Yerevan

April 22-24, 2013

CARCINOGENICITY AND TOXICITY OF METHYL TERTIARY-BUTYL ETHER (MTBE)

by

Professor Myron A. Mehlman

Mount Sinai School of Medicine and

University of Texas Medical Branch, Galveston TX

MTBE DISSOLVES WELL IN LIQUIDS

- **MTBE is a colorless liquid that 26 times more soluble in water that benzene, another carcinogen found in gasoline.**
- **Gasoline contains an average of 15% of MTBE.**
- **MTBE is not biodegradable.**

SOLUBILITY OF MTBE AND BENZENE

FOR THIS REASON, MTBE from leaks or spills:

1. **Does not remain in the same place;**
2. **Spreads in the soil in underground water;**
3. **Easily gets into the human water supply and can contaminate water used for drinking, cooking, bathing, showering, and the like.**

SUMMARY

- MTBE causes leukemias, lymphomas, kidney, testicular and liver tumors
- MTBE is converted to formaldehyde and tertiary butyl alcohol (TBA)
- TBA in water causes kidney and thyroid tumors
- Formaldehyde causes tumors of the nasal cavity, nasopharnyx, and sinuses in humans
- There is no safe level for MTBE

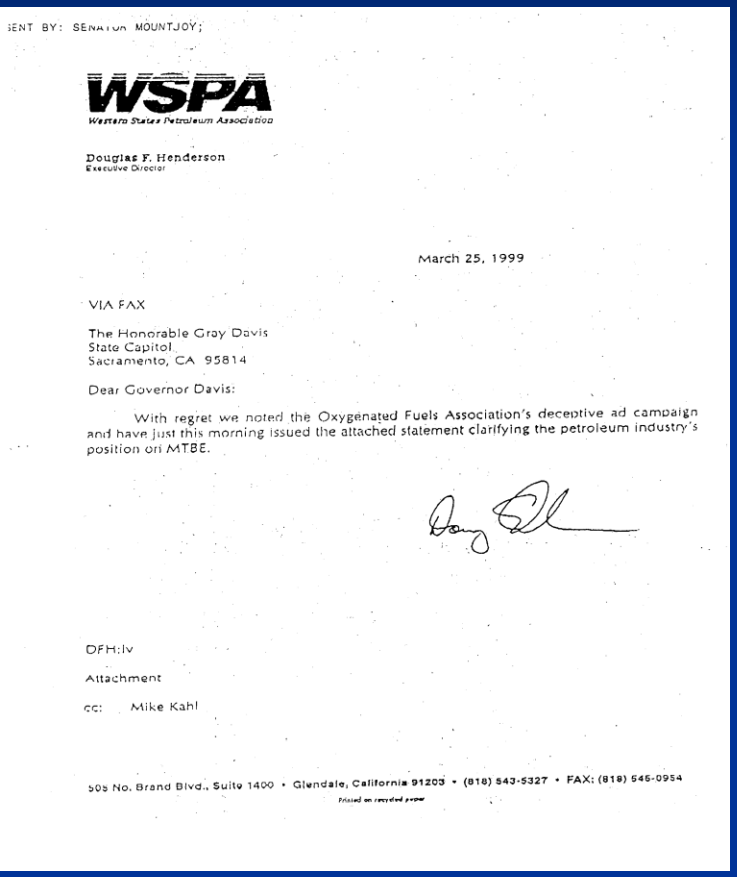
LACK OF BENEFIT

FROM USE OF MTBE

NAS SCIENTIFIC EVALUATION OF MTBE (1997)

- Data do not support the existence of MTBE benefits
- Levels of Carbon Monoxide were achieved prior to use of MTBE
- Oxygenated fuels (MTBE) increase Nitrous Oxide N_2O emission
- N_2O emissions are detrimental to ozone non-attainment areas

FAX from Western States Petroleum Association (WSPA) to the Hon. Gray Davis



SENT BY: SENATOR MOUNTJOY;

WSPA
Western States Petroleum Association

Douglas F. Henderson
Executive Director

March 25, 1999

VIA FAX

The Honorable Gray Davis
State Capitol
Sacramento, CA 95814

Dear Governor Davis:

With regret we noted the Oxygenated Fuels Association's deceptive ad campaign and have just this morning issued the attached statement clarifying the petroleum industry's position on MTBE.

DFH:lv

Attachment

cc: Mike Kahl

505 No. Brand Blvd., Suite 1400 • Glendale, California 91203 • (818) 543-5327 • FAX: (818) 545-0954

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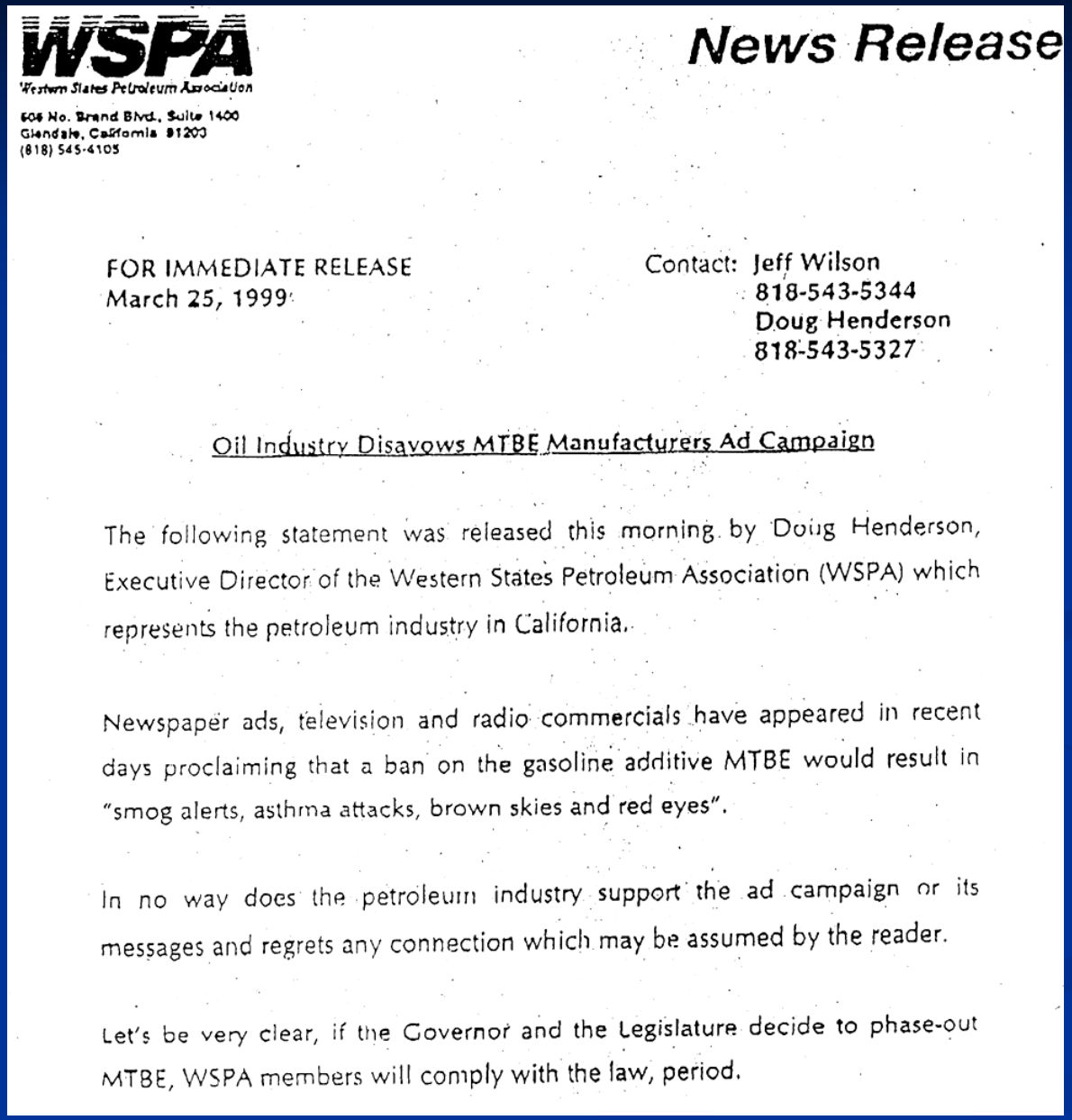
"With regret we noted the Oxygenated Fuels Association's deceptive ad campaign and have just this morning issued the attached statement clarifying the petroleum industry's position on MTBE."

