Scientific Abuse in Methanol / Formaldehyde Research Related to Aspartame

Please print and read completely through this document!

Back to Aspartame Scientific Abuse Main Page Back to Aspartame Toxicity Information Center

Table of Contents

Summary of Aspartame Methanol/Formaldehyde Toxicity

> "These are indeed extremely high levels for adducts of formaldehyde, a substance responsible for chronic deleterious effects that has also been considered carcinogenic.
> ....
> "It is concluded that aspartame consumption may constitute a hazard because of its contribution to the formation of formaldehyde adducts." (Trocho 1998)

"It was a very interesting paper, that demonstrates that formaldehyde formation from aspartame ingestion is very common and does indeed accumulate within the cell, reacting with cellular proteins (mostly

> enzymes) and DNA (both mitochondrial and nuclear). The fact that it accumulates with each dose, indicates grave consequences among those who consume diet drinks and foodstuffs on a daily basis." (Blaylock 1998)

Methanol from aspartame is released in the small intestine when the methyl group of aspartame encounters the enzyme chymotrypsin (Stegink 1984, page 143). A relatively small amount of aspartame (e.g., one can of soda ingested by a child) can significantly increase plasma methanol levels (Davoli 1986a).

Clinically, chronic, low-level exposure to methanol has been seen to cause headaches, dizziness, nausea, ear buzzing, GI distiurbances, weakness, vertigo, chills, memory lapses, numbness & shooting pains, behavioral disturbances, neuritis, misty vision, vision tunneling, blurring of vision, conjunctivitis, insomnia, vision loss, depression, heart problems (including disease of the heart muscle), and pancreatic inflammation (Kavet 1990, Monte 1984, Posner 1975).

The methanol from aspartame is converted to formaldehyde and then formic acid (DHHS 1993, Liesivuori 1991), although some of the formaldehyde appears to accumulate in the body as discussed above. Chronic formaldehyde exposure at **very** low doses has been shown to cause immune system and nervous system changes and damage as well as headaches, general poor health, irreversible genetic damage, and a number of other serious health problems (Fujimaki 1992, He 1998, John 1994, Liu 1993, Main 1983, Molhave 1986, National Research Council 1981, Shaham 1996, Srivastava 1992, Vojdani 1992, Wantke 1996). One experiment (Wantke 1996) showed that chronic exposure to formaldehyde caused systemic health problems (i.e., poor health) in children at an air concentration of only 0.043 - 0.070 parts per million!

Obviously, chronic exposure to an extremely small amount of formaldehyde is to be avoided. Even if formaldehyde adducts did not build up in the body from aspartame use, the regular exposure to excess levels of formaldehyde would still be a major concern to independent scientists and physicians familiar with the aspartame toxicity issue.

In addition to chronic formaldehyde poisoning, the excitotoxic amino acid derived from aspartame will almost certainly worsen the damage caused by the formladehyde. Synergistic effects from aspartame metabolites are rarely, if ever, mentioned by the manufacturer. Aspartame breaks down into a free-form (unbound to protein) excitotoxic amino acid which is quickly-absorbed (as long as it is not given in slow-dissolving capsules) and can raise the blood plasma

levels of this excitotoxin (Stegink 1987). It is well known that free-form excitotoxins can cause irreversible damage to brain cells (in areas such as the retina, hypothalamus, etc.) in rodents and primates (Olney 1972, Olney 1980, Blaylock 1994, Lipton 1994). In order to remove excess, cell-destroying excitotoxic amino acids from extracellular space, glial cells surround the neuron and supply them with energy (Blaylock 1994, page 39, Lipton 1994). This takes large amounts of ATP. However, formate, a formaldehyde metabolite, is an ATP inhibitor (Liesivuori 1991). Eells (1996b) points out that excitatory amino acid toxicity may be the "mediators of retinal damage secondary to formate induced energy depletion in methanol-intoxication." The synergistic effects from the combination of a chronic formaldehyde exposure from aspartame along with a free-form excitotoxic amino acid is extremely worrisome.
[One 12 oz serving of diet cola contains 188 mg of aspartame, 10.8 % of that would be methanol, or about 20 mg of methanol in each can. That is the equivalent of 18.7 mg of formaldehyde for each can of diet cola.]
It appears that methanol is converted to formate in the eye (Eells 1996a, Garner 1995, Kini 1961). Eells (1996a) showed that chronic, low-level methanol exposure in rats led to formate accumulation in the retina of the eye.
More details about chronic Methanol / Formaldehyde poisoning from aspartame can be found on the Internet at http://www.holisticmed.com/aspartame/aspfaq.html.

How did the manufacturer convince scientists and physicians that it is "safe" to be exposed regularly to low levels of an exceptionally toxic poison? Answer: Deceptive research and deceptive statements!

Hiding the Blood Plasma Methanol Increase From Aspartame Ingestion

On February 22, 1984, the acting FDA Commissioner, Mark Novitch stated (Federal Register 1984):

> "... aspartame showed no detectable levels of methanol in the blood of human subjects following the ingestion of aspartame at 34 mg/kg ...."

