Potential Health Effects of Gasoline and Its Constituents: A Review of Current Literature (1990–1997) on Toxicological Data

Luciano Caprino and Giuseppina I. Togna

Institute of Medical Pharmacology, University of Rome "La Sapienza," Rome, Italy

We reviewed toxicological studies, both experimental and epidemiological, that appeared in international literature in the period 1990–1997 and included both leaded and unleaded gasolines as well as their components and additives. The aim of this overview was to select, arrange, and present references of scientific papers published during the period under consideration and to summarize the data in order to give a comprehensive picture of the results of toxicological studies performed in laboratory animals (including carcinogenic, teratogenic, or embryotoxic activity), mutagenicity and genotoxic aspects in mammalian and bacterial systems, and epidemiological results obtained in humans in relation to gasoline exposure. This paper draws attention to the inherent difficulties in assessing with precision any potential adverse effects on health, that is, the risk of possible damage to man and his environment from gasoline. The difficulty of risk assessment still exists despite the fact that the studies examined are definitely more technically valid than those of earlier years. The uncertainty in overall risk determination from gasoline exposure also derives from the conflicting results of different studies, from the lack of a correct scientific approach in some studies, from the variable characteristics of the different gasoline mixtures, and from the difficulties of correctly handling potentially confounding variables related to lifestyle (e.g., cigarette smoking, drug use) or to preexisting pathological conditions. In this respect, this paper highlights the need for accurately assessing the conclusive explanations reported in scientific papers so as to avoid the spread of inaccurate or misleading information on gasoline toxicity in nonscientific papers and in mass-media messages. *Key words*: alkylbenzenes, antiknocking agents, benzene, gasoline, gasoline constituents, methanol, MTBE, toxicity. *Environ Health Perspect* 106:115–125 (1998). [Online 3 February 1998]
http://ehpnet1.niehs.nih.gov/docs/1998/106p115-125caprino/abstract.html

Gasoline is the generic term for petroleum fuel used mainly for internal combustion engines. It is complex, volatile, and inflammable and contains over 500 saturated or unsaturated hydrocarbons having from 3 to 12 carbons. The variable mixture characteristics depend on crude oil origin, differences in process techniques and blends, season to season changes, and the additives required to meet particular performance specifications.

In the strategy for reducing motor vehicle pollution by removing lead and many potentially toxic hydrocarbons in gasoline mixtures, the addition of oxygenates (alcohols and alcohol-derived ethers) has led to the development of reformulated fuels with lower quantities of benzene and aromatics without the use of heavy metal additives. Generally speaking, a common gasoline formulation contains approximately 62% alkanes, 7% alkenes, and 31% aromatics, as well as alcohols, ethers, and additives. The percentage composition may vary significantly according to regulations in force in different countries, not only among the various leaded compositions but also among the unleaded, the reformulated, and the oxygenated.

About 110 million people are exposed to gasoline constituents in the course of refueling at self-service gasoline stations (*1*), an operation that requires only a few minutes per week, accruing to approximately 100 min/year. During refueling, total hydrocarbon concentrations in the air fall within the range of 20–200 ppm by volume. Major toxic risk comes from breathing exhaust fumes and evaporative and refueling emissions rather than from occasional skin contact from spills. At modern service stations, designed to dispense gasoline quickly and safely, the typical consumer risk of suffering serious negative health effects due to exposure to gasoline is negligible. However, available information on general population exposure is either nonexistent, incomplete, or inconsistent with other data (*2*).

With increasing frequency over recent years, articles on gasoline appear in scientific and nonscientific printed matter. Among the scientific articles, some refer to new and interesting results, some provide already known information, and others give interesting but incomplete data. In the nonscientific area, some papers make ambiguous or incorrect considerations and provide interpretative explanations capable of instilling deep concern in public opinion on the dangers of gasoline.

In this paper, we examine a series of experimental and epidemiological toxicological studies that have appeared in international literature over the period 1990–1997, in regard to leaded and unleaded gasolines

as well as their components or additives. Certain constituents are mentioned that may not be present in all gasoline mixtures, but are mentioned because scientific studies published during the period contribute to a more exhaustive picture of the toxicological profile of gasolines.

Toxicity Studies on Gasoline

Experimental Animal Data

In 1992 the Dutch Directorate-General for Labour carried out an exhaustive review on potential gasoline toxicity (*3*). The report gives results of toxicity studies in different animal species treated with a gasoline having pretedermined quantities of the various constituents. Data on acute oral toxicity, acute and short-term inhalation exposure, intratracheal instillation and long-term toxicity (including carcinogenesis), teratogenic or embryotoxic activity, mutagenicity, and clastogenicity are included. The report refers to a species/sex-specific carcinogenic effect and, even if data are limited, suggests a lack of teratogenic and embryotoxic activity and little evidence of mutagenic and clastogenic effect.

Human and Epidemiological Studies

A relationship between gasoline exposure and the onset of renal and liver cancer, acute myeloid leukemia, myeloma, heart disease, changes in the central nervous system (CNS), skin alterations (including melanoma), and modifications of mucous membranes has been indicated.

Cancer, leukemia, and myeloma. An association between kidney cancer and exposure to gasoline has been suggested in some studies (*4–9*).

In 1993, Infante (*10*) referred to two studies in gasoline-exposed workers: the first study suggested an association with kidney cancer, but the second study did not. This apparent contradiction might be explained by other factors such as cigarette smoking, which was not sufficiently considered in the analysis (*10*). Other epidemiological studies published in 1993, which include a cohort of approximately 100,000 male refinery workers (*11*)

and another of 18,135 distribution employees (12), do not support an increased kidney or liver cancer risk when compared with general population. McLaughlin (13), in reviewing epidemiology of renal cell cancer, examined the following risk factors: cigarette smoking, gasoline, obesity, diet, and use of analgesics and diuretics. No link between gasoline exposure and renal cell cancer was found.

A previously unnotified risk of nasal cancer has recently been reported in service station workers in the Nordic countries by Lynge et al. (9). The study also reports an increased incidence of pharyngeal, laryngeal, and lung cancers.

A relationship between the development of acute leukemia and myeloma and exposure to petroleum products such as fuels and exhaust fumes has also been suggested (5,14).

Risk of acute myeloid leukemia has been studied in Sweden, and results indicate that other constituents of gasoline could potentiate the leukemic effect of benzene (15). A mortality study among 6,672 Canadian petroleum marketing and distribution workers and tank truck drivers, conducted by Schnatter et al. in 1993 (6), gave an overall mortality lower than the general Canadian population in marketing and distribution workers; leukemia findings were not evident in the latter category, but were significantly elevated in tank truck drivers. Infante (10) referred to three studies conducted in gasoline-exposed workers: one showed strong associations between gasoline exposure, leukemia, and multiple myeloma; the second suggested a slight association with leukemia, but did not analyze data for multiple myeloma; and the third was inconclusive due to problems linked with study design. In 1996 Collingwood et al. (16) reported that in a cohort study of 4,855 refinery workers in New Jersey, all of whom had been employed for a minimum of 1 year in an arc of time going from 1946 to 1979, mortality from overall leukemia and lymphatic and hematopoietic cancer was at the expected level; mortality from multiple myeloma was, however, lower than expected.

Exposure to gasoline vapors was classified by the International Agency for Research on Cancer (IARC) in 1989 as possibly carcinogenic to humans (Group 2B) (17), mainly on the basis of the established carcinogenicity of some constituents such as benzene.

Skin lesions and mucous membranes. In humans, gasoline causes irritation to eyes at exposures up to 200 ppm in the air over a period of 30 min (3). After gasoline application to skin, a decrease in glutathione

concentration, glutathione S-transferase activity, and lipid peroxidation was observed in liver and brain (18).

Some studies in refinery workers and gasoline-exposed workers indicated an increased mortality risk from malignant melanoma; whether this was the result of exposure to gasoline, benzene, or sunlight, or a combination of these factors has been difficult to establish (10).

Heart disease. No clear association has been found between gasoline exposure and refinery workers in regard to heart disease (6,7). Evaluation of risk is complicated by important related factors, e.g., cigarette smoking, a point that is particularly relevant when studying gasoline-exposed workers who, due to danger of explosion in their work environment, would naturally have a lower smoking factor than the general population (6).

Neurotoxicity. Occupational exposure to gasoline has been associated with numerous neurotoxicity signs including significant effects on intellectual capacity, modifications of psychomotor and visualmotor functions, and immediate and delayed memory (19). Other gasoline-induced neurotoxic effects (ataxia, tremor, acute or subacute encephalopathic syndrome) are ascribable to intentional use (gasoline sniffing) and not to occupational exposure (19).

Current epidemiological data are generally considered inadequate for a global assessment of health risk, but it is to be hoped that ongoing studies will remedy this situation.

Toxicity Studies on Unleaded Gasoline

Most of the animal toxicity studies that we reviewed were performed with an unleaded gasoline (UG) known as PS-6 [American Petroleum Institute (API), Washington, DC], a blend with the benzene content adjusted to 2% and regarded as a representative UG (20). The formulation for PS-6 gasoline was described in a 1995 API publication (21).

As with leaded gasoline, major toxicological problems concern carcinogenic potential, namely, liver tumors in female mice and renal tumors in male rats. In female rats, only a mild proximal tubular dysfunction was found (22).

Renal Tumors

In explaining renal tumors in F344 male rats exposed to UG, Raabe (23) suggested that the presence of hyaline droplets, or the increase in α2u-globulin in the renal tubules of UG-treated male rats, could be involved in the mechanism for this pathology. The increase was attributed to the higher composition of branched hydrocarbons in UG (24)

to which α2u-globulin could bind, thus inducing renal tubule cell death followed by a proliferative sequence that increases renal tubule tumors (23,25). In any case, no clear conclusion can yet be drawn concerning the role of α2u-globulin in the development of renal disease and the association between α2u-globulin nephropathy and renal carcinogenesis (25,26).

Extrapolation of male rat renal tubule tumors to humans is questionable (27): if α2u-globulin is involved in male rat kidney tumors, because it is a rat-specific protein and unique to the male rat (28–30), it would not relate to humans (30,31).

Liver Tumors

Standeven et al. (32,33) attempted to determine the mechanism of induction of liver tumors with concomitant uterine changes in B6C3F₁ female mice chronically exposed to UG (PS-6) vapors and concluded that high-level exposures could produce an increase in liver tumors in female mice due to interference with estrogen hormone function. Standeven et al. (34) demonstrated an induction of estrogen metabolism in isolated hepatocytes from UG-treated mice, which suggested a potential mechanism for apparent antiestrogenic activity of UG. Tilbury et al. (35) surmised that some biological effects, such as the induction of cell turnover or altered growth control, could play a role in the carcinogenic process in PS-6 gasoline-treated mice. Furthermore, Standeven and Goldsworthy (36,37) demonstrated an induction of CYP2B, a subfamily of cytochrome P450, in female mouse liver.