S/ Douglas F. Henderson,
Executive Director

Western States Petroleum Association (WSPA)



WSPA
Western States Petroleum Association
606 No. Brand Blvd., Suite 1400
Glendale, California 91203
(818) 545-4105

News Release

FOR IMMEDIATE RELEASE
March 25, 1999

Contact: Jeff Wilson
818-543-5344
Doug Henderson
818-543-5327

Oil Industry Disavows MTBE Manufacturers Ad Campaign

The following statement was released this morning by Doug Henderson, Executive Director of the Western States Petroleum Association (WSPA) which represents the petroleum industry in California.

Newspaper ads, television and radio commercials have appeared in recent days proclaiming that a ban on the gasoline additive MTBE would result in "smog alerts, asthma attacks, brown skies and red eyes".

In no way does the petroleum industry support the ad campaign or its messages and regrets any connection which may be assumed by the reader.

Let's be very clear, if the Governor and the Legislature decide to phase-out MTBE, WSPA members will comply with the law, period.

FOR IMMEDIATE RELEASE

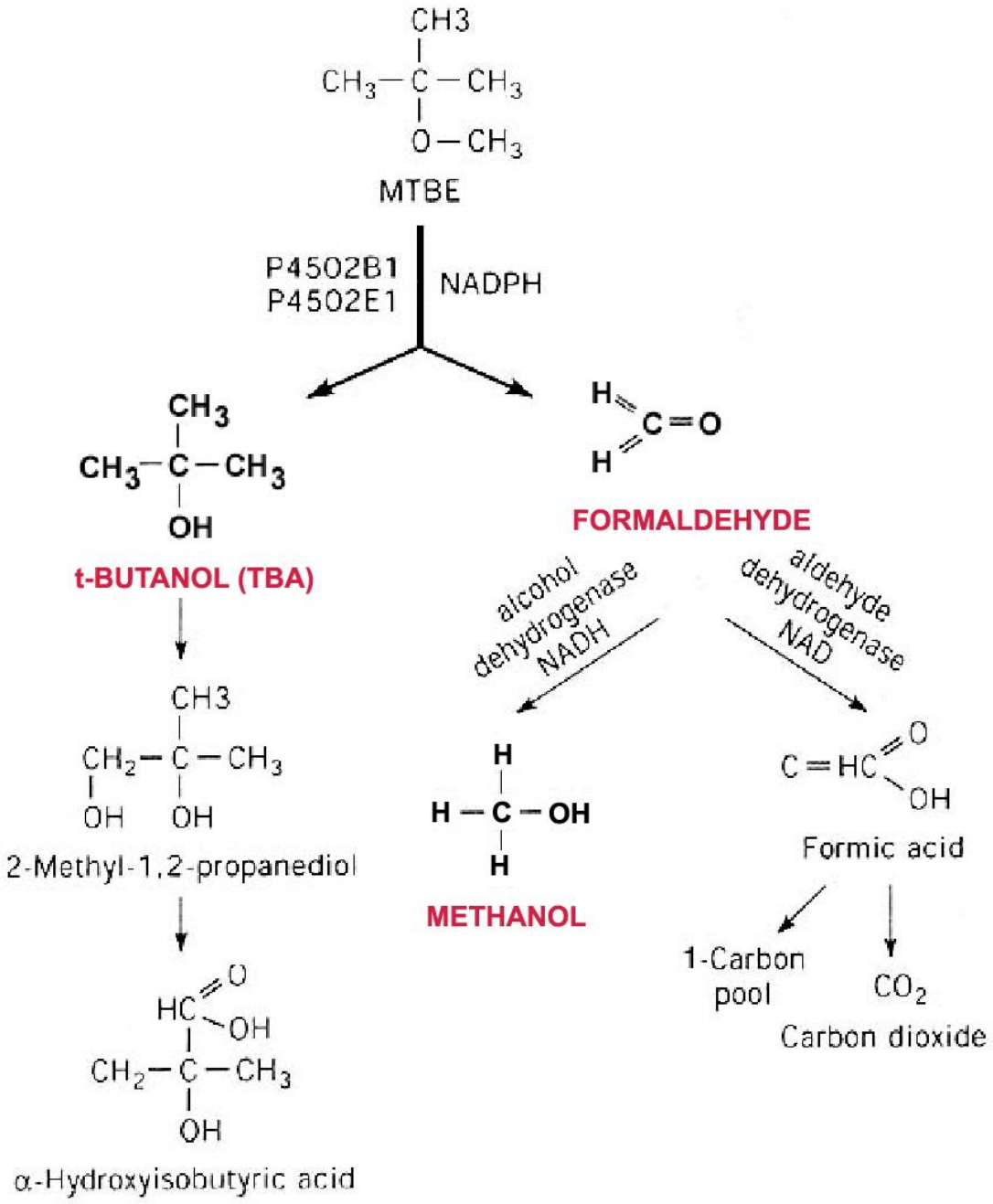
March 25, 1999 entitled "Oil Industry Disavows MTBE Manufacturers Ad Campaign"

WSPA NEWS RELEASE (Cont.)