The American Medical Association repeated this statement one year later (AMA 1985). This statement was repeated in American Family Physician in 1989 (Yost 1989). Shaywitz (1994) stated that there was no detectable levels of methanol in the blood after aspartame administration. Puthrasingam (1996)

stated that methanol from aspartame is "undetectable in peripheral blood or even in portal blood."

All of these statements were very convincing ... and very **wrong**! The statements were based on aspartame industry research which used an outdated plasma methanol measuring test (Baker 1969). The test they used had a limit of methanol detection of 4 mg/l. However, Cook (1991) measured an average baseline (unexposed) methanol level of ~0.6 mg/l. Others (Davoli 1986, d'Alessandro 1994, Osterloh 1996) have measured an average baseline methanol level of close to 1 mg/l. This means that a person's methanol levels would have to rise 350% to 600% before an increase would have been noticed by the industry researchers using this outdated test! An increase of less than 350% to 600% appeared as no increase at all!

Probably only a handful of people in the world would have noticed that by using a plasma methanol measuring test with limits of 4 mg/l, they avoided seeing an methanol level increase -- even though there was a large increase. Below are some of the experiments which used the inappropriate methanol measuring technique.

Research	**Aspartame Dosage Claimed to Not Raise Methanol Levels**	**Lowest Possilbe Methanol Measurement**	**Other Methanol Issues**
Frey 1976	77 mg/kg	Not stated	Test conducted after 12-hour fast. All methanol would have been converted to formaldehyde.
Stegink 1981	34 mg/kg	4 mg/l	Orange juice given despite discussion of high level of methanol in fruit.
Stegink 1983	34 mg/kg	4 mg/l	...
Leon 1989	75 mg/kg	4 mg/l	Test conducted after 12-hour fast. All methanol would have been converted to formaldehyde.
Stegink 1989	8 hourly doses of 10 mg/kg	4 mg/l	...
Stegink 1990	8 hourly doses of 10 mg/kg	4 mg/l	Fig. 4: Graph of blood methanol concentrations shown with all points well

			below 4 mg/l -- the lower limit of their methanol test.
Hertelendy 1993	15 mg/kg	4 mg/l	...
Shaywitz 1993	34 mg/kg	4 mg/l	...
Shaywitz 1994	34 mg/kg	4 mg/l	...

Note: 10 mg/kg is approximately a one liter bottle of diet soda for a 60 kg adult and 1.5 cans of diet soda for a 30 kg child. Children with aspartame freely-available can ingest between 27 mg/kg - 77 mg/kg (Frey 1976) and adults dieters have been shown to ingest between 8 mg/kg and 36 mg/kg (Porikos 1984).

In 1986, Davoli (1986a) published a study which showed that 6 mg/kg to 8.7 mg/kg of aspartame could significantly raise the plasma methanol levels. The methanol levels nearly doubled in some cases. While there were some logical errors in Davoli's conclusion (discussed below), the study proved that by using a reasonable methanol testing method, plasma methanol levels will increase from a relatively low dose of aspartame ingestion. The methanol measuring technique used by Davoli was published in 1985 (Davoli 1986b) and was sensitive to 0.012 mg/l.

Other researchers have used sensitive plasma methanol measurement techniques. d'Alessandro (1994) measured plasma methanol levels in humans well below 1 mg/l. Cook (1991) used a methanol test developed in 1981 to measure methanol plasma methanol levels in humans below 0.5 mg/l.

What did industry scientists know or should have known?

1. They knew and admited that their methanol testing procedure developed in 1969 was not sensitive enough to detect the large increases of plasma methanol levels when aspartame was given at doses of 34 mg/kg (Stegink 1984b).

2. They must have been aware that Davoli found methanol levels increase significantly when aspartame was given at doses of 6 mg/kg to 8.7 mg/kg. To believe that they were not aware of this, one has to believe

that none of the researchers choose to or knew how to conduct a simple Medline database search.

3. They should have known that there were several legitimate plasma methanol measurement techniques developed since 1969. Given that they admited their technique was not appropriate for aspartame doses of less than 34 mg/kg (Stegink 1984b), they should have at least looked to find an appropriate test.

4. Given that Leon (1989) was aware enough to test for formate levels, he must have been aware that all of the methanol from aspartame would have already converted to formaldehyde after a 12-hour fast.

I believe that Monsanto/NutraSweet and the aspartame industry are clearly taking advantage physicians and scientists who lack the time to carefully investigate each number in a study to see if there is deception. While these actions may not amount to "scientific fraud," it does amount to an abuse of the scientific method in my opinion.

Methanol and Fruit/Tomatos: Convince the World That a Poison is "Natural"

Monsanto/NutraSweet's all time favorite aspartame fairy tale is:

> "In addition, exposure to methanol from many fruits, vegetables, and juices in the normal diet is several times greater than that from beverages sweetened with APM [aspartame]." (Butchko 1991)

This statement from NutraSweet scientists has been repeated countless times (AMA 1985, FDA 1984, Hertelendy 1993, Lajtha 1994, Monsanto 1999, Nelson 1996, Stegink 1981, Stegink 1983, Yost 1989, etc.). This is very convincing ... but **deceptive and irrelevant**!