Toxicity Studies on Gasoline Constituents

Individual constituents of gasoline mixtures, regardless of their presence or quantity in any one formulation, have been examined because they have been the subjects of scientific publications that provide a contribution to knowledge already acquired on the relevant toxicological profile. Particular attention has been given to the new constituents recently adopted as gasoline additives.

Organic Compounds of Lead

To improve yield and performance, fuel combustion must be rapid, and the search for suitable antiknock agents has resulted in the development of alkyl leads (tetramethyl and tetraethyl lead) as cost-effective octane enhancers. Increase in the compression ratio began in the 1950s, leading to the need for higher octane fuels; therefore, lead concentrations were increased up to the limit of 1.14 g Pb/l.

A 1990 study carried out in employees, with an average of 14 years exposure to

organic compounds of lead, demonstrated that neurotoxic damage can result from exposure to such antiknock additives (38).

As a matter of fact, it has been well known for decades that organolead compounds are potent neurotoxics on the CNS and its development. In neonatal rats, these compounds produced persistent and dose-dependent behavioral hyperreactivity and hippocampal damage; a relationship between these effects via cholinergic, but not dopaminergic, pathways was hypothesized by Booze and Mactutus (39). In a recent study carried out on cultured E18 rat hippocampal neurons (40), triethyl lead, the major metabolite of tetraethyl lead, was shown to disrupt cytoskeletal elements, particularly neurofilaments, at very low levels (nanomolar concentrations).

In humans, the organolead compounds, especially tetraethyl lead, are known to have a toxic impact on the CNS, as suggested by pathological changes in brain stem neurons and subtle cognitive and neurological deficits. Infants are the most susceptible population (41–43). Other effects are nephropathy, hematologic alteration, hypertension, congenital malformations, growth and development deficiencies, and impairment of immune system responses. Due to the probable involvement of multiple etiologic factors in the above pathological situations, the actual scientific challenge is to develop sensitive methodologies capable of detecting the rate of organolead compound involvement.

Improvements brought about by the introduction of unleaded fuels determined a gradual decrease in lead content in gasoline, which in many countries has been associated with a lowering of blood lead levels in the general population (44–48). However, over the past two decades, research has demonstrated that adverse health effects occur at levels previously considered safe (49–51). Organometals, like organolead, are difficult to eliminate from the CNS, and the injuries induced usually result in permanent neurological deficits that cause medical as well as social–economical problems (52).

Oxygenates

Oxygenates are used as antiknock agents in place of lead derivatives and as substitutes for high octane aromatics in fuel (53,54); by permitting a more efficient fuel combustion, they diminish exhaust emissions of carbon monoxide and hydrocarbons. Oxygenate concentrations in gasoline formulations vary from 0.7% by volume in leaded gasoline [mostly methyl tertiary butyl ether (MTBE)] currently used in some European countries to 15% in some types of U.S. oxygenated gasolines.

Oxygenates include substances such as ethanol, methanol, MTBE, ethyl tertiary butyl ether (ETBE), tertiary butyl alcohol (TBA), and tertiary amyl methyl ether (TAME).

Ethanol. Ethanol is a chemical to which man is particularly exposed. It is widely used as an industrial solvent and is also consumed in alcoholic beverages. Abundant literature exists on the effect of ethanol ingestion (CNS, endocrine, renal, gastrointestinal, hepatic, and cardiovascular systems), which is outside the purpose of this paper.

In reference to ethanol use as a gasoline additive (approximatively 10% volume), it is worth noting that exposure to ethanol in gasoline should not increase toxicity risk for human health. In fact, the potential levels of exposure are much lower than the levels associated with the toxic effects observed in experimental animals or in humans, as described by Burbacher (19) and Reese and Kimbrough (55).

Methanol. Methanol can be used as a fuel either alone or as a gasoline additive. Its toxicological profile has been widely studied, and only recent references are reported here.

Methanol is well absorbed in humans following inhalation, ingestion, or cutaneous exposure; it produces a transient mild depression of the CNS with headache, vertigo, and vomiting. It is oxidized to formaldehyde in the liver and then to formic acid, which contributes to the metabolic acidosis that occurs in acute methanol poisoning. Intoxication has delayed onset characterized by acidosis, mental confusion, ocular toxicity with visual disturbance [recently suggested (56,57) as due to intraretinal metabolism of methanol, rather than to elevated blood formate levels], reversible or permanent blindness, and, in severe cases, death. These effects represent a classic example of lethal synthesis in which toxic metabolites can cause fatality after a characteristic latency period (58).

A significant increase in incidence of exencephalia and cleft palate has been observed in mice, as well as an increase in embryo/fetal death, after inhalation of high concentrations of methanol (59). Cummings (60) obtained similar results together with reduced uterine pregnancies and implantations in rats and mice. An *in vitro* study performed by Andrews et al. (61) reported a dysmorphogenic effect of methanol on rat and mouse embryos and suggested a higher sensitivity in the mouse to the developmental toxicity of methanol.

In a cellular culture of a specific and sensitive target, craniofacial tissue, methanol selectively affected sensitive cell populations and modified proliferation and cell fate (62). Lee et al. (63), studying effects of methanol

vapors on testicular morphology and on testosterone production in rats, hypothesized that methanol could potentially accelerate age-related degeneration of the testes.

Two papers on methanol inhalation toxicity that are especially pertinent to the subject include a 1995 study in which no interactive effects between methanol and gasoline were found in a short-term inhalation study in rats (64), and a study on perinatal exposure to low concentrations of methanol, which resulted in no significant abnormalities in the brains of treated rats (65).

There is little evidence from available information of human health effects from low-level exposure which demonstrates that methanol vapors from motor vehicle fuel can cause acute adverse effects to health (55,66). Lee et al. (67) demonstrated that after a 6-hr exposure to the current methanol threshold limit value (TLV) of 200 ppm, the formate does not accumulate in blood in human subjects at rest or during exercise. This result was confirmed by other authors (68,69).

The neurotoxic effects recorded at current TLVs (70) are not significant in assessing human risk from methanol as a fuel or additive; in fact, Costantini (66) found levels lower than 50 ppm in most exposure scenarios, but reported methanol exposure levels from methanol-fueled car emissions at approximately 150 ppm in public garages. For the most part, the general public's exposure to methanol would be brief but repetitive, and further studies on the relationship between chronic low-level exposure and subtle changes in CNS function need to be performed (19,66,71).

Methyl tertiary butyl ether. MTBE is an aliphatic ether, a volatile, colorless, and inflammable liquid, currently the most widely used oxygenate. It has been employed as an octane enhancer in gasoline blends at concentrations up to 7% since 1979. In 1992, in those areas in the United States where carbon monoxide exceeded national standards, MTBE was raised to 15% by volume to reduce atmospheric pollution. Raising the oxygen content in gasoline reduces emissions of carbon monoxide, especially in older cars.

Experimental animal data. Acute toxicity data show a low order of MTBE toxicity in rodents following inhalation, oral administration, or cutaneous exposure (72–75). In subchronic and chronic toxicity studies (75–79), MTBE appears to have low systemic toxicity; the main findings observed in rats were depressant effects on the CNS, typical of similar ethers. Such effects were transient and completely reversible (75,77,79): no histopathological changes in tissues of the peripheral or central nervous system occurred (75,79). Other target organs following repeated oral or inhalatory

exposure at high doses have been identified as liver, kidneys, and adrenal glands (77–79). No significant immunological, cardiovascular, hematological, or pulmonary effects in animals have been observed (73,76,77,79). Finally, MTBE appears to be slightly irritating to eyes and mucous membranes (72–74).

In rats and mice, MTBE is rapidly and completely absorbed by inhalation and ingestion, whereas absorption following dermal exposure is limited (80). The main metabolites deriving in equimolar amounts from the oxidative demethylation of MTBE are TBA and formaldehyde (55,81–83). TBA is oxidized to 2-methyl- 1,2-propanediol and α-hydroxyisobutyric acid (55,74,80,82). Brady et al. (81) indicated a selective increase in hepatic microsomal oxidase activity (P450) in rats treated with MTBE, showing that MTBE may stimulate its own metabolism. After inhalation exposure in rats, MTBE is rapidly exhaled (20–70% depending on dose); the remainder is eliminated through urine (55,80).

MTBE has not been found to induce adverse effects on fetal development in rabbits, rats, or mice (84–87). Furthermore, adverse effects on reproduction have not been observed in one- and two-generation studies in rats (88,89).

After high MTBE exposure, female mice showed increased incidence of hepatocellular adenoma and male rats showed increased incidence of renal tubular cell tumors and interstitial-cell testicular tumors (78). A nongenotoxic mechanism is supported by the substantial lack of *in vitro* and *in vivo* evidence of mutagenicity and other genotoxic endpoints in both mammalian and bacterial systems (90–95). It could be maintained that an MTBE carcinogenic effect can result from cellular injury, which is induced only by high doses (78).

In particular, the species- (mice) and sex- (female) specific MTBE hepatocellular adenoma at high doses suggests an involvement of antiestrogenic-like effects ascribable to MTBE. The antiestrogenicity is often linked to hepatic tumor promoting activity as described for UG and for several other chemicals (33). Evidence of an antiestrogenic effect was recently confirmed by Moser et al. (96,97). The question of how MTBE elicits these antiestrogenic effects remains unanswered. Experiments under way at the Chemical Industry Institute of Toxicology (CIIT) are showing that MTBE does not produce its antiestrogenic effects through interaction with the estrogen receptor (S. Borghoff, unpublished data).

In contrast with what has been previously suggested (98), a lack of involvement of formaldehyde (metabolic product of MTBE) in the onset of mouse liver tumors has recently been reported (99). In conclusion, nongenotoxic hormonally related mechanisms appear to be the most plausible explanation for the development of these tumors, as suggested by the National Research Council (100). In any case, such a manifestation in a single animal species (mouse) relating exclusively to the female sex, renders any extrapolation to humans questionable to say the least.

Kidney tumors in male rats are associated with concurrent nephrotoxicity characterized by increased concentrations of rat-specific α2u-globulin in renal tubules (77,78,101–103). A 1997 *in vitro* study (104) demonstrated that the binding of MTBE to this protein contributes to the uptake and accumulation of MTBE in male rat kidney *in vivo* (105).

Knowing the role of α2u-globulin in the renal toxicity of MTBE is useful in assessing human risk because the protein involved is present only in male rats and not in humans (28–31,106). Due to the above considerations, these kidney tumors cannot be used as weight of evidence in the assessment of human cancer risk. Finally, the increase in interstitial-cell testicular tumors in rats does not appear to be significant because an increase in testicular tumors is a common occurrence in aging rats of this strain (78,107,108).

A 1995 study (109) reported an increase in lympho-hematopoietic cancers in rats treated with high doses of MTBE dissolved in olive oil by oral gavage. This study is fraught with uncertainty because it employs only two doses, both high, of MTBE and was carried out in highly inbred rats having a significant incidence of spontaneous tumors of hemolymphoreticular tissue; furthermore, oral administration is subject to a hepatic first pass, and forced-feeding itself can induce a toxicological response. These considerations are shared by Mennear (110) who, furthermore, in accordance with an opinion issued by the National Toxicology Program working committee in 1986, contested the scientific validity of combining lymphomas and leukemias for statistical purposes.