"Newspaper ads, television and radio commercials have appeared in recent days proclaiming that a ban on the gasoline additive MTBE would result in 'smog alerts, asthma attacks, brown skies and red eyes.'"

"In no way does the petroleum industry support the ad campaign or its messages and regrets any connection which may be assumed by the reader."

MTBE METABOLISM



MTBE and its toxic metabolites, TBA, Formaldehyde, and Methanol

TOXICITY OF METHANOL

- Effects on vision including blindness
- No information on chronic low-level exposure
- Increases utilization of folic acid may result in:
  - Risk to pregnant women and fetuses
  - Neural tube defects *in utero*
  - Megaloblastic anemia
- Metabolism to formaldehyde in humans

HEALTH EFFECTS

IN

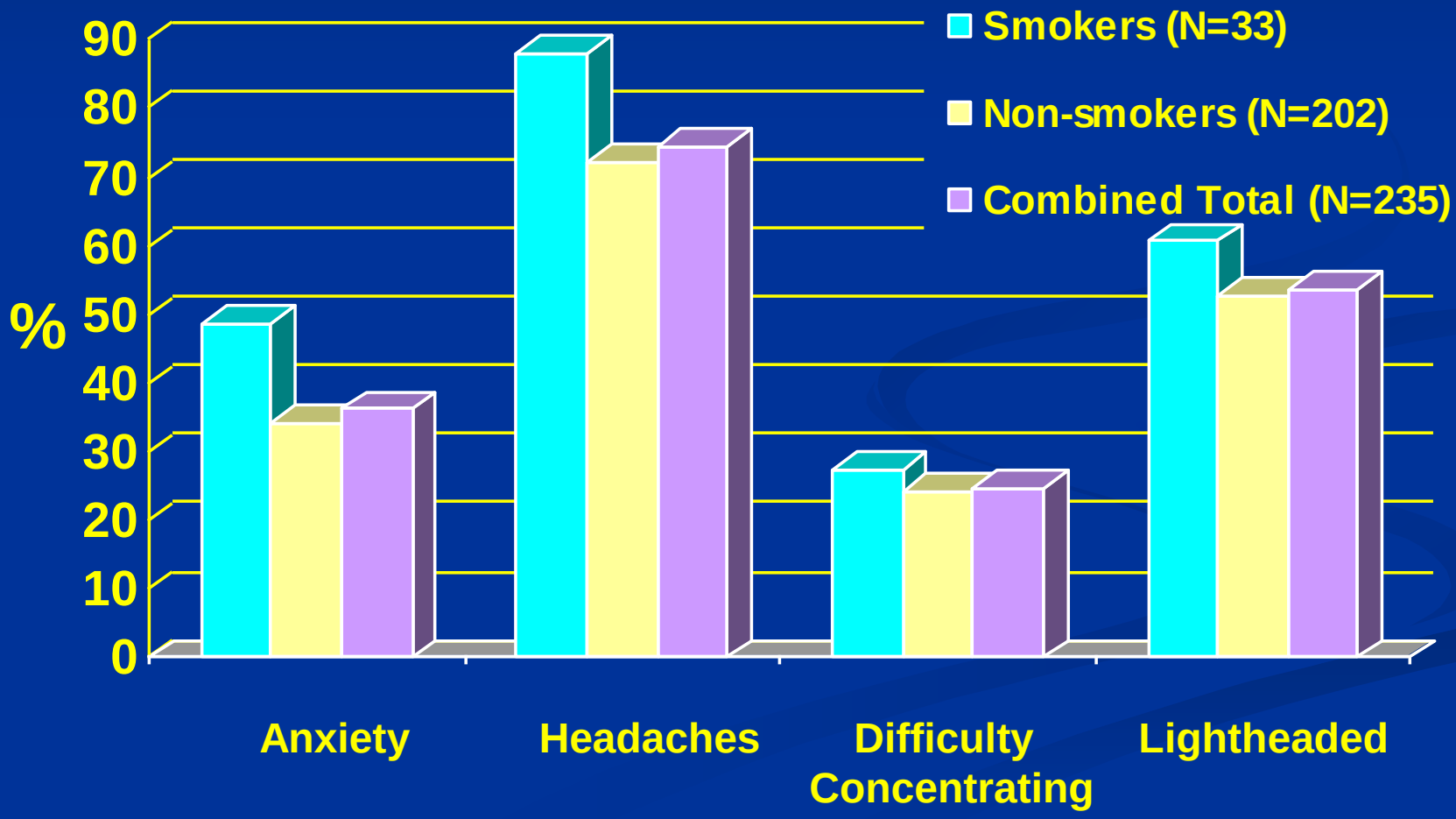
NEW JERSEY CONSUMERS

Clinical studies show that humans exposed to MTBE also have:

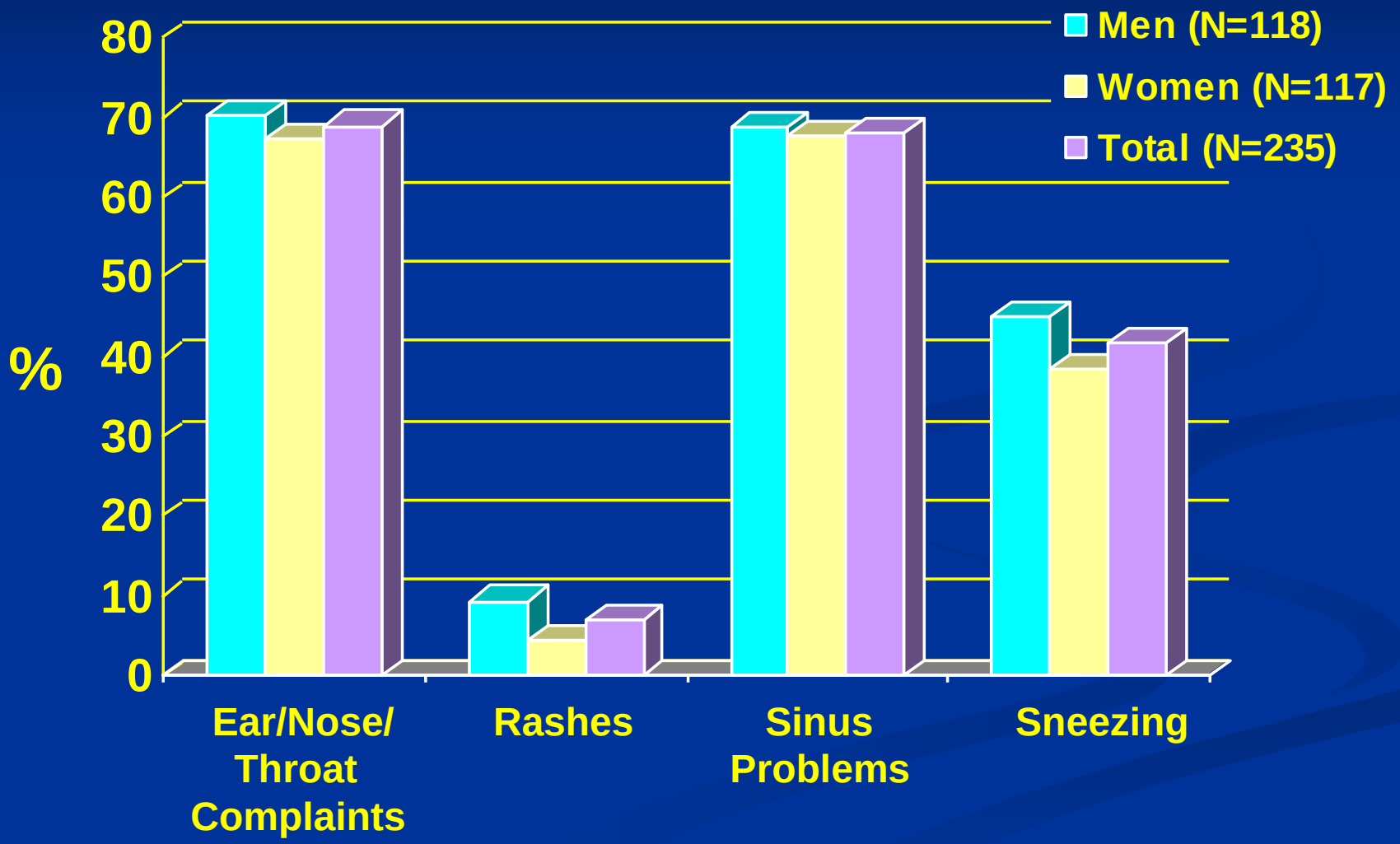
- Fatigue
- Shortness of breath
- Increases in asthma, bronchitis and respiratory illness
- Muscle aches

NJ MTBE-Exposed Individuals

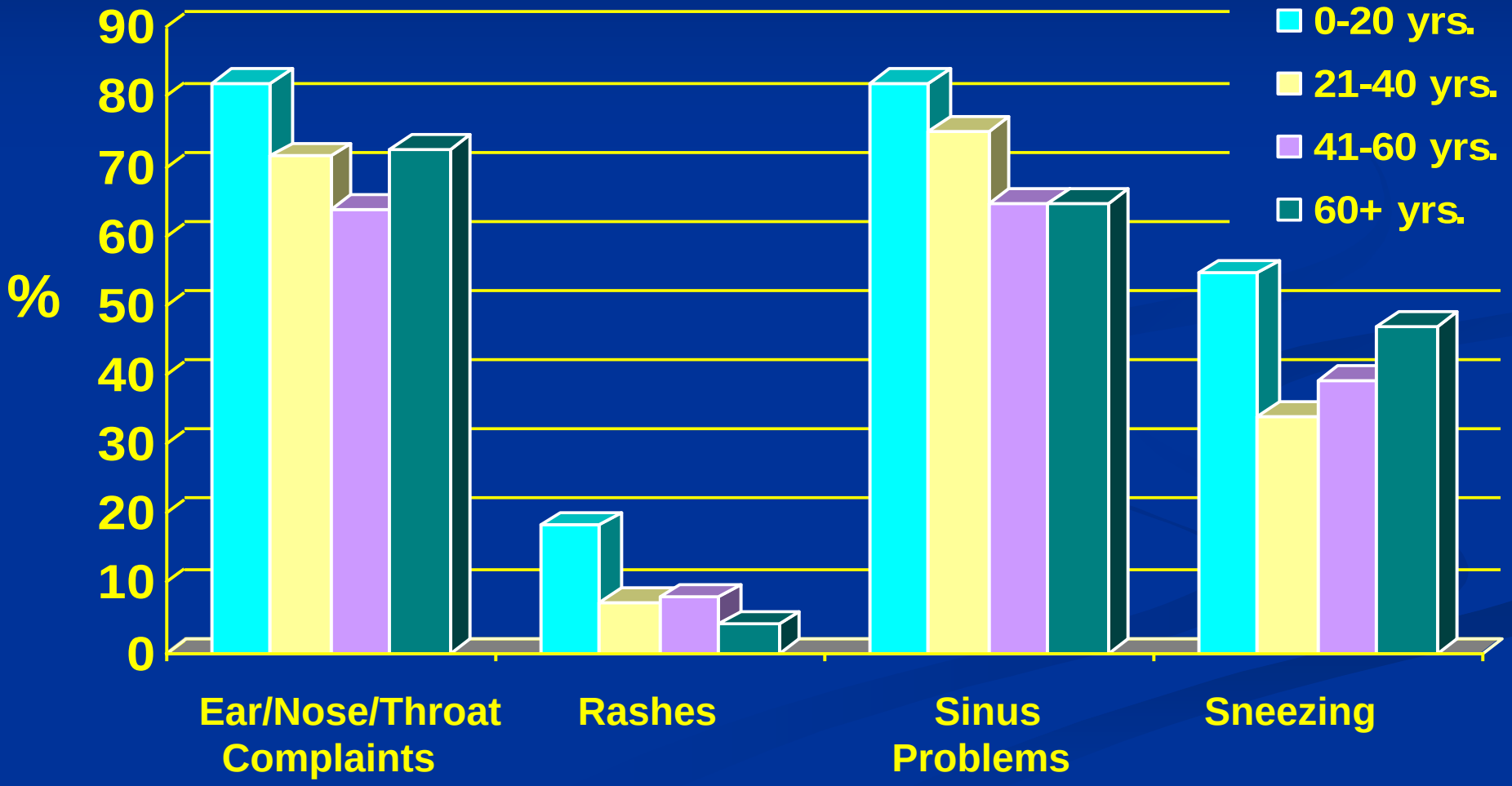
Neurological Symptoms – Smokers/Non-smokers