It is well known that alcoholic beverages such a wine contain a large amount of ethanol, a protective factor which prevents methanol poisoning by preventing the conversion of methanol to the highly toxic formaldehyde (Leaf 1952, Liesivuori 1991, Roe 1982). Because alcoholic beverages contain protective factors which prevent chronic poisoning from methanol metabolites (formaldehyde, formate), comparisons between the methanol derived from

aspartame and the methanol derived from alcoholic beverages are inappropriate.

Clinical reports and a small number of epidemiological studies appear to demonstrate that prolonged exposure to methanol air concentrations (in the workplace) of > 260 mg/m3 (200 ppm) can cause chronic methanol toxicity (Kavet 1990, Frederick 1984, Kingsley 1954-55). The weekly amount of methanol absorbed from a 260 mg/m3 workday exposure is (formula in Kavet 1990):

(260 mg/m3 * 6.67 m3/workday * 5 workdays * 60% absorption rate) / 70 kg adult
= 75 mg/kg weekly methanol

> Note: While this seems like a high weekly methanol dose, please keep in mind that 1) much lower levels may cause toxicity in some individuals; and 2) that aspartame breaks down into an excitotoxin which will likely enhance the toxicity of methanol metabolites as described above.

However, the ingestion of a moderate amount of apples or oranges (or juice equivalent) per week leads to a similar exposure to methanol (Lindinger 1997):

(750 mg methanol (1.5 kg fruit) * 7 days) / 70 kg adult
= **74 mg/kg weekly methanol**

Keep in mind that tomatoes may have more than five times the amount of methanol as that found in oranges (Kazeniac 1970, Nisperos-Carriedo 1990), so exposure to regular ingestion of tomatoes and tomato juice may produce very large amounts of methanol.

Lindinger (1997) points out that the amount of methanol released in the human body from a few apples or oranges is equivalent to:

> "...0.3 liters of brandy (40% ethanol) containing 0.5% of methanol (compared with ethanol), which would qualify as significantly methanol-contaminated liquor."

Because of the high amounts of methanol in fruits/tomatoes, enough that would clearly cause chronic methanol poisoning, these foods must contain protective factors (as does alcoholic beverages). If they did not contain protective factors, we would be seeing widespread methanol poisoning for persons who ingestion fruits and tomatoes regularly.

The manufacturer showed that the protective factor in fruits cannot be ethanol by itself (Sturtevant 1985), but there are a myriad of chemicals in fruits which might serve as protective factors.

What did industry scientists know or should have known?

1. They knew that alcoholic beverages contain protective factors which prevent chronic methanol poisoning (Sturtevant 1985).

2. Because industry scientists regularly announced that certain fruits contain extremely high levels of methanol, they should have taken the time to find out that fruits have protective factors which help prevent chronic poisoning from methanol metabolites.

Avoiding the Discussion of Chronic Methanol Toxicity

A number of Monsanto/NutraSweet public relations statements as well as statements from government officials imply that the amount of methanol obtained from aspartame is not toxic:

> "From estimates based on blood levels in methanol poisonings, it appears that the ingestion of methanol on the order of 200 to 500 mg/kg body weight is required to produce a significant accumulation of formate in the blood which may produce visual and central nervous system toxicity" (Federal Register 1984)

Lajtha (1994) claimed that "blood methanol concentrations greater than 200 to 100 mg/L are required for clinical neurotoxicity or for measurable formate formation." Non-scientists on the Internet often make similar claims. Shahangian (1984) claimed that the amount of formate (methanol and formaldehyde metabolite) is not enough to cause toxicity.

This sounds very convincing until one realizes that the doses they are refering to are the single doses required for death or near death in humans! Monsanto/NutraSweet and persons promoting aspartame will avoiding discussing chronic, low-level methanol or formaldehyde poisoning because once this issue is raised it becomes apparent that the manufacturer did

not conduct or even cite any legitimate studies on chronic, low-level methanol exposure in humans!

Only on very rare occassion will the manufacturer mention chronic methanol toxicity (Nelson 1996, Sturtevant 1985). When they do this, they always cite a study of infant monkeys (a species closely related to rhesus monkeys) (Reynolds 1984). A dose of 3,000 mg/kg of aspartame was given to the monkeys for nine months. This amounts to a daily methanol dose of 300 mg/kg -- a huge dose.

What Monsanto/NutraSweet fails to mention is 300 mg/kg of methanol has been estimated as the minimum **single dose** which can cause death in humans (Kavet 1991). If such a study were conducted on humans, nine months of daily ingestion of the minimum lethal single dose of methanol would clearly kill everyone in the study!. As pointed out by Roe (1982), methanol is significantly more toxic in humans than in monkeys or rodents. It is important to note that the free-form excitotoxin derived from aspartame and which will likely increase the formaldehyde/formate damage from aspartame, appears to be approximately twenty times more toxic in humans than in monkeys due to differences in excitotoxin metabolism (Olney 1988, Stegink 1979, page 90).

What did industry scientists know or should have known?