Also, a study on oral toxicity of MTBE has less value for estimating cancer risk to humans than an inhalation study when normal human exposure is by inhalation; furthermore, a single high concentrated oral dose is vastly different to any possible human exposure. It is therefore impossible to evaluate this study or accept its statement that "... MTBE must be considered an animal carcinogen" (109).

Finally, tumor findings in rats and mice are not relevant to humans and support the conclusion that exposure to MTBE does not pose an added cancer risk for the population in respect to whole gasoline, considering the current levels maintained in MTBE-oxygenated gasoline and the MTBE exposure levels in marketing and distribution workers, as well as in the general population (111–115).

The EPA, on the basis of limited animal evidence, has not provided a final carcinogenicity classification for MTBE, but tentatively suggested that MTBE be classified as a possible human carcinogen (Group C) (116).

Human and epidemiological studies. To date, information regarding MTBE effects on human health is limited. Some data (117–119) ensuing from clinical use (MTBE infusion for gallstone treatment) are irrelevant to the evaluation of MTBE toxicity when it is used as an additive to gasoline (55). In humans, the principal route of absorption remains inhalation (55,120); skin application shows little absorption (121). MTBE uptake and distribution in male volunteers has been reported (122). *In vitro* metabolism of MTBE in human liver has recently been studied by Hong et al. (123).

When MTBE-oxygenated fuels were introduced in the winter of 1992 in Fairbanks and Anchorage, Alaska (4 years later than in other states in the United States), acute health complaints were reported. These complaints were characterized by three types of nonspecific symptoms at varying levels in the respiratory tract and eyes (i.e., burning of the nose, throat, and eyes, cough), the gastrointestinal tract (nausea), and the CNS (headache, dizziness, feelings of disorientation).

While preliminary studies by public health officials seemed to indicate a positive association between these symptoms and acute exposure to MTBE-oxygenated gasoline (124,125), further data, either from studies in exposed workers (126–132) or from human exposure under controlled experimental conditions (133–136), did not substantiate these results. In Alaska, research using a wide-range questionnaire showed no exposure–response relationship (126), emergency room visits for headache did not increase (129), and insurance claim statistics for respiratory complaints revealed no significant difference to pre-MTBE-oxygenated fuel periods (131). Other studies in Stamford, Connecticut, and Albany, New York, did not show any association between symptoms and exposure (127,128). Results in favor of MTBE were also obtained in a study performed in 1994 in garage workers in New Jersey (130). A recent Finnish study (132) showed no statistically significant differences in neuropsychological symptoms

that occurred between chronically exposed tanker drivers and milk delivery drivers.

Finally, the results of experimental studies in humans in controlled MTBE exposure chambers showed no effects on health (133–136).

Several hypotheses have been formulated to explain these findings, which are in contrast with previously mentioned health complaints. The first is that certain individuals, abnormally sensitive to chemicals, may be particularly sensitive to low concentrations of MTBE. This was studied but not confirmed by Fiedler et al. (137). Another hypothesis infers an effect brought about by media exposure regarding antipathy toward the oxyfuels program, a form of suggestion that causes people to attribute symptoms to MTBE exposure. A third hypothesis blames the distinctive and unpleasant odor of MTBE for being a trigger for stress-related symptoms and for increasing existing symptom awareness.

MTBE determination methods in gasoline vapors and on MTBE degradation in soil systems have also been reported (138–140).

Tertiary butyl alcohol. Animal toxicity studies with TBA indicated the urinary tract is the target organ in rodents, with males being more sensitive than females (141). Takahashi et al. (142) confirmed that TBA, similar to MTBE, induces nephropathy in Fischer 344 male rats by increasing renal accumulation of hyaline protein, which is consistent with α2u-globulin. Increased incidence of renal tubular adenomas or carcinomas in male F344 rats with lifetime exposure to TBA via drinking water has been reported (143,144). In female mice, oral administration of TBA induced a statistically significant increase in thyroid adenomas (143,144). TBA does not show mutagenic activity (90,91,116,145).

In humans, irritation of eyes, nose, and skin have been reported after short-term exposure; defatting of the skin and dermatitis have been recorded after long-term exposure (146).

Tertiary amyl methyl ether. TAME received serious consideration as an oxygenate as early as 1991 (147). Although the octane content is slightly lower than in other ethers, it compares favorably for vapor pressure, boiling point, energy density, and water mixability.

TAME causes a significant but transient CNS depression akin to, but slightly more severe than, that resulting from MTBE exposure at the same levels (147,148).

In a short-term study in rats, oral treatment with TAME induced minimal changes in clinical chemistry and hematology findings and a reduction of food consumption

and animal body weights in high dose groups (149).

Studies with TAME did not demonstrate any evidence of genotoxicity in an Ames assay or in mouse micronucleus assay (147,149); a preliminary report submitted by Chevron (R.D. Cavalli, unpublished data) to the Toxic Substances Control Act section 8(e) coordinator refers to an increased incidence of cleft palate in some of the pups after exposure of pregnant mice to high concentrations, while no effects were noted in rats. The same report refers to a positive TAME concentration-related response in an *in vitro* study of chromosome effects in Chinese hamster ovary (CHO) cells after metabolic activation.

The kinetics and mechanisms of atmospheric removal of TAME have been well described in a 1994 report (150).

Ethyl tertiary butyl ether. ETBE can be used as a gasoline antiknock additive, but its use is limited due to the high cost of ethyl alcohol. In a CASE (Computer-Automated Structure Evaluation) study where the ETBE structure was compared with the structures of recognized determinants of carcinogenicity in rodents, ETBE was predicted to be neither a genotoxicant nor a carcinogen (93).

Other Additives

Ethylene dibromide (EDB) and ethylene dichloride (EDC). Leaded gasoline scavengers (EDB and EDC) are required to remove lead from engines. These compounds provide halogen atoms that react with lead to form the volatile products which escape through the exhaust. EDB and EDC are irritating to skin and eyes and are metabolized by an oxidative pathway (cytochrome P450) followed by conjugation (glutathione S-transferase) (151,152). Their metabolites play an important role in exerting toxicity (151–154).

In 1987, IARC classified EDB as probably carcinogenic to humans (Group 2A) (155) and EDC as possibly carcinogenic to humans (Group 2B) (156).

Methylcyclopentadienyl manganese tricarbonyl (MMT) is an effective octane enhancer used in Canada since 1976 (157); it was recently approved for use in the United States as a gasoline additive (158), but is not currently in use in Europe. According to Lynam et al. (159), due to MMT's low vapor pressure and short half-life in sunlight, it is unlikely that significant concentrations of MMT occur in the environment from its use as a gasoline additive.

The combustion of MMT in gasoline may be a source of environmental contamination and manganese exposure [it has been reported that over 99.9% of Mn from MMT is converted into inorganic oxides of

Mn during fuel combustion (159)]. The effects of Mn on lungs and on the nervous system are common knowledge. In some occupational studies, a relationship has been indicated between high inhalation exposure to Mn, neurological signs, and neurodegenerative disorders (160–165).

Information is scarce on potential health risk derived from MMT as a gasoline additive (157,166). In a Canadian study (166), it was reported that MMT use in gasoline is a potentially important source of Mn for the occupationally exposed population, even if recorded Mn values remain well below established limits for occupational and environmental airborne exposure. This was also reported by Frumkin and Solomon (158). Sierra et al. (167) obtained data on Mn environmental exposure in 35 garage mechanics and suggested that less than 10% of Mn exposure was due to MMT.

According to Frumkin and Solomon (158), the critical question is whether the additional population exposure resulting from widespread use of MMT converted to Mn could lead to toxic effects.

The disposition and toxicity of MMT in the brains of 12-month-old MMT-treated mice was reported in 1994 (168).

Benzene

Benzene is an aromatic organic hydrocarbon present in leaded gasoline, and it is sometimes added as a blending agent to UG to improve antiknock characteristics. European Union requirements state that the benzene added to leaded and unleaded gasolines must not exceed 5%; however, in some European countries, as in the United States, fuels are currently available with an even lower benzene content (1%).

The toxic effects of benzene, some of which also pertain to other aromatic hydrocarbons, are well known (169,170). Hematopoietic toxicity is the major effect and is unique to benzene.

Chronic occupational exposure to benzene (with inhalation as the main route of absorption) causes bone marrow injury and hematopoietic toxicity, including leukopenia, lymphocytopenia, aplastic anaemia and leukemia (acute myelogenous leukemia). Further epidemiological reports on leukemia have appeared in recent literature (171–173).

Unlike leukopenia and lymphocytopenia (174,175), benzene-induced leukemia has only been observed in humans: no satisfactory animal model exists that can consistently reproduce the human disease (176).

The mechanism of the leukemogenic effect of benzene is not fully understood. The modified base 8-hydroxy-deoxyguanosine has been suggested as a sensitive marker

of DNA damage due to hydroxyl radical attack at the C8 position of guanine (*177*). Biochemical mechanisms of leukemia have been reviewed and discussed by Snyder and Kalf (*178*). In 1987, IARC classified benzene as a human carcinogen (*179*).

Biotransformation in liver is thought to be necessary for its hematoxicity and carcinogenicity, and differences in species sensitivity have been ascribed to hepatic metabolism (*180,181*). Benzene biotransformation is complex, yielding glucuronide and sulfate conjugates of phenol, quinol, and catechol; L-Phenylmercapturic acid; muconaldehyde; and *trans-,trans*-muconic acid by ring scission. Furthermore, inhalation of benzene may stimulate microsomal mixed-function oxidase, cytochrome P450, responsible for the oxidation of benzene and for the generation of oxygen radicals (*182*). Formation of oxygen radicals could be a major cause of benzene toxicity, with involvement of multiple mechanisms including synergism between arylating and glutathione-depleting reactive metabolites and oxygen radicals (*183*). Because benzene and its hydroxylated metabolites are substrates for the same cytochrome P450 enzymes, competitive interactions among metabolites are possible (*184*).

Metabolic interactions between benzene and ethanol (*185*) and between benzene and gasoline (*186*) vapors have been reported.

A critical question is whether the low concentrations of benzene that occur in the environment derived from its use as a gasoline component could pose a significant human health risk (*187*). In this regard, Weisel et al. (*188*) state that the amount of metabolism by ring-opening pathway is greater at low exposure in humans than at high exposure, and maintain that care is needed when extrapolating potential health risk from high to low dose.

In a Swedish study, the increased risk of acute myeloid leukemia in gasoline station attendants was associated with the benzene content in gasoline (*15*). In their 1996 study, Raabe and Wong (*189*) combined studies in cohorts of petroleum workers in the United States and the United Kingdom in a single database for cell type-specific leukemia analysis; they did not find an increase in acute and chronic myeloid leukemia or in acute lymphocytic or chronic lymphocytic leukemia. There was also no excess risk of leukemia or acute myeloid leukemia reported in an Italian study (*190*) or in a Nordic study (*9*), both carried out in service station attendants.