NJ MTBE-Exposed Individuals
Allergic Symptoms by Gender

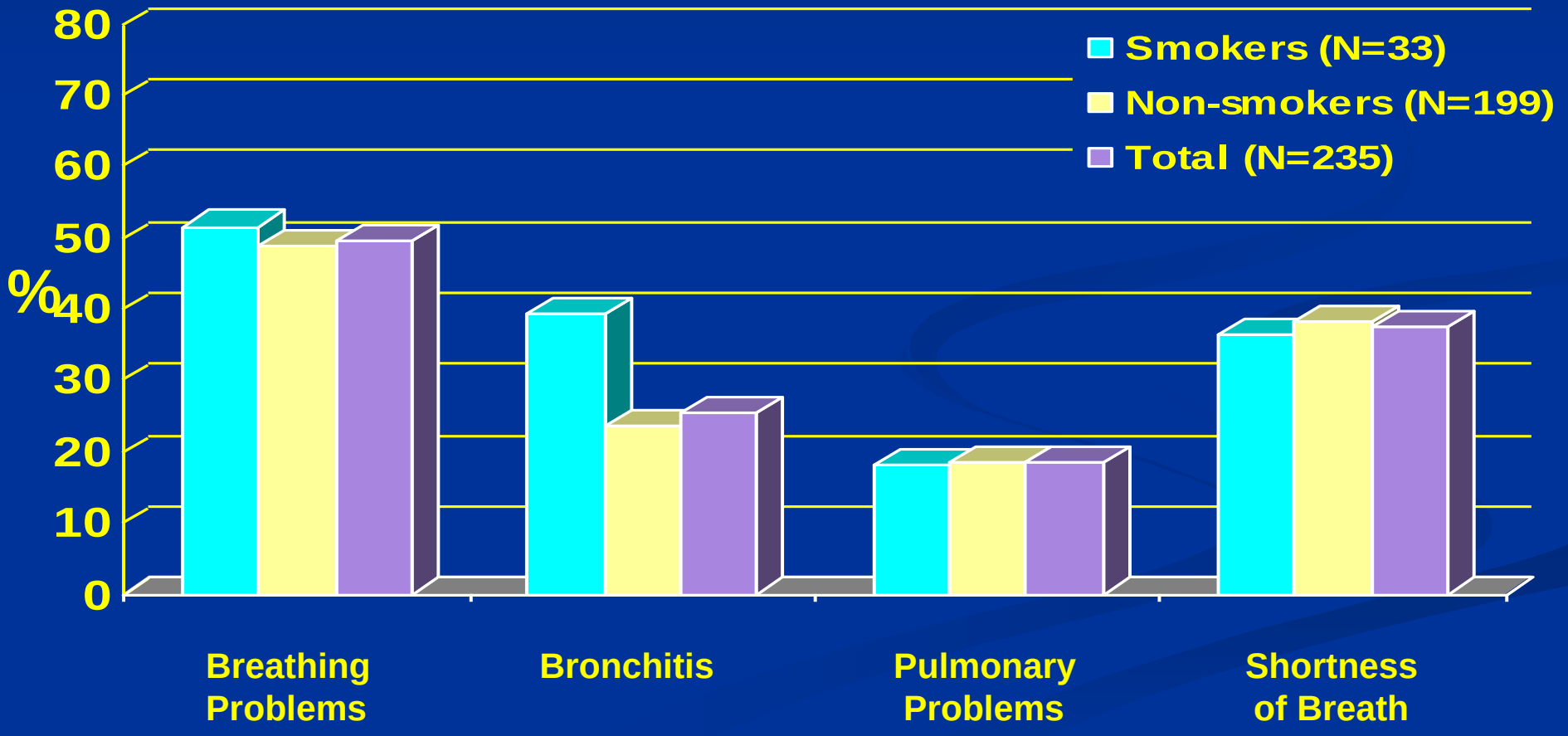


MTBE-Exposed Individuals
Allergic Symptoms by Age



MTBE-Exposed Individuals

Respiratory Symptoms - Smokers & Non-smokers



HEALTH EFFECTS IN ALASKA

MTBE STUDY IN ALASKA

a) During MTBE use (Phase I) &

b) After MTBE use in gasoline stopped (Phase II)

Health Complaints of Occupationally Exposed Workers in Phase I (December 1992) and Phase II (February 1993) of Exposure

Complaints	Phase I (N=18)	Phase II (N=28)
Headache	13 (72%)	1 (4%)
Eye irritation	12 (67%)	2 (7%)
Cough	5 (28%)	0 (0%)
Dizziness	8 (44%)	0 (0%)
Disorientation	6 (33%)	0 (0%)

Source: R.L. Moolenaar, Arch. Env. Health

Post-shift MTBE and TBA Serum Concentrations in 12 Workers Obtained in PHASE I (12/92) and PHASE II (2/95) of the Exposure Survey

	Phase I		Phase II		
	Median	Range	Median	Range	*p*
MTBE (µG/L)	1.34	0.2-31.5	.21	0.05-1.44	0.004
TBA (µG/L)	5.6	1.7-72.2	3.9	0.9-13.4	0.16

CASE REPORTS

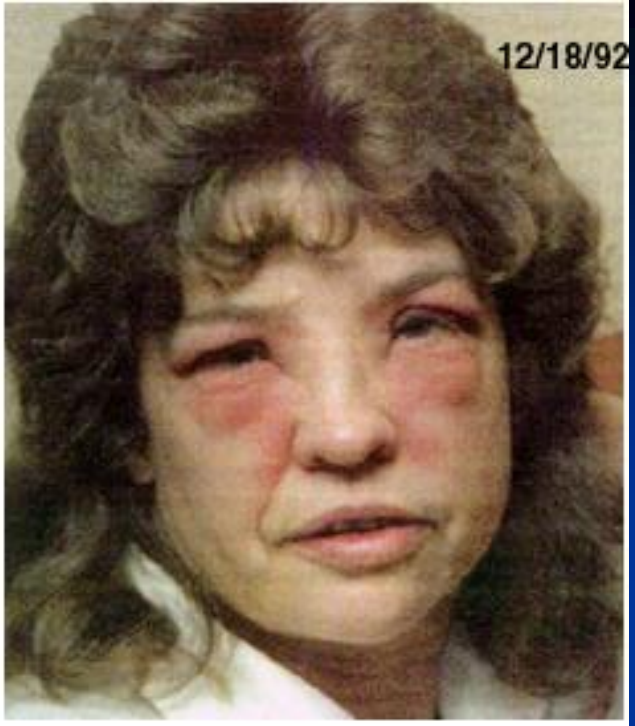
1. CP with eye irritation every time she was exposed to gasoline containing MTBE
2. JP with headaches and rashes
3. JTD with dizziness, eye irritation, breathing difficulties
4. JMcC with rashes on her face, treated with steroids
5. CR with eye burning, headaches and fatigue
6. Dr. SRS describes a patient
7. JMH with lightheadedness, sore throat, cough, headache