1. They knew that there was never a controlled, long-term study of methanol exposure in humans. Given that the manufacturer was expecting to dose the human population with aspartame for a lifetime and even generations, some might consider it criminal to sell a poison under these circumstances.

2. They should have known that an excitotoxin will likely increase the toxicity of the formaldehyde/formate based upon the way these chemicals produce cell damage and cell death. At the very least, the manufacturer should have exhausted all reasonable possibilities of synergistic reactions as opposed to using flawed research and flawed logic to explain away the countless cases of aspartame poisoning.

Convince Scientists & Physicians With Irrelevant and Flawed Formate Measurements

The FDA Commissioner has claimed (Federal Register 1984):

> "In the Searle [manufacturer] clinical study using abuse doses of aspartame equivalent to 20 mg/kg body weight of methanol, no significant increases were observed in plasma concentrations of formate, suggesting that the rate of formate production does not exceed its rate of urinary excretion."

The AMA (1985) claimed that abuse doses of aspartame have not been shown to increase blood formate levels. Stegink (1989, 1990) claimed that large doses of aspartame did not raise blood and urine formate levels significantly. Leon (1989) claimed to show no increase in urinary formate from a daily dose of 75 mg/kg of aspartame. Hertelendy (1993) claimed that there was not increase in urine or plasma formate levels from 15 mg/kg aspartame ingestion.

Since methanol metabolizes into formaldehyde and formaldehyde metabolizes into formate, all of these statements appear to point to safety ... at first glance. **But what the manufacturer does not tell you is that these tests are now known to be irrelevant and flawed!**

Formate (formic acid) measurement of the urine is not an appropriate test for low-level formaldehyde poisoning. (Keep in mind that extremely low doses of formaldehyde have been shown to cause chronic poisoning symptoms as discussed above.) Triebig (1989) states that formic acid excretion in the urine is a "unspecific and insensitive biological indicator for monitoring low-dose formaldehyde exposure." Schmid (1994) found that neither a single significant exposure to formaldehyde nor a week-long exposure to formaldehyde correlated with urine formic acid measurements. After testing subjects exposed to formaldehyde, Heinzow (1992) stated:

> "Excretion [of formic acid] in the general population is determined by endogenous metabolism of amino acids, purine- and pyrimidine-bases rather than the uptake and metabolism of precursors like formaldehyde. Hence in contrast to recent recommendations in environmental medicine, formic acid in urine is not an appropriate parameter for biological-monitoring of low level exposure to formaldehyde."

Therefore, all of the aspartame industry's urine formate measurements are useless for chronic methanol/formaldehyde poisoning from aspartame.

Blood formate measurements also appear to be inadequate for chronic, low-level methanol or formaldehyde poisoning. d'Alessandro (1994) stated:

> "While exposure to several different levels of methanol above the threshold limit [200 ppm] might demonstrate slight increases in formate concentrations, it seems doubtful that this measure would be useful for monitoring individual low-level exposure."

And after further study, Osterloh (1996) stated:

> "Previously, we reviewed exposure studies (both occupational and experimental) in which formate concentrations were measures, along with these data, as a basis for the conclusion that methanol, not formate, in serum can be used as a biological marker of exposures."

Three other reasons why aspartame industry formate measurements can be considered useless include:

1. Trocho (1998) showed a significant amount of formaldehyde from aspartame binding with proteins and accumulating in tissues rather than metabolizing into formate.

2. The average baseline (pre-exposure) measurements of formate in the aspartame industry research (e.g., Stegink 1981, 1989, 1990) is unexplicabally 1.5 to 3 times higher than any other independent researcher (d'Alessandro 1994, Baumann 1979, Buttery 1988, Heinrich 1982, Osterloh 1986, Osterloh 1996). As pointed out by Kavet (1990), high pre-exposure blood formate levels "may have masked any subtle increases that the aspartame may have caused."

3. A respected formaldehyde and formic acid exposure researcher has pointed out that several formate measurement techniques including the one used by aspartame industry researchers (Makar 1982) are "notoriously inaccurate." (Liesivuori 1986).

Unfortunately, there are still researchers who cite old tests of formate levels related to aspartame ingestion even though these tests have proven to be meaningless and flawed.

What did industry scientists know or should have known?

1. The industry researchers should have keep up-to-date on formate measurment research. Had they done that, they would have known that

such measurements are inappropriate for chronic, low-level methanol and formaldehyde exposure.

The "It is Found in the Body, so a Proven Poison Must be Safe" Excuse to Eat Poison

From time to time, it will be implied that because methanol and formaldehyde are in the body, it is perfectly safe to add more. Acting FDA Commissioner Mark Novitch stated the following (Federal Register 1984):

> "Normal metabolic processes such as purine and pyrimidine biosynthesis and amino acid metabolism require methyl groups from compounds like methanol. It also appears that either methanol or formaldehyde may serve as precursors for the methyl groups in choline synthesis."

