METHYL TERTIARY BUTYL ETHER (MTBE):
RISK OF NEUROTOXIC EFFECTS

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INTRODUCTION.

The decision as to the fate of MTBE has serious economic and public health ramifications. The argument that phasing out MTBE as an additive in oxygenated fuels would have serious economic consequences is based on the fact that-large amounts of MTBE are used in California and throughout the country. It is this widespread use, however, that provides the risk of exposure to a population of over 100 million Americans and requires that any potential or established risk to public health be taken with the outmost seriousness. Similarly, one can not make the argument that sufficient amounts of MTBE are being used widely enough to pose a risk to human health, without acknowledging that any decision as to its future use must take in consideration its economic consequences.

The best way to arrive at a policy decision regarding the future of MTBE as a gasoline additive is to rely strictly on solid science and careful and well-supported analysis of economic impact.

Policy is best when based on fact, not fear, communication and cooperation, rather than coercion.

The goal should be to protect the health of our citizens, the integrity of our natural environment, and the solvency of the economic institutions that provide an adequate supply of fuels. Enlightened policy does not require that any of those objectives be brushed aside. Any proposals should include measures to insure prevention of harm to human health and thoughtful consideration of how to best handle the economic and environmental consequences of any changes in current policy.

This testimony is intended to underscore the urgency of dealing with the potential risks to public health posed by the use of MTBE as an additive in oxygenated fuels. Concern during policy discussions has centered on risks of carcinogenicity, based on evidence in the peer-reviewed literature of MTBE's carcinogenic potential with chronic exposure to high enough doses in animal studies. Claims have also been made of associations with other pathological conditions which may merit further investigation.

My testimony, however, focuses on the primary effect of MTBE on the human body: alteration of nervous system function. The view that the use of MTBE poses a significant risk of neurotoxic effects and that this is an immediate public health concern is based on:

- the fact that MTBE is a neuroactive substance (section I of this written testimony)
- known plausible cellular mechanisms by which it disrupts normal function (section 2)
- animal studies which document its neurotoxicity (section 4a) and
- human epidemiological studies which document observed adverse effects symptomatic of nervous system disruption after exposure to MTBE (section 4b)

1. MTBE BELONGS TO A CLASS OF NEUROACTIVE SUBSTANCES

MTBE (Methyl Tertiary Butyl Ether) is an ether. Ethers are neuroactive.

Ethers were first isolated over 150 years ago, and became of interest, because of their ability to produce anesthetic effects in humans. Ether was first used as an anesthetic by dentist William Horton in Boston in 1846. It has been replaced as an anesthetic because the chemical characteristics that make some ethers useful as a gasoline additive, their flammability, created the risk of accidental fires.

Once MTBE reaches the bloodstream, after penetrating the body either through inhalation, ingestion or dermal absorption, the first and most abundantly perfused organs are the brain, kidney, and liver. The first biological target of MTBE and the organ most sensitive to its actions, is the nervous system.

2. MECHANISM OF ACTION: MTBE AFFECTS NERVE CELLS BY ITS EFFECTS ON MEMBRANE FLUIDITY

Cell membranes are lipid bilayers. MTBE, because of its solubility in lipids, alters membrane fluidity, potentially affecting all cells in the body. Nerve cells are more sensitive to agents which disrupt membrane integrity because their function is performed by membrane-bound molecules:

Transmission of information by nerve cells is accomplished through: a) generation of electrical impulses (action potentials) by changing conductances of ion channels (which are proteins extending through their membranes); b) through secretion of neurotransmitters at the end of nerve fibers (another process which depends on cell membrane integrity); and c) through responsiveness to neurotransmitters by receptor molecules inserted in the membranes of their dendrites.

The question then is, if MTBE is neuroactive, is there a significant risk of neurotoxic effects for humans at current levels of exposure?

3. IN 1988 ITC FOUND MTBE TO POSE AN UNREASONABLE RISK OF NEUROTOXICITY

In March 1988, the Interagency Testing Committee (ITC), after review of a number of substances which included MTBE, gave MTBE an “A” finding. An “A” finding was assigned to substances which present an unreasonable risk of neurotoxicity and for which there is substantial human exposure.

The “A” finding on MTBE required conducting a core test battery for neurotoxicity, including a functional observational battery, motor activity tests, and neuropathological evaluations after acute and subchronic exposure.

The ITC is a multidisciplinary advisory panel composed of one member of EPA, OSHA, Council on Environmental Quality, NIOSH, NIEH, NCI, NSF and the Department of Commerce. It issued 24 reports to EPA between 1977 and 1989, proposing 100 chemicals for inclusion in the priority list testing under section 4 of TSCA. Its finding on MTBE came before it was used as a gasoline additive as extensively as it is now and before its use became controversial.

After negotiations with industry, EPA (Office of Toxic Substances) issued a consent decree (March 1988, Federal Register, volume 53 - 10391) mandating neurotoxicity evaluation. Industry proposed testing to be performed by the Bushy Run Research Center, owned by Union Carbide. Tests were completed and a report written in September 1989 (Report 52-533, September 19, 1989). The results indicate MTBE has neurotoxic effects.