Furthermore, an analysis of the published case–control studies conducted in 1996 by Bezabeh et al. (*191*) indicated that exposure to petroleum products and employment in petroleum-related occupations does not represent a risk factor for multiple myeloma. Wong and Raabe (*192*) recently published a study in a multinational cohort of more than 250,000 petroleum workers; the pooled analysis indicates no increased risk of multiple myeloma as a result of exposure to benzene.

A genotoxic effect at relatively low levels of benzene exposure (0.1 ppm) has been reported in a recent study in humans (*193*). Various papers reporting benzene blood levels in groups occupationally exposed to gasoline indicate that occupational activities are significant determinants of blood benzene concentrations (*194–197*). A global evaluation of risks from benzene exposure is reported by Paustenbach et al. (*198*) and Hughes et al. (*199*).

Alkylbenzenes: Toluene and Xylene

Alkylbenzenes are single ring aromatic compounds containing one (toluene) or more (xylene) saturated aliphatic side chains.

Toluene and xylene, occurring in small amounts in gasoline blends and standard gasoline formulations as a result of the octane process, are mainly absorbed by inhalation (acute irritation of eyes and respiratory tract) and through the skin. Direct skin contact promotes defatting of the keratin layer, with vasodilation, erythema, and dry, scaly dermatitis. Xylenes are more potent skin irritants than benzene or toluene (*55*).

Other than liver, kidney, and heart damage, dysfunction in the CNS is the principal health consequence of exposure to alkylbenzenes. The effects vary from severe neurological disorder (acute inhalation due to sniffing abuse) to deficits in neurobehavioural function in occupationally exposed groups.

Neurobehavioral effects deriving from subacute exposure to toluene have been investigated in rats (*200*) and mice (*201*). In a rat model for Parkinson's disease, Cintra et al. (*202*) observed that toluene challenged the dopaminergic nigrostriatal system. Persistent damage to CNS functions resulting from rat subchronic exposure to *m*-xylene has also been reported (*203*).

Pryor et al. (*204*) observed that chronic exposure to toluene produced an irreversible progressive time- and dose-dependent hearing loss. While this auditory impairment was recorded in laboratory animals at high toluene exposures as compared to permissible exposure levels (*205*), Liu and Fechter (*206*) demonstrated that the toxic effect in cochlear cells can be observed *in vitro* at toluene concentrations that are more realistic for human occupational exposure. Finally, effects on the thyroid gland (mild reduction of follicle size) have been reported after toluene inhalation in female rats (*207*).

Recent papers on embryotoxic potential indicate that toluene (at much higher levels than those in the natural environment) induce some fetotoxic, but not teratogenic, effects (*208–210*), while xylenes appeared to be embryotoxic/fetotoxic and teratogenic, causing an increase in preimplantation losses, skeletal anomalies, reduced fetal body weight, and delayed development (*211,212*). Wilkins (*213*) presented a 1997 update on toluene teratogenicity.

Because of the wide industrial use of these alkylbenzenes, studies continue to describe the effects of these compounds in occupationally exposed groups (*214–217*). Due to the scarce information available, the long-term effects on human health from the use of alkybenzenes as additives in gasoline remain uncertain (*19,218*).

Greenberg (*219*) pointed out that because subgroups that are sensitive to neurobehavioral effects of toluene exist, adequate measures of protection for the general population are required [even if atmospheric levels of toluene in urban environments are about 10 times lower that the inhalation reference concentration (RfC) fixed at 0.1 ppm for general populations chronically exposed to toluene]. Lagorio et al. (*194*), Hakkola and Saarinen (*196*), and Lawryk et al. (*220*) presented evaluations of levels in various exposure scenarios.

The principal metabolites of alkylbenzenes appear to have a low order of toxicity and are readily excreted. Thus, toluene is oxidized at the level of the methyl group to benzoic acid, which is conjugated with glycine to form hippuric acid and then excreted. Hippuric acids are also metabolites of xylene. Tardif et al. (*221*) suggested that there is a metabolic interaction between toluene and xylene that affects the metabolic disposition of both chemicals. An exhaustive picture of toluene and xylene effects in plants and acquatic animals has been reported by Nielsen and Howe (*208*) and Crookes et al. (*211*).

In 1989, IARC reviewed the database for toluene (*222*) and xylene (*223*) and concluded that there was inadequate evidence for carcinogenicity of both compounds in humans and in experimental animals; thus, toluene and xylene were not classifiable as to their carcinogenicity in humans (Group 3). In a 1990 study, no evidence of carcinogenic activity was found in male or female F344 rats and B6C3F$_1$ mice exposed to toluene by inhalation (*224*).

Final Considerations

Toxicological data obtained in laboratory animals (including carcinogenic, teratogenic, and mutagenic activities) and epidemiological results from human studies in relation to

gasoline exposure (published during the last 7 years) provide a broad picture of the current aspects of the essential toxicological properties of gasoline.

Knowledge of the intrinsic toxic properties of gasoline and its constituents is undoubtedly important, but to identify the potential toxicity, i.e., the damage (including carcinogenic effects) that can occur in man and his environment under normal conditions of use, is even more important.

Concerning gasoline carcinogenicity, any potential cancer risk in humans from gasoline cannot yet be identified with precision for several reasons:

• The diverse and different constituents of gasolines (leaded, unleaded, oxygenated, reformulated gasolines)
• The inconclusive evidence of carcinogenic risk in animals from some constituents
• The carcinogenic effect ascribed to some constituents detected in experimental animals but ascribable to mechanisms (e.g., α2u-globulin) that are not present in humans
• The insufficient data for determination of long-term effects in occupationally exposed cohorts
• The inadequate information on general population exposure.

Despite this, it should be noted that many individual investigators (*109, 225–229*) who report results of carcinogenicity studies in experimental animals (often with insignificant or only borderline incidence of carcinogenic events) often suggest direct extrapolation of such results to humans. This abnormal situation is further aggravated by interpretative manipulation of valid study data by nonexperts or by scientific dabblers, and by diffusion through newspapers and other mass-media messages of real and presumed hazards deriving from gasolines. Lotti (*230*), referring to any toxicological study, indicated that the simple modification of a form of expression by using "a variety of figures of speech, lexical forms and rhetorical emphasis" can send completely different messages.

In reference to the carcinogenic potential of a chemical, the assumption that what is carcinogenic in animals is also carcinogenic in humans is "biologically plausible and prudent," according to IARC (*231*), and there are many scientists who agree. No single investigator or expert of mass-media communication can claim carcinogenicity and/or toxicity for a chemical. Only a responsible health regulatory agency (such as IARC, the EPA, etc.) can adequately express judgment on the toxicity and carcinogenicity of any chemical (including gasoline) in laboratory animals after reviewing and assessing all available data, discarding irrele-

vant and confounding data, and utilizing up-to-date studies in toxicokinetics, metabolism, and receptor binding. Indeed, every chemical entity represents a unique case due to its structure, toxicological properties, and circumstances of use (*232*).

This overview provides a reference source, covering the period *1990–1997*, for the toxicological aspects of gasoline and its constituents. By reviewing and summarizing the concordant and conflicting results of such studies, we intended to highlight the considerable difficulties that exist for any precise identification of potential toxic effects on health, meaning the risk for humans, especially in relation to the need for a correct and adequate handling of other variables such as preexisting pathological conditions, cigarette smoking, drug use, etc. Furthermore, wide margins of uncertainty in risk assessment from gasoline exposure also derive from the variable characteristics of the different gasoline mixtures, as well as from incomplete results or incorrect scientific approach and/or performance of some toxicological studies.

Thus, the problem regarding the potential toxicity of gasoline is still open, even though it is clear that modern unleaded gasolines present less risk to human health due to the lower quantities of benzene and lead. With further changes in the formulation of gasoline, manufacturing processes, and methods of distribution, the future promises even lower levels of risk to health and the environment.

The evaluation of potential health effects of gasoline represents a very complex process, with wide margins of uncertainty. On the other hand, uncertainty is a characteristic of any scientific conclusion, while certainties are frequently, perhaps justifiably, requested by regulatory authorities in order to make better decisions and correct political choices. Moreover: "The demand for [an absolute] certainty is a sign of weakness, and by persisting, induces paralysis" [Mark Rutherford (*233*)].

REFERENCES

1. Wixtrom RN, Brown SL. Individual and population exposures to gasoline. J Expo Anal Environ Epidemiol 2:23–78 (1992).
2. Akland GG. Exposure of the general population to gasoline. Environ Health Perspect 101(suppl 6):27–32 (1993).
3. Dutch Expert Committee for Occupational Standards. Health Based Recommended Occupational Exposure Limit for Gasoline. RA 3/92. Den Haag, Netherlands: Directorate General of Labour, 1992.
4. Partanen T, Heikkila P, Hernberg S, Kauppinen T, Moneta G, Ojajarvi A. Renal cell cancer and occupational exposure to chemical agents. Scand J Work Environ Health 17:231–239 (1991).
5. Enterline PE. Review of new evidence regarding the relationship of gasoline exposure to kidney cancer and leukemia. Environ Health Perspect 101(suppl 6):101–103 (1993).
6. Schnatter AR, Katz AM, Nicolich MJ, Thériault G. A retrospective mortality study among Canadian petroleum marketing and distribution workers. Environ Health Perspect 101(suppl 6):85–99 (1993).
7. Rushton L. A 39-year follow-up of the UK oil refinery and distribution center study: results for kidney cancer and leukemia. Environ Health Perspect 101(suppl 6):77–84 (1993).
8. Mellemgaard A, Engholm G, McLaughlin JK, Olsen JH. Occupational risk factors for renal-cell carcinoma in Denmark. Scand J Work Environ Health 20:160–165 (1994).
9. Lynge E, Andersen A, Nilsson R, Barlow L, Pukkala E, Nordlinder R, Boffetta P, Grandjean P, Heikkila P, Horte LG. Risk of cancer and exposure to gasoline vapors. Am J Epidemiol 145:449–458 (1997).
10. Infante PF. State of the science on the carcinogenicity of gasoline with particular reference to cohort mortality study results. Environ Health Perspect101(suppl 6):105–109 (1993).
11. Poole C, Dreyer NA, Satterfield MH, Levin L, Rothman KJ. Kidney cancer and hydrocarbon exposures among petroleum refinery workers. Environ Health Perspect101(suppl 6):53–62 (1993).
12. Wong O, Harris F, Smith TJ. Health effects of gasoline exposure. II. Mortality patterns of distribution workers in the United States. Environ Health Perspect 101(suppl 6):63–76 (1993).
13. McLaughlin JK. Renal cell cancer and exposure to gasoline: a review. Environ Health Perspect 101(suppl 6):111–114 (1993).
14. Lindquist R, Nilsson B, Eklund G, Gahrton G. Acute leukemia in professional drivers exposed to gasoline and diesel. Eur J Haematol 47:98–103 (1991).
15. Jakobsson R, Ahlbom A, Bellander T, Lundberg I. Acute myeloid leukemia among petrol station attendants. Arch Environ Health 48:255–259 (1993).
16. Collingwood KW, Raabe GK, Wong O. An updated cohort mortality study of workers at a northeastern United States petroleum refinery. Int Arch Occup Environ Health 68:277–288 (1996).
17. IARC. Gasoline. In: IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol 45: Occupational Exposure in Petroleum Refining; Crude Oil and Major Petroleum Fuels. Lyon:International Agency for Research on Cancer, 1989;159–201.
18. Raza H, Qureshi MM, Montague W. Alteration of glutathione, glutathione S-transferase and lipid peroxidation in mouse skin and extracutaneous tissues after topical application of gasoline. Int J Biochem Cell Biol 27:271–277 (1995).
19. Burbacher TM. Neurotoxic effects of gasoline and gasoline constituents. Environ Health Perspect 101(suppl 6):133–141 (1993).
20. Loury DJ, Smith-Oliver T, Butterworth BE. Assessment of unscheduled and replicative DNA synthesis in rat kidney cells exposed in vitro or in vivo to unleaded gasoline. Toxicol Appl Pharmacol 87:127–140 (1987).
21. API. Results of Toxicological Studies Conducted for the American Petroleum Institute Health and Environmental Sciences Department. API Publication No. 45592. Washington, DC:American Petroleum Institute, 1995.
22. Vyskocil A, Cizkova M. Nephrotoxic effects of unleaded petrol in female rats. J Appl Toxicol 16:55–56 (1996).
23. Raabe GK. Review of the carcinogenic potential of gasoline. Environ Health Perspect 101(suppl 6):35–38 (1993).
24. Borghoff SJ, Youtsey NL, Swenberg JA. A comparison of European high test gasoline and PS-6 unleaded gasoline in their abilities to induce α_{2u}-globulin nephropathy and renal cell proliferation. Toxicol Lett 63:21–33 (1992).
25. Borghoff SJ, Short BG, Swenberg JA. Biochemical mechanism and pathobiology of α_{2u}-globulin nephropathy. Annu Rev Pharmacol Toxicol 30:349–367 (1990).
26. Melnick RL. An alternative hypothesis on the role of chemically induced protein droplet (α2u-globulin) nephropathy in renal carcinogenesis. Regul Toxicol Pharmacol 16:111–125 (1992).