On the Internet, this is a popular technique used to try to convince people that methanol and formaldehyde exposure is safe. What the FDA Commissioner and other persons unfamiliar with this issue did not point out is that chronic poisoning from low-level methanol and formaldehyde exposure is already accepted in the medical community. In fact, children who were chronically-exposed to formaldehyde in the air at concetrations of 0.05 parts per million (ppm) developed systemic health problems after several months (Wantke 1996). This is equivalent to a daily exposure of only 0.75 mg of formaldehyde (or less if 100% of the formaldehyde is not absorbed):

> 0.05 ppm formaldehyde ~= 0.075 mg/m3
> 0.075 mg/m3 * 10 m3/workday = **0.75 mg/day (for a workday/schoolday)**

Other researchers have noted formaldehyde toxicity symptoms appearing at chronic, low-level exposure (Srivastava 1992):

> "Complaints pertaining to gastrointestinal, musculoskeletal and carbiovascular systems were also more frequent in exposed subjects. In spite of formaldehyde concentrations being well within the prescribed ACGIH [American Conference of Governmental Industrial Hygienists] limits of 1 ppm...."

This proves that formaldehyde levels in the body must be very tightly-

controlled since a very low daily exposure leads to health problems. Even a very small, regular increase can lead to chronic, low-level poisoning.

Davoli (1986) showed that aspartame significantly increases plasma methanol levels. However, he mistakenly concluded that because the post-aspartame administration methanol levels did not rise above the baseline methanol levels of every other human being, those levels might not be toxic. What Davoli failed to consider, however, is that 1) we know that methanol and formaldehyde levels in the body must be tightly controlled because exposure to very low levels of these chemicals have been shown to lead to chronic toxicity; and 2) that people have their own individual metabolism so that a slight addition of formaldehyde to the current tightly-controlled level in one individual could cause toxicity even though it might not rise above the baseline level of another individual's formaldehyde level. As one can see from the Davoli (1986) study, the administration of aspartame lead to a fairly sudden and significant increase in plasma methanol levels and would be expected to cause a significant formaldehyde exposure.

Formaldehyde & Formic Acid in Foods: A Final Attempt to Prove a Poison is "Safe"

> "... formaldehyde [exposure from aspartame is] comparable to a serving of fresh broccoli." (Weber 1999)

Every once in a while there will be a statement pointing out that some foods have relatively high levels of formaldehyde and formic acid. **What is not pointed out is that formaldehyde in food is much less toxic than formaldehyde from air exposure or formaldehyde from aspartame exposure due to the way the body metabolizes it.**

Restani (1991) points out that formaldehyde can be found in seafood, honey, fruits, vegetables, etc. Restani (1991) points to a human study showing where 200 mg of formaldehyde per day was ingested for 13 weeks without showing adverse effects. This would be equivalent to an daily air exposure of:

> 200 mg/day / 10 m3/workday = 20.0 mg/m3 = **13.3 ppm**

13.3 ppm daily air exposure is many times over the 0.05 levels which caused chronic toxicity in Wantke (1996) and many times over the American

Conference of Governmental Industrial Hygienists limit of 1 ppm which was shown to cause chronic toxicity in Srivastava (1992).

This proves that formaldehyde found in foods is either not absorbed well:

> "Ingestion represents a minor route of [formaldehyde] exposure because the dilution factor and the binding to the macromolecules present in food reduce substantially the [formaldehyde] concentration that enters into contact with the gastrointestinal mucosa" (Restani 1991)

Or formaldehyde may be broken down by the digestive system. With aspartame, however, the methanol has been proven to be absorbed and then after it is already in the bloodstream, it is converted to formaldehyde (or directly to formate in certain tissues such as the retina).

Formaldehyde Dose: Fabricating Numbers

One way to convince at least a few people that it is 'safe' to be poisoned with aspartame is to simply make up numbers that appear to show that formaldehyde exposure from aspartame is low. One author claimed that formaldehyde exposure was only 30 micrograms -- a figure off by a factor of over 400,000 for the aspartame dose that was used! The following web page calculates and discusses the dose of formaldehyde exposure and accumulation due to aspartame ingestion:

http://www.holisticmed.com/aspartame/fm.html

References

AMA 1985. "Aspartame: Review of Safety Issues," Journal of the American Medical Association, Volume 254, No. 3, page 400-402.

Baker, R.N., A.L. Alenty, J.F. Zack, 1969. "Simultaneous Determination of Lower Alcohols, Acetone and Acetaldehyde in Blood by Gass Chromatography," Journal of Chromatographic Science, Volum 7, pages 312-314, 1969.

Baumann, K., J. Angerer, 1979. "Occupational Chronic Exposure to Organic Solvents. VI. Formic Acid Concentration in Blood and Urine as an Indicator of Methanol Exposure," International Archives of Occupational and Environmental Health, Volume 42, page 241.

Blaylock, Russell L., 1994. "Excitotoxins: The Taste That Kills," Health Press, Santa Fe, New Mexico, c1994.

Blaylock, Russell L., Neurosurgeon, 1998. Personal communication on December 30, 1998.

Butchko, Harriett H., Frank N. Kotsonis 1991. "Acceptable Daily Intake vs Actual Intake: The Aspartame Example," Journal of the American College of Nutrition, Volume 10, No. 3, page 258-266.