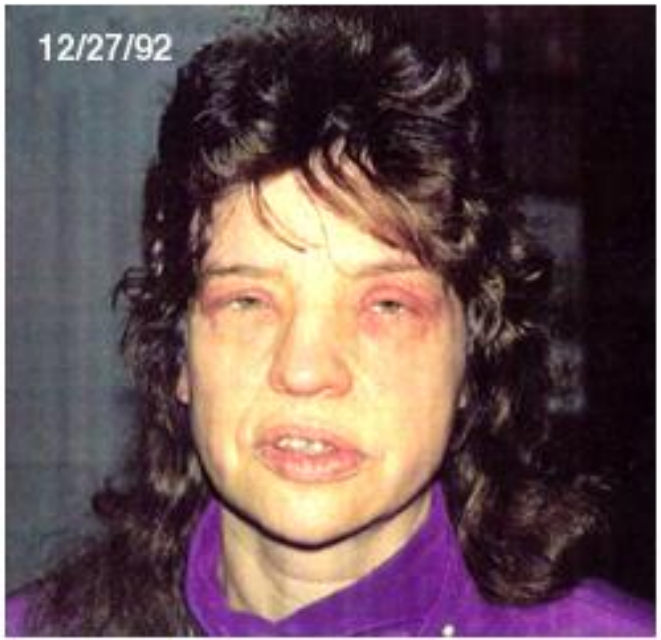
C.P. from Alaska wrote in her log:

"12/27/92 My husband pumped gas in the car. My chest started to hurt. A rash began on my face, and my eyes were itching. By the next day, there was a red rash and swelling on my face and around my eyes."

"1/27/93 I was behind a truck and could smell the gas. My head and chest started to hurt. I had headaches most of the next 2 days."


11/7/92


12/18/92


12/27/92


1/22/93

On 10/7/96 JDP, a NJ gas station owner, wrote:

"My employees get headaches regularly and real nauseated when dispensing fuel. We are thinking about wearing gas masks this year."

"One of my mechanics breaks out in a terrible rash if any of the oxy fuel gets on his skin."

"When I pump gas myself, I go home with severe headaches."

JTD, a 31 year old landscaper from North Carolina, wrote:

"I have been exposed to MTBE in my drinking water. I bathed in it, cooked with it, and cleaned my contact lens cases with it."

"I wake up at night and can't get my breath. My nose burns, I am very dizzy at times. My right eyelid has been swollen for about 8 months; my eye doctors told me that something was irritating my eye."

On 9/5/96, JMcC, a 40 y/o nurse educator wrote:

"In June of 1995, a large truck passed me and the fumes from the exhaust hit me in the face. The next day, I woke up with a red, irritated, swollen face that looked like poison ivy. My family doctor said I had dermatitis from a chemical burn and prescribed steroids. I had to take two courses of steroids - the rash came back after the first course."

"This happened three more times in 1995. Now I have to avoid all exposure to car exhaust. Trips to the supermarket, shopping mall, . . . can be hazardous to my health."

On 3/28/95 CR, a 36 y/o female tow truck driver from Wisconsin, wrote:

"Symptoms started with eye burning, headache, sleeping all the time. I knew it was the gas by the end of January, 1995."

"I get all 3 RFG's or oxygenates. Some cars are very toxic -- they smell up my whole lot of about one acre. Who knows which [oxygenate] is worst; our gas pumps aren't marked."

Dr. SRS, an internist from Maine, wrote on 7/20/95:

"G.F., one of my patients had lethargy, headache, sore throat, and nausea in February and March of 1995."

"In April 1995 when gasoline spilled on his hands, they became sore, red, and later began bleeding. He developed headaches, nose bleeds and burning eyes when he inhaled gasoline fumes. About April 1995, he learned that the gasoline he had been working with without any trouble since 1970 was changed to the reformulated type."

JMH, a 53 y/o retired woman from New Jersey, wrote:

"Lightheadedness, sore throat, cough, headache occur quickly while sitting in the car at the gas pump."

"I often have to get out of the car and stand away from the pumps because of the dizziness from the gas odor."

CARCINOGESIS

AT BIRTH

EQUAL CHANCE OF ILLNESS, CANCER, DEATH

AFTER SOME TOXIC EXPOSURE

HEALTH

ILLNESS
DEATH

DNA TRANSFORMATION

- A DNA adduct is a piece of DNA covalently bound to a (cancer-causing) chemical
- Adduct formation changes the DNA molecule and prevents normal replication resulting in mutations that can lead to carcinogenesis
- The formation of adducts is thought to be the first step in carcinogenesis
- MTBE forms adducts with DNA in animals (Du et al., 2005) and in humans (Vodjani & Brautbar 1999) experimentally exposed to MTBE

Du et al. (2005) Fudan University, Shanghai, China

- **Reported formation of MTBE-DNA adducts in liver, kidney, and lung**
- **Formation of MTBE-DNA adducts occurred in a linear, log/log, dose response relationship.**
- **MTBE-DNA adduct formation peaked at twelve hours after MTBE administration. Adducts declined rapidly five days after administration.**

Du HF, Xu LH, Wang HF, et al. (2005) Formation of MTBE-DNA adducts in mice measured with accelerator mass spectrometry. Environ Toxicol 20:397-401.