27. Rodgers IS, Baetcke KP. Interpretation of male rat renal tubule tumors. Environ Health Perspect 101(suppl 6):45–52 (1993).

28. Mitsumoki K, Elwell MR. Proliferative lesions in the male reproductive system of F344 rats and B6C3F1 mice: incidence and classification. Environ Health Perspect 77:11–21 (1988).

29. Lehman-McKeeman LD, Caudill D. Alpha 2u-globulin is the only member of the lipocalin protein superfamily that binds to hyaline droplet inducing agents. Toxicol Appl Pharmacol 116:170–176 (1992).

30. Swenberg JA. α_{2u}-Globulin nephropathy: review of the cellular and molecular mechanisms involved and their implications for human risk assessment. Environ Health Perspect 101(suppl 6):39–44 (1993).

31. U.S. EPA. α2u-Globulin: Association with Chemically Induced Renal Toxicity and Neoplasia in the Male Rat. Risk Assessment Forum. EPA 625/3-91/019F. Washington, DC:U.S.Environmental Protection Agency, 1991.

32. Standeven AM, Wolf DC, Goldsworthy TL. Interactive effects of unleaded gasoline and estrogen on liver tumor promotion in female B6C3F1 mice. Cancer Res 54:1198–1204 (1994).

33. Standeven AM, Wolf DC, Goldsworthy TL. Investigation of antiestrogenicity as a mechanism of female mouse liver tumor induction by unleaded gasoline. CIIT Activities 14:1–6 (1994).

34. Standeven AM, Blazer DG III, Goldsworthy TL. Investigation of antiestrogenic properties of unleaded gasoline in female mice. Toxicol Appl Pharmacol 127:233–240 (1994).

35. Tilbury L, Butterworth BE, Moss O, Goldsworthy TL. Hepatocyte cell proliferation in mice after inhalation exposure to unleaded gasoline vapor. J Toxicol Environ Health 38:293–307 (1993).

36. Standeven AM, Goldsworthy TL. Promotion of preneoplastic lesions and induction of CYP2B by unleaded gasoline vapor in female B6C3F1 mouse liver. Carcinogenesis 14:2137–2141 (1993).

37. Standeven AM, Goldsworthy TL. Identification of hepatic mitogenic and cytochrome P-450-inducing fractions of unleaded gasoline in B6C3F1 mice. J Toxicol Environ Health 43:213–224 (1994).

38. Seeber A, Kiesswetter E, Neidhart B, Blaszkewicz M. Neurobehavioral effects of a long-term exposure to tetraalkyllead. Neurotoxicol Teratol 12:653–655 (1990).

39. Booze RM, Mactutus CF. Developmental exposure to organic lead causes permanent hippocampal damage in Fischer-344 rats. Experientia 46:292–297 (1990).

40. Audesirk T, Shugarts D, Cabell-Kluch L, Wardle K. The effects of triethyl lead on the development of hippocampal neurons in culture. Cell Biol Toxicol 11:1–10 (1995).

41. Needleman HL, Schell A, Bellinger D, Leviton A, Allred EN. Long-term effects of childhood exposure to lead at low dose; an eleven-year follow-up report. New Engl J Med 322:83–88 (1990).

42. National Research Council. Measuring lead exposure in infants, children and other sensitive populations. Washington, DC:National Academy Press, 1993.

43. Goyer RA. Results of lead research: prenatal exposure and neurological consequences. Environ Health Perspect 104:1050–1054 (1996).

44. Kawada T, Tri-Tugaswati A, Yasuo K, Suzuki S. Relationships between mean lead levels in the atmosphere and in blood from data published since 1977. Asian Pac J Public Health 7:233–235 (1994).

45. Pirkle JL, Brody DJ, Gunter EW, Kramer RA, Paschal DC, Flegal KM, Matte TD. The decline in blood lead levels in the United States. JAMA 272:284–291 (1994).

46. Wietlisbach V, Rickenbach M, Berode M, Guillemin M. Time trend and determinants of blood lead levels in a Swiss population over a transition period (1984–1993) from leaded to unleaded gasoline use. Environ Res 68:82–90 (1995).

47. Bono R, Pignata C, Scursatone E, Rovere R, Natale P, Gilli G. Updating about reductions of air and blood lead concentrations in Turin, Italy, following reductions in the lead content of gasoline. Environ Res 70:30–34 (1995).

48. Schuhmacher M, Belles M, Rico A, Domingo BL, Corbella J. Impact of reduction of lead in gasoline on the blood and hair lead levels in the population of Tarragona Province, Spain, 1990–1995. Sci Total Environ 184:203–209 (1996).

49. Goyer RA. Lead toxicity: current concerns. Environ Health Perspect 100:177–187 (1993).

50. Blood lead levels—United States, 1988–1991. MMWR Morb Mortal Wkly Rep 43:545–548 (1994).

51. Silbergeld EK. Lead poisoning: the implications of current biomedical knowledge for public policy. Md Med J 45:209–217 (1996).

52. Chang LW. The neurotoxicology and pathology of organomercury, organolead, and organotin. J Toxicol Sci 15:S125–S151 (1990).

53. Schuetzle D, Siegl WO, Jensen TE, Dearth MA, Kaiser EW, Gorse R, Kreucher W, Kulik E. The relationship between gasoline composition and vehicle hydrocarbon emissions: a review of current studies and future research needs. Environ Health Perspect 102(suppl 4):3–12 (1994).

54. Born GL, Lucas SV, Scott RD, DeFries TH, Kishan S. Effect of use of low oxygenate gasoline blends upon emissions from California vehicles. Govt Reports Announcements & Index (GRA&I), Issue 23, 1994.

55. Reese E, Kimbrough RD. Acute toxicity of gasoline and some additives. Environ Health Perspect 101(suppl 6):115–131 (1993).

56. Garner CD, Lee EW, Louis-Ferdinand RT. Muller cell involvement in methanol-induced retinal toxicity. Toxicol Appl Pharmacol 130:101–107 (1995).

57. Garner CD, Lee EW, Terzo TS, Louis-Ferdinand RT. Role of retinal metabolism in methanol-induced retinal toxicity. Toxicol Environ Health 44:43–56 (1995).

58. Methanol toxicity. Agency for toxic substances and disease registry. Am Fam Physician 47:163–171 (1993).

59. Rogers JM, Mole ML, Chernoff N, Barbee BD, Turner CI, Logsdon TR, Kavlock RJ. The developmental toxicity of inhaled methanol in the CD-1 mouse, with quantitative dose–response modeling for estimation of benchmark doses. Teratology 47:175–188 (1993).

60. Cummings AM. Evaluation of the effects of methanol during early pregnancy in the rat. Toxicology 79:205–214 (1993).

61. Andrews JE, Ebron-McCoy M, Logsdon TR, Mole LM, Kavlock RJ, Rogers JM. Developmental toxicity of methanol in whole embryo culture: a comparative study with mouse and rat embryos. Toxicology 81:205–215 (1993).

62. Abbott BD, Logsdon TR, Wilke TS. Effects of methanol on embryonic mouse palate in serum-free organ culture. Teratology 49:122–134 (1994).

63. Lee E, Brady AN, Brabec MJ, Fabel T. Effects of methanol vapors on testosterone production and testis morphology in rats. Toxicol Ind Health 7:261–275 (1991).

64. Poon R, Chu I, Bjarnason S, Vincent R, Potvin M, Miller RB, Valli VE. Short-term inhalation toxicity of methanol, gasoline, and methanol/gasoline in the rat. Toxicol Ind Health 11:343–361 (1995).

65. Stern S, Reuhl K, Soderholm S, Cox C, Sharma A, Balys M, Gelein R, Yin C, Weiss B. Perinatal methanol exposure in the rat. I. Blood methanol concentration and neural cell adhesion molecules. Fundam Appl Toxicol 34:36–46 (1996).

66. Costantini MG. Health effects of oxygenated fuels. Environ Health Perspect 101(suppl 6):151–160 (1993).

67. Lee EW, Terzo TS, D'Arcy JB, Gross KB, Schreck RM. Lack of blood formate accumulation in humans following exposure to methanol vapor at the current permissible exposure limit of 200 ppm. Am Ind Hyg Assoc J 53:99–104 (1992).

68. D'Alessandro A, Osterloh JD, Chuwers P, Quinlan PJ, Kelly TJ, Becker CE. Formate in serum and urine after controlled methanol exposure at the threshold limit value. Environ Health Perspect 102:178–181 (1994).

69. Osterloh JD, D'Alessandro A, Chuwers P, Mogadeddi H, Kelly TJ. Serum concentrations of methanol after inhalation at 200 ppm. J Occup Environ Med 38:571–576 (1996).