Buttery, J.E., B.R. Chamberlain, 1988. "A Simple Enzymatic Method for the Measurement of Abnormal Levels of Formate in Plasma," Journal of Analytical Toxicology, Volume 12, page 292-294.

Cook, M.R., F.J. Bergman, et al., 1991. "Effects of Methanol Vapor on Human Neurobehavioral Measures," Research Report No. 42 (Peer Reviewed), Health Effects Institute, 141 Portland Street, Suite 7300, Cambridge, MA 02139, (617) 621-0266, August 1991.

d'Alessandro, Alessandra, et al., 1994, "Formate in Serum and Urine after Controlled Methanol Exposure at the Threshold Limit Value," Environmental Health Perspectives, Volume 102, No. 2, February, 1994, page 178-181.

Davoli, E., et al., 1986a. "Serum Methanol Concentrations in Rats and in Men After a Single Dose of Aspartame," Food and Chemical Toxicology, Volume 24, No. 3, page 187-189.

Davoli, E., et al., 1986b. "Trace Analysis of Methanol in Rat Serum by Headspace High Resolution Gass Chromatography/Selected Ion Monitoring," Journal of Chromatographic Science, Volume 24, pages 113-116, 1986.

DHHS 1993. "Methanol Toxicity," American Family Physician, Volume 71(1):163-171, January 1993. Adapted from Case Studies in Environmental Medicine published by the Agency For Toxic Substances and Disease Registry, U.S. Department of Helath and Human Services.

Eells, Janis T., et al., 1996a. "Formate-Induced Alterations in Retinal Function in Methanol-Intoxicated Rats," Toxicology and Applied Pharmacology, Volume 140, page 58-69.

Eells, Janis T., 1996b. "Mechanism of Methanol-Induced Retinal Alterations," NIH Grant Application, Project No. 5 R01 ES06648-03, FY96, NIH CRISP Database: gopher://gopher.nih.gov:70/11/res/crisp

Federal Register 1984. "Food Additives Permitted for Direct Addition to Food for Human Consumption; Aspartame," Volume 49, No. 36, February 22, 1984, page 6672-6682.

Frederick, Linda J., et al., 1984. "Investigation and Control of Occupational Hazards Associated with the Use of Spirit Duplicators," American Industrial Hygiene Association Journal, Volume 45, No. 1, page 51-55.

Frey, Gunther H., 1976. "Use of Aspartame By Apparently Healthy Children and Adolescents," Journal of Toxicology and Environmental Health, Volume 2, page 401-415.

Fujimaki, H., et al., 1992. "Mast Cell Response to Formadehyde," International Archives of Allergy & Immunology, Volume 98, No. 4, page 324-331.

Garner, C.D., et al. 1995. "Role of Retinal Metabolism in Methanol-Induced Retinal Toxicity," Journal of Toxicology and Environmental Health, Volume 44, No. 1, pages 43-56.

He, J.L., L.F. Jin, H.Y. Jin, 1998. "Detection of Cytogenetic Effects in Peripheral Lymphocytes of Students Exposed to Formaldehyde With Cytokinesis-Blocked Micronucleus Assay," Biomedical Environmental Science, Volume 11, No. 1, pages 87-92.

Heinrich, R., J. Angerer, 1982. "Occupational Chronic Exposure to Organic Solvents. X. Biological Monitoring Parameters for Methanol Exposure," International Archives of Occupational and Environmental Health, Volume 50, page 341.

Heinzow, B., T. Ellrott 1992. "Formic Acid in Urine -- A Significant Parameter in Environmental Diagnosis?" Zentralbl Hyg Umweltmed, Volume 192, No. 5, page 455-461.

Hertelendy, Zsolt, et al., 1993. "Biochemical and Clinical Effects of Aspartame in Patients with Chronic, Stable Alcoholic Liver Disease," The American Journal of Gastroenterology, Volume 88, No. 5, 1993.

John, E.M., et al., 1994. "Spontaneous Abortion Among Cosmetologists," Epidemiology, Volume 5, No. 2, page 147-155.

Kavet, Robert, Kathleen M. Nauss, 1990. "The Toxicity of Inhaled Methanol Vapors," Critical Reviews in Toxicology, Volume 21, Issue 1, page 21-50.

Kazeniac, S.J., R.M. Hall, 1970. "Flavor Chemistry of Tomato Volatiles," Journal of Food Science, Volume 35, page 519-530.

Kingsley, W.H., F.G. Hirsch, 1954-1955. "Toxicological Considerations in Direct Process Spirit Duplication Machines," Compen. Medicine, Volume 40, page 7-8.

Kini, M.M., J.R. Copper, 1961. "Biochemistry of Methanol Poisoning--III: The Enzymic Pathway For the Conversion of Methanol to Formaldehyde," Biochemical Pharmacology, Volume 8, pages 207-215, 1961.

Lajtha, Abel, Margaret Reilly, David Dunlop, 1994. "Aspartame Consumption: Lack of Effects on Neural Function," Journal of Nutritional Biochemistry, Volume 5, page 266-283.

Leaf, G., L.J. Zatman 1952, "A Study of the conditions Under Which Methanol May Exert a Toxic Hazard in Industry," British Journal of Industrial Medicine, Volume 9, page 19- 31.