4. MTBE IS NEUROTOXIC

4a. ANIMAL INHALATION STUDIES REVEAL NEUROTOXIC EFFECTS OF MTBE

The Bushy Run Research Center studies, conducted on rats exposed to 4 concentrations through inhalation (0, 8900, 4,000 and 8,000 ppm) showed that MTBE caused depression of Central Nervous System activity which was more apparent at higher doses.

Amongst the effects observed after acute exposure were:

- ataxia
- duck walk gait
- labored respiration
- decreased muscle tone
- decreased body temperature
- decreased treadmill performance
- decreased hind-limb grip strength
- increased hind-limb splay, piloerection and lacrimation
- increased mean latency to rotate on an inclined screen

In the studies after sub-chronic exposure:

Effects similar to those caused by acute exposure were observed although the authors questioned their toxicological significance.

Significant changes in body temperature, motor activity and fore limb strength were observed.

Absolute brain weight was lower in animals exposed to 8,000 ppm. Unfortunately, the authors did not examine or report what specific cell populations in the central nervous system account for the brain weight loss.

Given the results of animal studies, does MTBE pose a risk of neurotoxicity in humans at the exposure levels resulting from its use as a gasoline additive?

4B. HUMAN EPIDEMIOLOGICAL DATA SHOWS A CORRELATION BETWEEN ROUTINE EXPOSURE TO MTBE AND SYMPTOMS OF NERVOUS SYSTEM DISRUPTION

In response to the 1990 amendments to the Clean air Act, Alaska converted to the use of oxygenated fuel containing 15% by volume MTBE in mid-October 1992. MTBE had not previously been added to gasoline in Alaska either as an octane enhancer or as an oxygenate.

Within the first 3 weeks of November 1992, reports of headaches, dizziness and nausea poured into a local telephone hotline.

In response to the complaints, a study was conducted by the Alaska Department of Health and Social Services and the Centers for Disease Control in December 1992, and January and February 1993.

Workers who were exposed in the workplace and commuters subjected to nonoccupational exposure were evaluated while MTBE was in use and after use of oxygenated fuels was suspended in Alaska.

Air concentrations of MTBE were monitored.

Blood levels of MTBE in the subjects was measured.

The results observed were as follows:

In areas where MTBE was added to gasoline, MTBE was detectable in the blood of occupationally exposed persons and the general public.

Persons exposed to and with higher blood levels of MTBE more frequently reported headaches, eye irritation, nausea, dizziness, burning of the nose and throat, coughing, spaciness or disorientation, and vomiting, compared to those with lower blood levels of MTBE.

Exposure to gasoline without MTBE did not result in increased symptoms.

4c. POLICY RESULTS OF THE CDC and ALASKA's DHSS EPIDEMIOLOGICAL STUDIES

Use of oxygenated fuels with MTBE was suspended in Alaska.

Alaska has been able to comply with the requirements of the Clean Air Act. Measures other than the use of reformulated gasoline, including comprehensive inspection and maintenance program resulted in a dramatic improvement in air quality and allowed for an immediate suspension of the use of MTBE while alternatives were sought. Ethanol was later introduced as a replacement for MTBE in Anchorage.

4d. SYMPTOMS OF NERVOUS SYSTEM DISRUPTION HAVE BEEN REPORTED IN SEVERAL STATES

Complaints indicative of adverse health effects similar to those reported in Alaska have been reported in Montana, New Jersey, Wisconsin, Maine, Connecticut, Pennsylvania, Texas and Colorado.

In April 1993, the Centers for Disease Control conducted studies in Stamford Connecticut similar to those in Alaska with the cooperation of the Connecticut Health Department. Again, the subjects with the highest blood MTBE levels had a higher incidence of symptoms of disruption of nervous system function.

A study conducted in Albany, New York yielded negative results. Comparisons may be misleading, however, because the blood levels of MTBE were significantly much lower than in Alaska and Connecticut (levels for gasoline station attendants, for example, were 15.19 micrograms per liter in Stamford vs. 0.42 micrograms per liter in Albany). A study comparing selected populations of southern and northern New Jersey did not include analysis of blood samples and its results are therefore more difficult to interpret.

4e. ORIGINAL STUDIES INDICATING NEUROTOXIC EFFECTS OF MTBE HAVE BEEN MISREPRESENTED OR IGNORED: A CAUTIONARY NOTE.

The results of the Alaska studies have been misrepresented by CAL EPA in its April 1997 report (p. 9) when stating that they "were unable to associate them [complaints] with MTBE exposure." The authors of the studies strongly object to that characterization. Reviews by Federal agencies have tried to downplay the results.

Similarly, a November 1993 review by the ORD of the US-EPA misrepresents the Stamford CDC studies by creating categories of subjects which dilute the results. Whereas the relevant correlation to examine is that between blood levels and symptoms of adverse effects, they compare the median of one or another occupational category, diluting the strength of the correlation between MTBE blood levels and health effects. That and other reviews give equal or more weight to negative results in Albany than to those obtained in Alaska and Stamford, with complete disregard to the clear differences in blood levels.