ADDUCT FORMATION BY MTBE

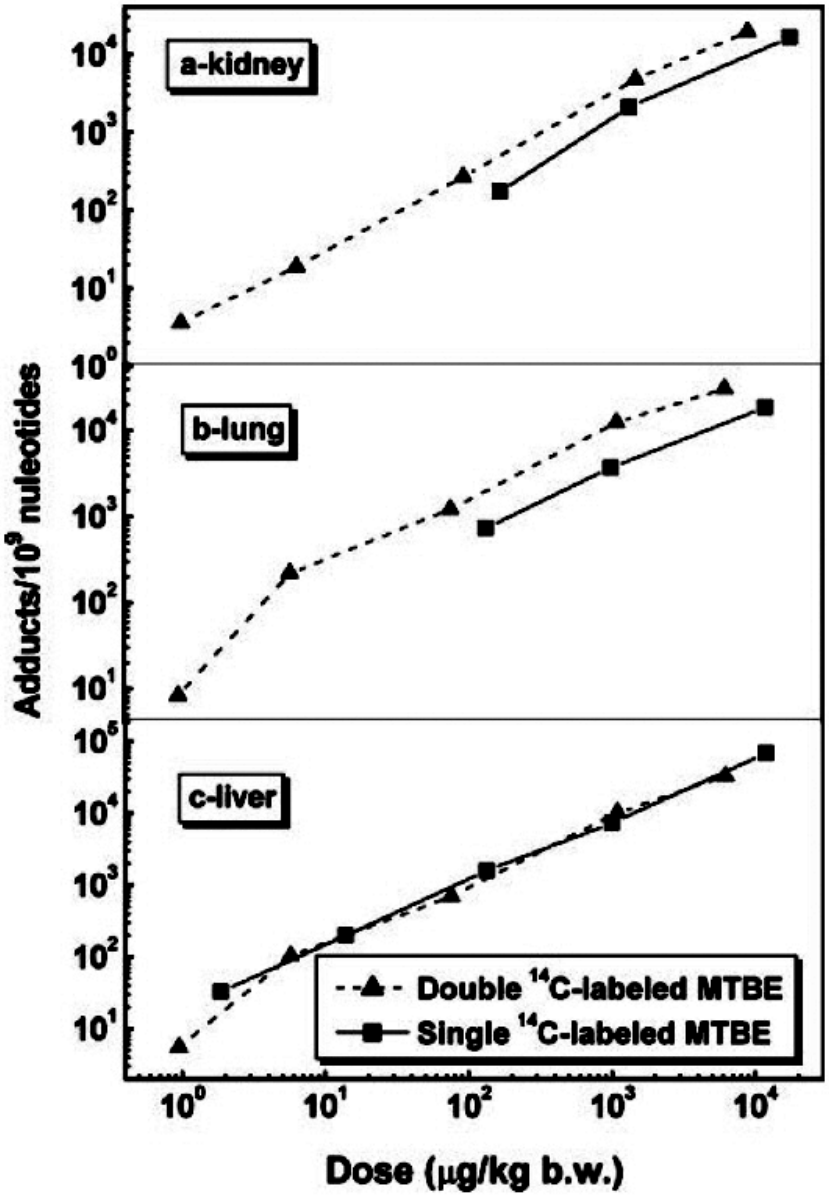


Fig. 2. The DNA adduction comparison of doubly ^{14}C-labeled MTBE (Du et al., 2005) and singly ^{14}C-labeled MTBE in mouse kidney (a), lung (b), and liver (c). The numerical values in these figures are mean values of two to four parallel samples.

Dose-dependent DNA adduct formation reported by Du et al. (2005) [dotted lines] were reproduced by Yuan et al. (2007) *Environmental Toxicology* 22:360-635 [solid lines].

VODJANI & BRAUTBAR STUDY (1998)

- Subjects were exposed to MTBE and benzene at concentrations above permissible levels through drinking, bathing and showering with contaminated water.

- The majority of subjects had severe headaches, fatigue, exhaustion, cognitive dysfunction, abdominal pain, indigestion, and depression that were correlated with the exposure period.

VODJANI & BRAUTBAR STUDY (1999)

GROUP I - Exposed Subjects:

20 subjects exposed to MTBE through ingestion and bathing in contaminated water for 8 months.

GROUP 2 - Control Group:

20 healthy control subjects with no exposure to MTBE other than pumping gas into personal vehicles once a week, comparable to the exposed group.

FINDINGS:

- Lymphocyte DNA adducts were significantly increased in the exposed group compared to the healthy controls
- The DNA adducts represent genotoxic damage, which signals initiation of carcinogenicity

Song et al. (2002)

- **Found that exposure of mouse fibroblasts to MTBE caused a dose-response increase in a standard (Comet) assay**
- **Concluded that MTBE could directly cause DNA damage**

Song C, Zhang Z, Chen X, et al. (2002) [Study on three kinds of gasoline oxygenates-induced DNA damage in mice fibroblasts.] Zhonghua Lao Don't Wei Sheng Zhi Ye Bing Za Zhi 20:362-364.

Yang et al. (2005)

- **Found that exposure of three types of rat and mouse cells to MTBE caused a dose-response relationship**
- **Concluded that MTBE induced genotoxicity on DNA and single strand breaks of cells**

Yang H, Kong L, Zhao JS. (2005) [DNA damage induced by methyl tertiary-butyl ether in vivo and in vitro.] Ahonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi 23:352-365.

Yuan et al. (2007)

- **Found that low concentrations of MTBE and TBA bind to form DNA adducts in mouse liver, lung and kidney**

Yuan Y, Wang HF, Sun HF, et al. 2007. Adduction of DNA with MTBE and TBA in mice studied by accelerator mass spectrometry. Environ Toxicol 22: 630–635.

Chen et al. (2008)

- **Found that MTBE could induce a variety of DNA damage including single-strand breaks, double-strand breaks, and oxidative base modifications**

Chen CS, Hseu YC, Liang SH et al. (2008) Assessment of genotoxicity of methyl-tert-butyl ether, benzene, toluene, ethylbenzene, and xylene to human lymphocytes using comet assay. J Hazardous Materials 153:351–356.

WEIGHT of EVIDENCE

for

CARCINOGENICITY

CRITERION FOR EVALUATION OF CARCINOGENICITY[1]

Studies must show an increase in tumors in experimental animals:

1) In multiple species or at multiple tissue sites; or

2) By multiple routes of exposure; or

3) To an unusual degree with regard to incidence, site, type of tumor, or age of onset.[1]

[1] National Toxicology Program Report on Carcinogenesis.

The International Agency for Research on Cancer (IARC) of the World Health Organization Monographs Report[1]:

- **119 chemicals evaluated have shown evidence of carcinogenicity in animals but no human data are available;**
- **Only 9 of these chemicals are subjects of epidemiological surveys**

[1] **Tomatis, 1985; Tomatis, 1988.**

The International Agency for Research on Cancer (IARC) of the World Health Organization Monograph (1987) Report:

- Of the 44 agents for which there is sufficient or limited evidence of carcinogenicity in humans, all 37 that have been tested adequately produce cancer in at least one animal species.
- Therefore, it is biologically plausible and prudent to regard agents for which there is sufficient evidence of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans.

Based on the NTP and IARC data, there is general agreement among experts in chemical carcinogenesis that a substance that causes cancer in significant numbers of experimental animals in well-conducted studies poses a presumptive carcinogenic risk to humans, even in the absence of confirmatory epidemiological data.