Leon, Arthur S., et al., 1989. "Safety of Long-Term Large Doses of Aspartame," Archives of Internal Medicine, Volume 149, page 2318-2324.

Liesivuori, Jyrik, 1986. "Slow Urinary Elimination of Formic Acid in Occupationally Exposed Farmers," Annals of Occupational Hygiene, Volume 30, No. 3, page 329-333.

Liesivuori, Jyrki, Heikki Savolainen, 1991. "Methanol and Formic Acid Toxicity: Biochemical Mechanisms," Pharmacology & Toxicology, Volume 69, page 157-163.

Lindinger, W., J. Taucher, A. Jordan, A. Hansel, W. Vogel, 1997. "Endogenous

Production of Methanol after the Consumption of Fruit," Alcoholism: Clinical and Experimental Research, Volume 21, No. 5, pages 939-943.

Lipton, Stuart A., Paul A. Rosenberg, 1994. "Excitatory Amino Acids as a Final Common Pathway for Neurologic Disorders," New England Journal of Medicine, Volume 300, No. 9, page 613-622.

Liu, Kai-Shen, et al., 1993. "Irritant Effects of Formaldehyde Exposure in Mobile Homes," Environmental Health Perspectives, Volume 94, page 91-94.

Main, D.M., T.J. Hogan, 1983. "Health Effect of Low-Level Exposure to Formaldehyde," Journal of Occupational Medicine, Volume 25, page 896-900.

Makar, A.B., T.R. Tephly, 1982. "Improved Estimation of Formate in Body Fluids and Tissues," Clinical Chemistry, Volume 28, page 385, 1982.

Molhave, L., et al., 1986. "Dose-Response Relation of Volitile Organic Compounds in the Sick Building Syndrome," Clinical Ecology, Volume 4, No. 2, page 52-56.

Monsanto (NutraSweet) 1999. "Frequently Asked Questions," NutraSweet Web Page, http://www.nutrasweet.com/

Monte, Woodrow C., 1984. "Aspartame: Methanol and the Public Health," Journal of Applied Nutrition, Volume 36, No. 1, page 42-54.

National Research Council 1981. "Formaldehyde and Other Aldehydes," National Research Council, National Academy Press, Washington, D.C., c1981.

Nelson, Richard (VP Public Affairs, NutraSweet Company), Internet post to several USENET newsgroups, October 24, 1996. View at web address: http://x8.dejanews.com/getdoc.xp?AN=191830590&CONTEXT=916551634.1925513337&hitnum=29

Nisperos-Carriedo, Myrna O., Philip E. Shaw, 1990. "Comparison of Volatile Flavor Components in Fresh and Processed Orange Juices,"Journal of Agriculture & Food Chemistry, Volume 38, page 1048-1052.

Olney, John W., et al., 1972. "Glutamate-Induced Brain Damage of Infant Primates," Journal of Neuropathology and Experimental Neurology, Volume

31, page 464-488.

Olney, John W., et al., 1980. "Brain Damage in Mice From Voluntary Ingestion of Glutamate and Aspartate," Neurobehavioral Toxicology and Teratology, Volume 2, page 125-129.

Olney, John W., 1988. "Excitotoxic Food Additives: Functional Teratological Aspects," In Progress in Brain Research, Volume 73 -- Biochemical Basis of Functional Neuroteratology: Permanent Effects of Chemicals on the Developing Brain, Edited by Boer, G.J., et al., Elsevier, New York, c1988.

Osterloh, J., 1986. "The Utility of Tetrabromophenophthalein Methyl Ester (TBPME) Spot Test for the Identification of Drug Positive Urines," Journal of Analytical Toxicology, Volume 10, page 255.

Osterloh, John D., A. d'Alessandro, P. Chuwers, H. Mogadeddi, T. Kelly, 1996. "Serum Concentrations of Methanol After Inhalation of 200 ppm," Journal of Occupational and Environmental Medicine, Volume 38, Issue 6, pages 571-576.

Porikos, Katherine P., Theodore B. Van Italie, 1984. "Efficacy of Low-Calorie Sweeteners in Reducing Food Intake: Studies with Aspartame" IN Stegink, L., Filer L., 1984. "Aspartame: Physiology and Biochemistry," Marcel Dekker, Inc., N.Y., page 273-286.

Posner, Herbert S., 1975. "Biohazards of Methanol in Proposed New Uses," Journal of Toxicology and Environmental Helath, Volume 1, page 153-171.

Puthrasingam S., et al., 1996. "Aspartame Pharmacokinetics - The Effect of Ageing," Age and Ageing, Volume 25, Number 3, pages 217-220.

Restani, Patrizia, Corrado Galli, 1991. "Oral Toxicity of Formaldehyde and Its Derivatives," Critical Reviews in Toxicology, Volume 21, Issue 5, pages 315-328.

Reynolds, W. Ann, A.F. Bauman, Lewis Stegink, L.J. Filer, Jr., S. Naidu 1984. "Developmental Assessment of Infant Macaques Receiving Dietary Aspartame or Phenylalanine," IN Stegink, L., Filer L., 1984. "Aspartame: Physiology and Biochemistry," Marcel Dekker, Inc., N.Y., page 405-423.

