration of ADH I in the body. Even traces of ethanol in the blood, however, would seem to indicate the absence of available sites remaining for the oxidation of the much less competitive methanol, allowing most dietary methanol to pass freely into the general circulation.

What follows is a biochemical game of musical chairs as methanol travels round and round the circulation waiting for the ethanol levels to reach zero and the music to stop. The closest ADH I free to service the methanol will convert it to

formaldehyde. If this happens in the liver, where there are ample supplies of aldehyde dehydrogenase, metabolism to carbon dioxide will proceed safely. In mammary epithelium, however, where human class I alcohol dehydrogenase is highly expressed<sup>[#358]</sup> but active aldehyde dehydrogenase<sup>[#216]</sup> is scarce, methanol placed formaldehyde could become a problem. Formaldehyde is a class I carcinogen<sup>[#11]</sup> and mutagen<sup>[#449]</sup> with methanol providing its only easy avenue into this tissue. In the vasculature of the brain<sup>[#218]</sup> and other ADH I positive organs, the consequences may be similarly troublesome. The obvious way to prevent formaldehyde from damaging this sensitive tissue is to keep the music playing, a solution dependent on our ability to answer the following questions: Just how much ethanol is essential in this seemingly inscrutable U-shaped curve? What measures should we take to combat this chemical Trojan horse, thereby reducing the methanol contamination in the diet of civilization and making it more like the diet of our ancient ancestors? Both research areas present intriguing inquiries, but as a food scientist, I would stress the relative ease and greater benefits of investigating the latter.

### **Proposed test of the hypothesis:**

Under strict medical supervision this hypothesis would best be tested on experimental subjects suffering from relapsing multiple sclerosis. Without here getting into great detail the preferred mode of administration of small amounts of ethanol would be via gaseous administration at sufficient, carefully controlled, atmospheric concentration to maintain a constant 1-2 parts per million ethanol concentrations in the test subjects bloodstream. At such low levels, well below the ambient concentrations of ethanol in the average pub environment, ethanol is quite safe and not detectable in the air via the olfactory system of most people. A water vaporization control would work well and be conducive to a double blind study. Vaporous administration of ethanol is well covered in the literature and is used frequently to induce alcohol intoxication of test animals for toxicity testing purposes.



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