70. Cook MR, Bergman FJ, Cohen HD, Gerkovich MM, Graham C, Harris RK, Siemann LG. Effects of methanol vapor on human neurobehavioral measures. Res Rep Health Eff Inst 42:1–45 (1991).

71. Taylor RT. Methanol Toxicity in Mice/Primate Cells. Fedrip Database. Springfield, VA: National Technical Information Service, 1995.

72. Duffy JS, Del Pup JA, Kneiss JJ. Toxicological evaluation of methyl tertiary butyl ether (MTBE): testing performed under TSCA consent agreement. J Soil Contam 1:29–37 (1992).

73. von Burg R. Toxicology update. J Appl Toxicol 12:73–74 (1992).

74. Nordic Chemicals Group, Sderlund E, Elvestad K. Health effects of selected chemicals 2. Methyl tertiary butyl ether. Nord 29:137–164 (1993).

75. Daughtrey WC, Gill MW, Pritts IM, Douglas JF, Kneiss JJ, Andrews LS. Neurotoxicological evaluation of methyl tertiary-butyl ether in rats. J Appl Toxicol 17:S57–64 (1997).

76. Savolainen H, Pfaffli P, Elovaara E. Biochemical effects of methyl tertiary butyl ether in extended vapor exposure of rats. Arch Toxicol 57:285–288 (1985).

77. Robinson M, Bruner RH, Olson GR. Fourteen and ninety day oral toxicity studies of methyl tertiary butyl ether in Sprague-Dawley rats. J Am Coll Toxicol 9:525–540 (1990).

78. Bird MG, Burleigh-Flayer HD, Chun JS, Douglas JF, Kneiss JJ, Andrews LS. Oncogenicity studies of inhaled methyl tertiary-butyl ether (MTBE) in CD-1 mice and F-344 rats. J Appl Toxicol 17:S45–55 (1997).

79. Lington AW, Dodd DE, Ridlon SA, Douglas JF, Kneiss JJ, Andrews LS. Evaluation of 13-week inhalation toxicity study on methyl t-butyl ether (MTBE) in Fisher 344 rats. J Appl Toxicol 17:S37–44 (1997).

80. Miller MJ, Ferdinandi ES, Klan M, Andrews LS, Douglas JF, Kneiss JJ. Pharmacokinetics and disposition of methyl t-butyl ether (MTBE) in Fischer-344 rats. J Appl Toxicol 17:S3–12 (1997).

81. Brady JF, Xiao F, Ning SM, Yang CS. Metabolism of methyl tertiary-butyl ether by rat hepatic microsomes. Arch Toxicol 64:157–160 (1990).

82. Hutcheon DE, Arnold JD, ten Hove W, Boyle J III. Disposition, metabolism, and toxicity of methyl tertiary butyl ether, an oxygenate for reformulated gasoline. J Toxicol Environ Health 47:453–464 (1996).

83. Li D, Zhu M, Yang XY, Cheng WB, Mo GQ, Wang XF. Pharmacokinetics of methyl tert-butyl ether (MTBE) in rats. Chin J Pharmacol Toxicol 5:287–290 (1991).

84. Conaway CC, Schoeder RE, Snyder NK. Teratology evaluation of methyl tertiary butyl ether in rats and mice. J Toxicol Environ Health 16:797–809 (1985).

85. Neeper-Bradley T, Tyl R, Fisher L, Tarasi D, Fait D, Dodd D. Developmental toxicity study in inhaled methyl tertiary butyl ether (MTBE) in New Zealand white rabbits and CD-1 mice (abstract). Toxicologist 10:41 (1990).

86. Sonawane B. Assessment of potential developmental toxicity risk of methyl tertiary butyl ether (MTBE) (abstract). Teratology 49:388 (1994).

87. Bevan C, Tyl RW, Neeper-Bradley TL, Fisher LC, Panson RD, Douglas JF, Andrews LS. Developmental toxicity evaluation of methyl tertiary-butyl ether (MTBE) by inhalation in mice and rabbits. J Appl Toxicol 17:S21–29 (1997).

88. Biles RW, Schroeder RE, Holdsworth CE. Methyl tertiary butyl ether inhalation in rats: a single generation reproduction study. Toxicol Ind Health 3:519–534 (1987).

89. Bevan C, Neeper-Bradley TL, Tyl RW, Fisher LC, Panson RD, Kneiss JJ, Andrews LS. Two-generation reproductive toxicity study of methyl tertiary-butyl ether (MTBE) in rats. J Appl Toxicol 17:S13–19 (1997).

90. Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K, Speck W. Salmonella mutagenicity tests: III. Results from the testing of 255 chemicals. Environ Mol Mutagen 9:1–110 (1987).

91. McGregor DB, Brown A, Cattanach P, Edwards I, McBride D, Caspary WJ. Responses of the L5178Y tk+tk⁻mouse lymphoma forward mutation assay: II. 18 Coded chemicals. Environ Mol Mutagen 11:91–118 (1988).

92. Galvin JB, Ridlon SA, Vergnes JS, Morabit ER. In vivo bone marrow cytogenetic assay of methyl tertiary butyl ether. Presented at the International Symposium on the Health Effects of Gasoline, 11–13 November 1991, Miami, FL.

93. Rosenkranz HS, Klopman G. Predictions of the lack of

genotoxicity and carcinogenicity in rodents of two gasoline additives: methyl and ethyl-*t*-butyl ethers. In Vitro Toxicol 4:49–54 (1991).

94. Cinelli S, Ciliutti P, Falezza A, Meli C, Caserta L, Marchetti S, Seeberg AH, Vericat JA. Absence of mutagenicity of methyl tertiary butyl ether. Toxicol Lett Suppl 1: 300 (1992).

95. McKee RH, Vergnes JS, Galvin JB, Douglas JF, Kneiss JJ, Andrews LS. Assessment of the *in vivo* mutagenic potential of methyl tertiary-butyl ether. J Appl Toxicol 17:S31–36 (1997).

96. Moser GJ, Wong BA, Moss OR, Goldsworthy TL. Unleaded gasoline and methyl tertiary butyl ether induce similar short term effects in mouse liver. Toxicologist 15:1235 (1995).

97. Moser GJ, Wong BA, Wolf DC, Moss OR, Goldsworthy TL. Comparative short-term effects of methyl tertiary butyl ether and unleaded gasoline vapor in female B6C3F1 mice. Fundam Appl Toxicol 31:173–183 (1996).

98. Mackerer CR, Angelosanto FA, Blackburn GR, Schreiner CA. Identification of formaldehyde as the metabolite responsible for the mutagenicity of methyl tertiary-butyl ether in the activated mouse lymphoma assay. Proc Soc Exp Biol Med 212:338–341 (1996).

99. Casanova M, Heck H.d'A. Lack of evidence for the involvement of formaldehyde in the hepatocarcinogenicity of methyl tertiary-butyl ether in CD-1 mice. Chem Biol Interact 105:131–143 (1997).

100. National Research Council. Toxicological and Performance Aspects of Oxygenated Motor Vehicle Fuels. Washington, DC: National Academic Press, 1996.

101. Borghoff SJ, Prescott-Matthews JS, Poet TS. The mechanism of male rat kidney tumors induced by methyl *tert*-butyl ether and its relevance in assessing human risk. CIIT Activities 16:1–8 (1996).

102. Chun JS, Kintigh WJ. Methyl Tertiary Butyl Ether: Twenty-eight Day Vapor Inhalation Study in Rats and Mice. BRRC Report 93N1241. Export, PA:Bushy Run Research Center, 1993.

103. Prescott-Mathews JS, Wolf DC, Wong BA, Borghoff SJ. Methyl *tert*-butyl ether causes alpha 2u-globulin nephropathy and enhanced renal cell proliferation in male Fischer-344 rats. Toxicol Appl Pharmacol 143:301–314 (1997).

104. Poet TS, Borghoff SJ. *In vitro* uptake of methyl *tert*-butyl ether in male rat kidney: use of a two-compartment model to describe protein interactions. Toxicol Appl Pharmacol 145:345–348 (1997).

105. Borghoff SJ, Murphy JE, Medinsky MA. Development of physiologically based pharmacokinetic model for methyl *tertiary*-butyl ether and *tertiary*-butanol in male Fisher-344 rats. Fundam Appl Toxicol 30:264–275 (1996).

106. Olson MJ, Johnson JT, Reidy CA. A comparison of male rat and human urinary proteins: implications for human resistance to hyaline droplet nephropathy. Toxicol Appl Pharmacol 102:524–536 (1990).

107. Turek FW, Desjardins C. Development of leyding cell tumors and onset of changes in the reproductive and endocrine systems of aging F344 rats. J Natl Cancer Inst 63:969–975 (1979).

108. Haseman JK, Arnold J. Tumor incidence in Fischer 344 rats: NTP historical data. In: Pathology of the Fisher Rat (Boorman GA, Eustis SL, Elwell MR, Montgomery CA Jr, MacKenzie WF, eds). San Diego CA:Academic Press, 1990;555–564.

109. Belpoggi F, Soffritti M, Maltoni C. Methyl tertiary butyl ether (MTBE)—a gasoline additive—causes testicular and lympho-haematopoietic cancers in rats. Toxicol Ind Health 11:119–149 (1995).

110. Mennear JH. MTBE: not carcinogenic [letter]. Environ Health Perspect 103:985–986 (1995).

111. Hartle R. Exposure to methyl *tert*-butyl ether and benzene among service station attendants and operators. Environ Health Perspect 101(suppl 6):23–26 (1993).

112. Almaguer D. Health Hazard Evaluation Report HETA 93-0884-2344, National Center for Environmental Health, Albany, New York. Govt Reports Announcements & Index (GRA&I), Issue 07, 1994.

113. McKee R, Melyneux M, Simpson BJ. The Health Risks Associated with Gasoline Containing MTBE. Brussels:Concawe, 1995.

114. White MC, Johnson CA, Ashley DL, Buchta TM, Pelletier DJ. Exposure to methyl tertiary-butyl ether from oxygenated gasoline in Stamford, Connecticut. Arch Environ Health 50:183–189 (1995).

115. Huber AH. Human exposure estimates of methyl tertiary butyl ether (MTBE). Govt Reports Announcements & Index (GRA&I), Issue 10, 1995.

116. U.S. EPA. Assessment of Potential Health Risks of Gasoline Oxygenated with Methyl Tertiary Butyl Ether (MTBE). EPA 600/R-93/206. Washington, DC:Environmental Protection Agency, 1993.

117. Neoptolemos JP, Hall C, O'Connor HJ, Murray WR, Carr-Locke DL. Methyl-tert-butyl-ether for treating bile duct stones: the British experience. Br J Surg 77:32–35 (1990).

118. Leuschner U, Hellstern A, Schmidt K, Fischer H, Guldutuna S, Hubner K, Leuschner M. Gallstone dissolution with methyl tert-butyl ether in 120 patients—efficacy and safety. Dig Dis Sci 36:193–199 (1991).