Roe, O., 1982. "Species Differences in Mehtanol Poisoning," CRC Critical

Reviews In Toxicology, October 1982, page 275-286.

Schmid, K., et al., 1994. "The Importance of Formic Acid Excretion in the Urine for Environmental and Occupational Medicine Questions," Zentralbl Hyg Umweltmed, Volume 196, No. 2, page 139-152.

Shaham, J., Y. Bomstein, A. Meltzer, Z. Kaufman, E. Palma, J. Ribak, 1996. "DNA--protein Crosslinks, a Biomarker of Exposure to Formaldehyde--in vitro and in vivo Studies," Carcinogenesis, Volume 17, No. 1, page 121-125.

Shahangian, Shahram, K. Owen Ash, 1984. "Aspartame Not a Source of Formate Toxicity," Clinical Chemistry, Volume 30, No. 7, pages 1264-1265, 1984.

Shaywitz, B.A., et al., 1993. "Evaluation of Aspartame on Behavior and Cognitive Function in Children With Attention Deficit Disorder (ADD)," Journal of Clinical and Experimental Neuropsychology, Volume 15, page 407

Shaywitz, Bennett A., et al., 1994b. "Aspartame, Behavior, and Cognitive Function in Children With Attention Deficit Disorder," Pediatrics, Volume 93, page 70-75.

Srivastava, A.K., et al., 1992. "Clinical studies of employees in a sheet-forming process at a paper mill," Veterinary and Human Toxicology, Volume 34, No. 6, page 525-527.

Stegink, Lewis D., W.A. Reynolds, L.J. Filer, et al. 1979. "Comparative Metabolism of Glutamate in the Mouse and Man," In Filer L.J. Jr., Garattini, S., Dare MR, Reynolds WA, Wurtman RJ (eds): "Glutamic Acid: Advances in Biochemistry and Physiology," Raven Press, New York 1979, pages 85-102.

Stegink, Lewis D., et al., 1981. "Blood Methanol Concentrations in Normal Adult Subject Administered Abuse Doses of Aspartame," Journal of Toxicology and Environmental Health, Volume 7, page 281-290.

Stegink, Lewis D., L. Filer, G.L. Baker, 1983. "Blood Methanol Concentrations in One-Year-Old Infants Administered Graded Doses of Aspartame," Journal of Nutrition, Volume 113, page 1600-1606.

Stegink, Lewis D., Filer L., 1984a. "Aspartame: Physiology and Biochemistry," Marcel Dekker, Inc., N.Y.

Stegink, Lewis D., 1984b. "Aspartame Metabolism in Humans: Acute Dosing Studies" IN Stegink, L., Filer L., 1984. "Aspartame: Physiology and Biochemistry," Marcel Dekker, Inc., N.Y., page 509-553.

Stegink, Lewis D., et al. 1987a. "Plasma Amino Acid Concentrations in Normal Adults Administered Aspartame in Capsules or Solution: Lack of Bioequivalence," Metabolism, Volume 36, No. 5, page 507-512.

Stegink, Lewis D., et al., 1989. "Effect of Repeated Ingestion of Aspartame-Sweetened Beverage on Plasma Amino Acid, Blood Methanol, and Blood Formate Concentrations in Normal Adults," Metabolism, Volume 38, No. 4, page 357-363.

Stegink, Lews D., et al., 1990. "Repeated Ingestion of Aspartame-Sweetended Beverages: Further Observations in Individuals Heterozygous for Phenylketonuria," Metabolism, Volume 39, No. 10, page 1076-1081.

Sturtevant, F., 1985. "Does Aspartame Cause Methanol Toxicity" (Letter To The Editor), Food and Chemical Toxicology, Volume 23, No. 10, page 961, 1985.

Triebig, G., et al., 1989. "Formaldehyde exposure at various workplaces," Science of the Total Envirnment, Volume 79, No. 2, page 191-195.

Trocho, C., et al., 1998. "Formaldehyde Derived From Dietary Aspartame Vinds to Tissue Components in vivo," Life Sciences, Vol. 63, No. 5, pp. 337+, 1998

Vojdani, A., 1992. "Immune Alteration Associated With Exposure to Toxic Chemicals," Toxicol Ind Health, Volume 8, No. 5, page 239-254.

Wantke, F., C.M. Demmer, P. Tappler, M. Gotz, R. Jarisch, 1996. "Exposure to Gaseous Formaldehyde Induces IgE-Mediated Sensitization To Formaldehyde in School-Children," Clinical and Experimental Allergy, Volume 26, pages 276-280.

Weber, James Matthew, 1999. Internet post to USENET newsgroup on January 5, 1999 by former G.D. Searle (owner by Monsanto) employee. Reference post on the web at:
http://x8.dejanews.com/getdoc.xp?AN=428867791&CONTEXT=916601874.9

49026972&hitnum=0

Yost, David A., 1989. "Clinical Safety of Aspartame," American Family Physician, Volume 39, Number 2, pages 201-206, 1989.