Whatever the intent is, one should be cautious and not rely on "reviews" and "assessments" of the literature but consult the original studies, with a definite preference for studies the results of which have been published in peer-reviewed journals. The only reliable measure of exposure is a quantitative and pharmacokinetic analysis of blood levels, with measurement of symptoms at relevant time points in relation to changes in blood levels. Guesses about exposures based on measurement of air levels are misleading and at best dilute the results.

If the results of the studies mentioned in 4a and 4b are indicative of neurotoxic effects of MTBE, why is there such little public awareness and reporting of adverse health effects?

5. NEUROTOXIC EFFECTS COMMONLY GO UNDETECTED AND THEIR CAUSE UNIDENTIFIED

One of the major problems in establishing the risk of neurotoxicity for a human population is that irreversible neurotoxic effects are often not detected, nor accurately diagnosed. Even in the case of reversible, acute effects, the association of overt symptoms with exposure to the causative agent is rarely established. Usually, no one is looking for them and neither the public nor most doctors are trained to identify, recognize and interpret symptoms of neurotoxicity.

Damage to the nervous system is more commonly expressed as loss of nerve cells, or impaired peripheral nerves, as opposed to visible abnormal growth as it is the case with cancer. Loss of neural tissue does not cause detectable biochemical changes that can serve as indicators.

Doctors are not taught in medical school to look for neurotoxic effects. When patients complain, doctors rarely conduct assays for the presence of neurotoxic substances in blood samples. It is also extremely rare, for example, for a doctor to have the equipment to measure speed of conduction of peripheral nerves.

Nervous tissue is the most delicate, vulnerable and irreparable of all tissues. While other tissues can regenerate, a lost nerve cell is lost forever. Nerve cells can not divide. They are not replaced. Thus, damage to the nervous system is irreparable and cumulative.

Often, as attested by even serious debilitating diseases, like Parkinson's disease or Alzheimer's disease, neuropathies do not present an immediate risk of death. Yet they harm the most essential, intimate human organ, that associated with all uniquely human qualities: the brain.

The impact on an individual's quality of life when an impairment is sustained in memory, intelligence or motor skills is incalculable. The cumulative effect for society of diminished intellectual capacity (analytical abilities, information processing abilities, memory, intelligence) at the level of a population, is hard to assess. The devastating emotional impact is clear for those with relatives or friends suffering from neurological diseases.

As long as systematic, comprehensive epidemiological studies are not conducted with human populations currently exposed to inhalation or ingestion of MTBE in the air or contaminated water, uncertainty will remain about the possibility of neurotoxic effects for the general population or for specially vulnerable sub-populations.

At best, a massive experiment is being conducted and no one is collecting the data. At worst, significant neurological damage is being sustained by segments of the population with unknown and possibly immeasurable consequences.

6. ADDITIONAL BRIEF NOTES REGARDING RISK OF EXPOSURE

6a. ENVIRONMENTAL FATE

Gasoline contains other components long recognized as hazardous for human health. Therefore, people will tend to exercise some degree of caution when handling reformulated gasoline.

The discovery of MTBE contamination in wells, however, raises additional concerns. When leakage from underground tanks or pipes occurs, MTBE diffuses faster and farther than other gasoline components and it stays in the environment longer. Its solubility in water and its high partition coefficient with soil allows it to diffuse faster than other components of gasoline and its rate of degradation is slower, especially when not vulnerable to photolysis.

People may be exposed to MTBE without their knowledge. Exposure to low levels of MTBE by ingestion increases the exposure burden already present through inhalation.

6b. DEGRADATION PRODUCTS OF MTBE AND ADDITIONAL RISKS OF PROLONGED EXPOSURE

The two main products of MTBE degradation are toxic. As MTBE degrades and ceases to directly pose a risk it creates substances, formaldehyde and TBA (TERTIARY BUTYL ALCOHOL), which pose well documented risks to human health.

The enzyme that catalyzes MTBE in the human body saturates. Therefore larger doses or prolonged exposure does not only have a cumulative effect but exposure to additional MTBE poses a larger risk.

7. POLICY RECOMMENDATIONS

The safest course of action would be to responsibly phase out MTBE and replace it with a safer alternative. If this alternative is chosen, sufficient time should be allowed for an orderly and cost-effective transition to alternatives which would accomplish the same fuel-efficiency and clean-air goals.

While MTBE use in reformulated fuels is phased out, as long as any significant amounts remain in the environment (i.e., in contaminated wells) or if MTBE continues to be used as a gasoline additive, minimum protective measures should include:

1. Strict monitoring of levels of MTBE and its degradation products - in particular TBA and formaldehyde - in the air and water.

2. Thorough monitoring of MTBE and TBA blood levels when there is likelihood of exposure.

3. Require industry to effectively inform residents or workers in areas where MTBE is present of what are the symptoms associated with MTBE exposure. Provide hot-line to take in reports.

4. Serious epidemiological investigation of complaints of adverse health effects.

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