119. Van Sonnenberg E, Zakko S, Hofmann A, D'Agostino H, Jinich H, Hoyt D, Miyai K, Ramsby G, Moossa A. Human gallbladder morphology after gallstone dissolution with methyl tertbutyl ether. Gastroenterology 100:1718–1723 (1991).

120. Long G, Meek ME, Savard S. Methyl tertiary butyl ether: evaluation of risks to health from environmental exposure in Canada. Environ Carcinog Ecotox Rev C12:389–395 (1994).

121. Sivak A, Murphy J. A review of health effects data on the oxygenated fuel additive methyl tertiary butyl ether. In: Proceedings of International Alcohol Fuels Symposium, 12–15 November 1991, Florence, Italy. Milan:Ecofuel on behalf of International Organizing Committee, 1991;957–962.

122. Johanson G, Nihlen A, Lof A. Toxicokinetics and acute effects of MTBE and ETBE in male volunteers. Toxicol Lett 82:713–718 (1995).

123. Hong JY, Yang CS, Lee M, Wang YY, Huang WQ, Tan Y, Patten CJ, Bondoc FY. Role of cytochromes P450 in the metabolism of methyl tert-butyl ether in human livers. Arch Toxicol 71:266–269 (1997).

124. CDC. An Investigation of Exposure to Methyl Tertiary Butyl Ether in Fairbanks, Alaska. Atlanta, GA:Centers for Disease Control and Prevention, 1993.

125. Moolenaar RL, Hefflin BJ, Ashley DL, Middaugh JP, Etzel RA. Methyl tertiary butyl ether in human blood after exposure to oxygenated fuel in Fairbanks, Alaska. Arch Environ Health 49:402–409 (1994).

126. Beller M, Middaugh J. Potential illness due to exposure to oxygenated fuels, Fairbanks, Alaska. In: Proceedings of Conference on MTBE and Other Oxygenates: A Research Update, 26–28 July 1993, Falls Church, VA. Research Triangle Park, NC:U.S. Environmental Protection Agency, National Center for Environmental Assessment, 1995;D2–D6.

127. CDC. An Investigation of Exposure to Methyl Tertiary Butyl Ether among Motorists and Exposed Workers in Stamford, Connecticut. Atlanta, GA:Centers for Disease Control and Prevention, 1993.

128. CDC. An Investigation of Exposure to Methyl Tertiary Butyl Ether among Motorists and Exposed Workers in Albany, New York. Atlanta, GA:Centers for Disease Control and Prevention, 1993.

129. Chandler B, Middaugh J. Potential illness due to exposure to oxygenated fuels—Anchorage, Alaska. In: Proceedings of the Conference on MTBE and Other Oxygenates: A Research Update, 26–28 July 1993, Falls Church, VA. Research Triangle Park, NC:U.S. Environmental Protection Agency, National Center for Environmental Assessment, 1995;D7–D11.

130. Mohr SN, Fiedler N, Weisel C, Kelly-McNeil K. Health effects of MTBE among New Jersey garage workers. Inhal Toxicol 6:553–562 (1994).

131. Gordian ME, Huelsman MD, Brecht ML, Fisher DG. Health effects of methyl tertiary butyl ether (MTBE) in gasoline in Alaska. Arch Environ Med 37:101–103 (1995).

132. Hakkola M, Honkasalo ML, Putkkinen P. Neuropsychological symptoms among tanker drivers exposed to gasoline. Occup Med 46:125–130 (1996).

133. Gerrity T, Prah J, Devlin R, Goldstein G, Otto D, Ashley D, Buckley T. Acute Responses of Healthy Human Subjects to Exposure to MTBE. EPA report HERL-AB-93-307. Research Triangle Park, NC:US. Environmental Protection Agency, 1993.

134. Nihlen A, Walinder R, Johanson G. Toxicokinetics and irritative effects of methyl tertiary butyl ether in man. Presented at the Fourth Conference of the International Society for Exposure Analysis, 18–21 September 1994, Research Triangle Park, NC.

135. Prah JD, Goldstein GM, Otto D, Ashley D, House D, Cohen KL, Gerrity T. Sensory, symptomatic, inflammatory and ocular responses to and the metabolism of methyl tertiary butyl ether in a controlled human exposure experiment. Inhal Toxicol 6:521–538 (1994).

136. Cain WS, Leaderer BP, Ginsberg GL, Andrews LS, Cometto-Muniz JE, Gent JF, Buck M, Berglund LG, Mohsenin V, Monahan E, Kjaergaard S. Acute exposure to low-level methyl tertiary butyl ether (MTBE): human reactions and pharmacokinetic response. Inhal Toxicol 8:21–48 (1996).

137. Fiedler N, Mohr SN, Kelly-McNeill K, Kopen HM. Response of sensitive groups to MTBE. Inhal Toxicol 6:539–552 (1994).

138. Lioy PJ, Weisel CP, Jo W, Pellizzari E, Raymer JH. Microenvironmental and personal measurements of methyl tertiary butyl ether (MTBE) associated with automobile use and activities. J Expo Anal Environ Epidem 4:427–441 (1994).

139. Harper M, Fiore AA. Determination of methyl *tert*-butyl ether in air using a diffusive sampler. Appl Occup Environ Hyg 10:616–619 (1995).

140. Yeh CK, Novak JT. The effect of hydrogen peroxide on the degradation of methyl and ethyl *tert*-butyl ether in soils. Water Environ Res 67:828–834 (1995).

141. Lindamood C III, Farnell DR, Giles HD, Prejean JD, Collins JJ, Takahashi K, Maronpot RR. Subchronic toxicity studies of *t*-butyl alcohol in rats and mice. Fundam Appl Toxicol 19:91–100 (1992).

142. Takahashi K, Lindamood C III, Maronpot RR. Retrospective study of possible α_{2u}-globulin nephropathy and associated cell proliferation in male Fischer 344 rats dosed with *t*-butyl alcohol. Environ Health Perspect 101(suppl 5):281–286 (1993).

143. Cirvello JD, Radovsky A, Heath JE, Farnell DR, Lindamood C. Toxicity and carcinogenicity of *t*-butyl alcohol in rats and mice following chronic exposure in drinking water. Toxicol Ind Health 11:151–165 (1995).

144. NTP. Toxicology and Carcinogenesis Studies of *t*-Butyl alcohol (CAS No. 76-65-0) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). TR 436. Research Triangle Park, NC:National Toxicology Program, 1995.

145. Brooks TM, Meyer AL, Hutson DH. The genetic toxicology of some hydrocarbon and oxygenated solvents. Mutagenesis 3:227–232 (1988).

146. NIOSH. Tert-butyl alcohol. In: Occupational Safety and Health Guidelines for Chemical Hazards. Publication No 92–110. Cincinnati, OH:National Institute for Occupational Safety and Health, 1992.

147. Rock K. TAME: technology merits, toxicology testing and regulatory challanges. Presented at the National Conference on Octane Quality and Reformulated Gasolines, 24–26 March 1992, New Orleans, LA.

148. White RD, Daughtrey WC, Wells MS. Health effects of inhaled tertiary amyl methyl ether and ethyl tertiary butyl ether. Toxicol Lett 82:719–724 (1995).

149. Daughtrey C, Bird MG. Genotoxic and twenty-eight-day subchronic toxicity studies on tertiary amyl methyl ether. J Appl Toxicol 15:313–319 (1995).

150. Atmospheric chemistry of tertiary-amyl methyl ether (TAME). Govt Reports Announcements & Index (GRA&I), Issue 18, 1994.

151. Alexeeff GV, Kilgore WW, Li MY. Ethylene dibromide: toxicology and risk assessment. Rev Environ Contam Toxicol 112:49–122 (1990).

152. Romert L, Magnusson J, Ramel C. The importance of glutathione and glutathione transferase for somatic mutations in *Drosophila melanogaster* induced *in vivo* by 1,2-dichloroethane. Carcinogenesis 11:1399–1402 (1990).

153. Ballering LA, Nivard MJ, Vogel EW. Characterization of the genotoxic action of three structurally related 1,2-dihaloalkanes in *Drosophila melanogaster*. Mutat Res 285:209–217 (1993).

154. Storer RD, Cartwright ME, Cook WO, Soper KA, Nichols WW. Short-term carcinogenesis bioassay of genotoxic procarcinogens in PIM transgenic mice. Carcinogenesis 16:285–293 (1995).

155. IARC. Ethylene dibromide. In: IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans. Suppl 7: Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. Lyon:International Agency for Research on Cancer, 1987;204–205.

156. IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans. Suppl 7: Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. Lyon:International Agency for Research on Cancer, 1987.

157. Loranger S, Zayed J. Environmental and occupational exposure to manganese: a multimedia assessment. Int Arch Occup Environ Health 67:101–110 (1995).

158. Frumkin H, Solomon G. Manganese in the US gasoline supply. Am J Ind Med 31: 107–115 (1997).

159. Lynam DR, Pfeifer GD, Fort BF, Gelbcke AA. Environmental assessment of MMT fuel additive. Sci Total Environ 93:107–114 (1990).

160. Iregren A. Psychological test performance in foundry workers exposed to low levels of manganese. Neurotoxicol Teratol 12:673–675 (1990).

161. Zayed J, Ducic S, Campanella G, Panisset JC, André P, Masson H, Roy M. Facteurs environnementaux dans l'étiologie de la maladie de Parkinson. Can J Neurol Sci 17:286–291 (1990).

162. Calne DB. Neurotoxins and degeneration in the central nervous system. Neurotoxicology 12:335–340 (1991).

163. Hua MS, Huang CC. Chronic occupational exposure to manganese and neurobehavioral function. J Clin Exp Neuropsychol 13:495–507 (1991).

164. Wennberg A, Hagman M, Johansson L. Preclinical neurophysiological signs of parkinsonism in occupational manganese exposure. Neurotoxicology 13:271–274 (1992).

165. Mergler D, Huel G, Bowler R, Iregren A, Bélanger S, Baldwin M, Tardif R, Smargiassi A, Martin L. Nervous system dysfunction among workers with long-term exposure to manganese. Environ Res 64:151–180 (1994).

166. Zayed J, Gerin M, Loranger S, Sierra P, Begin D, Kennedy G. Occupational and environmental exposure of garage workers and taxi drivers to airborne manganese arising from the use of methylcyclopentadienyl manganese tricarbonyl in unleaded gasoline. Am Ind Hyg Assoc J 55:53–58 (1994).

167. Sierra P, Loranger S, Kennedy G, Zayed J. Occupational and environmental exposure of automobile mechanics and nonautomotive workers to airborne manganese arising from the combustion of methylcyclopentadienyl manganese tricarbonyl (MMT). Am Ind Hyg Assoc J 56:713–716 (1995).

168. Komura J, Sakamoto M. Chronic oral administration of methylcyclopentadienyl manganese tricarbonyl altered brain biogenic amines in the mouse: comparison with inorganic manganese. Toxicol Lett 73:65–73 (1994).