Findings of an extensive animal study by Staffa and Mehlman (1979):

- **Evidence from the ED_{01} Study of 24,192 animals provides massive and overwhelming experimental profiles, and the database lends support to regulatory policies [of the EPA and FDA].**
- **No level of exposure to a toxic substance greater than zero can be assumed to be without potentially harmful effects.**

CANCERS CAUSED BY BENZENE & MTBE IN ANIMALS

	BENZENE		MTBE
Cancers	Animals	Humans	Animals
Kidney	Yes	Yes	Yes
Leukemia	Yes	Yes	Yes
Lymphoma	Yes	Yes	Yes
Hemolymphoreticular	Yes	Yes	Yes
Liver	Yes	Yes	Yes

CARCINOGENICITY OF MTBE IN ANIMALS

Route	Organ	Animal	Author
Inhalation	Kidney, testes	Mouse	Chun et al., 1992
Inhalation	Liver	Mouse	Burleigh-Flayer et al., 1992
Oral	Lymphoma and leukemia	Female rat	Belpoggi et al., 1995
Oral	Testes (Leydig cell)	Male rat	Belpoggi et al., 1998

CARCINOGENICITY OF MTBE

Animal	Organ	Statistically Significant
Male Rat	Kidney	Yes
Male Rat	Testes	Yes
Male Rat	Hemolympho-reticular	Yes
Male Mouse	Liver	Yes
Female Mouse	Liver	Yes

Source: Mehlman, 1994.

Collegium Ramazzini Position

In 1996, the Collegium Ramazzini concluded that exposure to MTBE in gasoline should be avoided in order to prevent needless illness of both consumers and workers. The Collegium Ramazzini urges that the toxicity of MTBE be fully and vigorously examined because it is not prudent to permit wide environmental releases of a compound that may cause acute illness as well as cancer.

ATSDR

ASSESSMENT OF CARCINOGENICITY OF MTBE

The White House National Science and Technology Council report (1997) concludes that, "There is sufficient evidence that MTBE is an animal carcinogen" and that, "the weight of evidence supports MTBE as having carcinogenic hazard potential for humans."

Keller *et al.* (1998), in a report commissioned by the Governor and the State of California Legislature, concluded that MTBE is an animal carcinogen with potential to cause cancers in humans.

Froines et al. (1998)

In a large, comprehensive report entitled "An Evaluation of the Scientific Peer-Reviewed Research and Literature on the Human Health Effects of MTBE and its Metabolites . . ." published by the University of California, Davis, CA *(http://tsrpt.ucdavis.edu)* concluded the following:

Froines et al. (1998)

- There are no human studies on which an evaluation of the carcinogenicity of MTBE can be based;
- Substantial evidence from chronic studies in animals (rats and mice) show that MTBE is carcinogenic;
- We conclude that MTBE is an animal carcinogen with the potential to cause cancer in humans.

EVALUATION

"In benefit risk evaluation, provided that experimental data support the evidence of carcinogenicity, MTBE is a true carcinogen.

"Given the large population exposed, I would remove it [MTBE]."

Cesare Maltoni, July 22, 1994

REGULATION

EPA Office of Drinking Water

"The good news is that this means that the OGWDW would not issue a Health Advisory for MTBE - the bad news is that they would release a fact sheet on MTBE with recommended acceptable drinking water concentrations between 2 and 10 ppb. These values would represent the 10^{-4} to 10^{-6} risk range."

(Memo to API members from API staff lobbyist, 5/1/1996.)

STATE RECOMMENDATIONS, MTBE STANDARD

CALIFORNIA	14 ppb
NEW YORK STATE	10 ppb
U.S. EPA PROPOSED	2-10 ppb

Title 15A, Section 2L - Groundwater Classification of North Carolina Standards General Statutes, Section 102 Definitions (24) "Suitable for Drinking" defines "suitable for drinking" to mean:

" a quality of water which does not contain substances in concentrations which either singularly or in combination if ingested onto human body, may cause death, disease, behavioral abnormalities, congenital defects, genetic mutations, or result in an incremental lifetime cancer risk in excess of 1×10^{-6}, or render the water unacceptable due to aesthetic qualities including taste, odor, or appearance.

ATSDR – SAR ANALYSIS

Memo dated April 25, 1997

From Moiz Mumtaz, ATSDR

To: Myron Mehlman

“. . . The probability of MTBE being a male rat carcinogen is high.”

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS: REPORT OF THE CARCINOGENS SUBCOMMITTEE

Summary review of the RG2 Committee

- Dr. R. Melnick, on behalf of the NIEHS, nominated MTBE for listing "as reasonably anticipated to be a human carcinogen."
- John Bailar's motion to list MTBE as carcinogenic to humans was defeated by a vote of six to five.
- Members who voted not to list:

Belinsky	Frederick	Hecht
Kelsey	Medinsky	Zahn

- Members who voted to list MTBE as carcinogenic:

Bailar	Bingham	Hooper
Mirer	Russo	

- US EPA[1] classified MTBE as a "possible" human carcinogen.
- MTBE has been characterized as an animal carcinogen.
- IARC indicated that there is not enough data to classify MTBE as a human carcinogen. This does not mean that MTBE is not carcinogenic to humans.

[1] Federal Register. Friday, March 24, 2000. Part VII, Environmental Protection Agency, 40 CRF par 75J. MTBE: Advance notice of intent to initiate rule making under TSCA to eliminate or limit the use of MTBE.

IARC UNDERGRADED MTBE - Part 1

- Published carcinogenicity studies are both:
  - Underinterpreted
  - Misrepresented by IARC
- Not all available data were used in the IARC evaluation
- Some studies were discounted due to powerful industry influence
- IARC claimed some studies tested MTBE using a non-standard (gavage) protocol
- IARC failed to mention that Leydig Cell tumors were found in both oral and inhalation studies

Huff J. (2002) IARC Monographs, industry influence and upgrading, downgrading, and undergrading chemicals. Int J Environ Health 8:249-270.

IARC UNDERGRADED MTBE - Part 2

- Uterine sarcomas in the low oral dose group were not mentioned.
- Tumors caused by TBA, a major metabolite of MTBE, were not reported.
- Kidney tumors were attributed to a non-specific effect of α-2microglobulin.
- The NTP Board of Scientists voted 5 to 6 for not listing MTBE in their Report on Carcinogenesis.
- A substantial number of NIEHS scientists believe that MTBE should be listed as a human carcinogen.

Huff J. (2002) IARC Monographs, industry influence and upgrading, downgrading, and undergrading chemicals. Int J Environ Health 8:249-270.

CONSIDER THE SOURCE

BIASED OUTCOME DUE TO SOURCE OF FUNDING

	Number of studies & effect reported	
Outcome: Source of funding	Harm	No harm
Governmental	94	10
Chemical Corporations	0	11
Total	94	22

From: Michaels (2006)

CONCLUSION

- MTBE in gasoline is dangerous
- MTBE causes leukemias, lymphomas, testicular, kidney and liver tumors
- MTBE is converted to formaldehyde and tertiary butyl alcohol (TBA)
- Formaldehyde causes leukemias, lymphomas, tumors of the nasal cavity, nasopharynx, and sinuses in humans
- TBA in water causes kidney and thyroid tumors
- There is no save level for MTBE