169. Snyder CA. Organic solvents. In: Immunotoxicology and Immunopharmacology (Dean JH, Luster MI, Munson AE, Kimber I, eds). New York:Raven Press, 1994;183–190.

170. Savitz DA, Andrews KW. Review of epidemiologic evidence on benzene and lymphatic and hematopoietic cancers. Am J Ind Med 31:287–295 (1997).

171. Ruijten MW, Hooisma J, Brons JT, Habets CE, Emmen HH, Muijser H. Neurobehavioral effects of long-term exposure to xylene and mixed organic solvents in shipyard spray painters. Neurotoxicology 15:613–620 (1994).

172. Bates K, Christian F, Civai M, Claydon M, Dreetz C. Review of European oil industry benzene exposure data (1986–1992). Govt Reports Announcements & Index (GRA&I) Issue 12, 1995.

173. Rothman N, Li GL, Dosemeci M, Bechtold WE, Marti GE, Wang YZ, Linet M, Xi LQ, Lu W, Smith MT. Hematotoxicity among Chinese workers heavily exposed to benzene. Am J Ind Med 29:236–426, 1996.

174. Hsieh GC, Parker RD, Sharma RP, Hughes BJ. Subclinical effects of groundwater contaminants. III: Effects of repeated oral exposure to combination of benzene and toluene on immunologic responses in mice. Arch Toxicol 64:320–328 (1990).

175. Shankar U, Kumar A, Rao GS, Dwivedi PP, Pandya KP,

Ray PK. Modulation of benzene induced toxicity by protein A. Biochem Pharmacol 46:517–524 (1993).

176. Goldstein BD, Warren J. HEI's mobile air toxics project. Environ Health Perspect 101:256–258 (1993).

177. Lagorio S, Tagesson C, Forastiere F, Iavarone I, Axelson O, Carere A. Exposure to benzene and urinary concentrations of 8-hydroxydeoxyguanosine, a biological marker of oxidative damage to DNA. Occup Environ Med 51:739–743 (1994).

178. Snyder R, Kalf GF. A perspective on benzene leukemogenesis. Crit Rev Toxicol 24:177–209 (1994).

179. IARC. Benzene. IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans. Suppl 7: Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. Lyon:International Agency for Research on Cancer, 1987;120–127.

180. Orzechowski A, Schwarz LR, Schwegler U, Bock KW, Snyder R, Schrenk D. Benzene metabolism in rodent hepatocytes: role of sulphate conjugation. Xenobiotica 25:1093–1102 (1995).

181. Schlosser PM, Bond JA, Medinsky MA. Benzene and phenol metabolism by mouse and rat liver microsomes. Carcinogenesis 14:2477–2486 (1993).

182. Subrahmanyam VV, Ross D, Eastmond DA, Smith MT. Potential role of free radicals in benzene-induced myelotoxicity and leukemia. Free Radical Biol Med 11:495–515 (1991).

183. Yardley JA, Anderson D, Parke DV. The toxicity of benzene and its metabolism and molecular pathology in human risk assessment. Br J Ind Med 48:437–444 (1991).

184. Medinsky MA, Kenyon EM, Seaton MJ, Schlosser PM. Mechanistic considerations in benzene physiological model development. Environ Health Perspect 104(suppl 6):1399–1404 (1996).

185. Medinsky MA, Schlosser PM, Bond JA. Critical issues in benzene toxicity and metabolism: the effect of interactions with other organic chemicals on risk assessment. Environ Health Perspect 102(suppl 9):119–124 (1994).

186. Travis CC, Fox MT, Simmons WM, Lyon BF. Co-exposure to gasoline vapor decreases benzene metabolism in Fischer-344 rats. Toxicol Lett 62:231–240 (1992).

187. Paxman D, Rappaport SM. Analysis of OSHA's short-term exposure limit for benzene. Regul Toxicol Pharmacol 11:275–287 (1990).

188. Weisel C, Yu R, Roy A, Georgopoulos P. Biomarkers of environmental benzene exposure. Environ Health Perspect 104(suppl 6):1141–1146 (1996).

189. Raabe GK, Wong O. Leukemia mortality by cell type in petroleum workers with potential exposure to benzene. Environ Health Perspect 104(suppl 6):1381–1392 (1996).

190. Lagorio S, Forastiere F, Iavarone I, Rapiti E. Vanacore N, Perucci CA, Carere A. Mortality of filling station attendants. Scand J Work Environ Health 20:331–338 (1994).

191. Bezabeh S, Engel A, Morris CB, Lamm SH. Does benzene cause multiple myeloma? An analysis of the published case–control literature. Environ Health Perspect 104(suppl 6):1393–1398 (1996).

192. Wong O, Raabe GK. Multiple myeloma and benzene exposure in a multinational cohort of more than 250,000 petroleum workers. Regul Toxicol Pharmacol 26:188–199 (1997).

193. Nilsson RI, Nordlinder RG, Tagesson C, Walles S, Jarvholm BG. Genotoxic effects in workers exposed to low levels of benzene from gasoline. Am J Ind Med 30:317–324 (1996).

194. Lagorio S, Forastiere F, Iavarone I, Vanacore N, Carere A. Exposure assessment in a historical cohort of filling station attendants. Int J Epidemiol 22(suppl 2):51–56 (1993).

195. Popp W, Rauscher D, Muller G, Angerer J, Norpoth K. Concentrations of benzene in blood and S-phenylmercapturic and t,t-muconic acid in urine in car mechanics. Int Arch Occup Environ Health 66:1–6 (1994).

196. Hakkola M, Saarinen L. Exposure of tanker drivers to gasoline and some of its components. Ann Occup Hyg 40:1–10 (1996).

197. Moolenaar RL, Hefflin BJ, Ashley DL, Middaugh JP, Etzel RA. Blood benzene concentrations in workers exposed to oxygenates fuel in Fairbanks, Alaska. Int Arch Occup Environ Health 69:139–143 (1997).

198. Paustenbach DJ, Bass RD, Price P. Benzene toxicity and risk assessment, 1972–1992: implications for future regulation. Environ Health Perspect 101(suppl 6):177–200 (1993).

199. Hughes K, Meek ME, Bartlett S. Benzene: evaluation of risks to health from environmental exposure in Canada. Environ Carcinog Ecotox Rev 12:161–171 (1994).

200. Saito K, Wada H. Behavioral approaches to toluene intoxication. Environ Res 62:53–62 (1993).

201. Tegeris JS, Balster RL. A comparison of the acute behavioral effects of alkylbenzenes using a functional observational battery in mice. Fundam Appl Toxicol 22:240–250 (1994).

202. Cintra A, Andbjer B, Finnman UB, Hagman M, Agnati LF, Hoglund G, Fuxe K. Subacute toluene exposure increases DA dysfunction in the 6-OH dopamine lesioned nigrostriatal dopaminergic system of the rat. Neurosci Lett 217:61–65 (1996).

203. Gralewicz S, Wiaderna D, Tomas T. Development of spontaneous, age-related nonconvulsive seizure electrocortical activity and radial-maze learning after exposure to m-xylene in rats. Int J Occup Med Environ Health 8:347–360 (1995).

204. Pryor G, Rebert C, Kassay K, Kuiper H, Gordon R. The hearing loss associated with exposure to toluene is not caused by a metabolite. Brain Res Bull 27:109–113 (1991).

205. Crofton KM, Lassiter T, Rebert CS. Solvent-induced ototoxicity in rats: an atypical selective mid-frequency hearing deficit. Hear Res 80:25–30 (1994).

206. Liu Y, Fechter LD. Toluene disrupts outer hair cell morphometry and intracellular calcium homeostasis in cochlear cells of guinea pigs. Toxicol Appl Pharmacol 142:270–277 (1997).

207. Poon R, Chu I, Bjarnason S, Potvin M, Vincent R, Miller RB, Valli VE. Inhalation toxicity study of methanol, toluene, and methanol/toluene mixtures in rats: effects of 28-day exposure. Toxicol Ind Health 10:231–245 (1994).

208. Nielsen IR, Howe P. Environmental Hazard Assessment: Toluene. TSD/1. London:Department of the Environment, 1993.

209. Ono A, Sekita K, Ohno K, Hirose A, Ogawa Y, Saito M, Naito K, Kaneko T, Furuya T, Matsumoto K. Reproductive and developmental toxicity studies of toluene. I. Teratogenicity study of inhalation exposure in pregnant rats. J Toxicol Sci 20:109–134 (1995).

210. Ono A, Sekita K, Ogawa Y, Hirose A, Suzuki S, Saito M, Naito K, Kaneko T, Furuya T, Kawashima K, Yasuhara K, Matsumoto K, Tanaka S, Inoue T, Kurokawa Y. Reproductive and developmental toxicity studies of toluene. II. Effects of inhalation exposure on fertility in rats. J Environ Pathol Toxicol Oncol 15:9–20 (1996).

211. Crookes MJ, Dobson S, Howe PD. Environmental Hazard Assessment: Xylenes. TSD/12. London: Department of the Environment, 1993.

212. Hass U, Lund SP, Simonsen L, Fries AS. Effects of prenatal exposure to xylene on postnatal development and behavior in rats. Neurotoxicol Teratol 17:341–349 (1995).

213. Wilkins HL. Teratogen update: toluene. Teratology 55:145–151 (1997)

214. Uchida Y, Nakatsuka H, Ukai H, Watanabe T, Liu YT, Huang MY, Wang YL, Zhu FZ, Yin H, Ikeda M. Symptoms and signs in workers exposed predominantly to xylenes. Int Arch Occup Environ Health 64:597–605 (1993).

215. Ukai H, Takada S, Inui S, Imai Y, Kawai T, Shimbo S, Ikeda M. Occupational exposure to solvent mixtures: effects on health and metabolism. Occup Environ Med 51:523–529 (1994).

216. Smargiassi A, Mutti A, Bergamaschi E, Belanger S, Truchon G, Mergler D. Pilot study of peripheral markers of catecholaminergic systems among workers occupationally exposed to toluene. Neurotoxicology 17:769–775 (1996).

217. Foo SC, Ngim CH, Salleh I, Jeyaratnam J, Boey KW. Neurobehavioral effects in occupational chemical exposure. Environ Res 60:267–273 (1993).

218. Wood RW, Cox C. A repeated measures approach to the detection of the acute behavioral effects of toluene at low concentrations. Fundam Appl Toxicol 25:293–301 (1995).

219. Greenberg MM. The central nervous system and exposure to toluene: a risk characterization. Environ Res 72:1–7 (1997).

220. Lawryk NJ, Lioy PJ, Weisel CP. Exposure to volatile organic compounds in the passenger compartment of automobiles during periods of normal and malfunctioning operation. J Expos Anal Environ Epidem 5:511–531 (1995).

221. Tardif R, Plaa GL, Brodeur J. Influence of various mixtures of inhaled toluene and xylene on the biological monitoring of exposure to these solvents in rats. Can J Physiol Pharmacol 70:385–393 (1992).

222. IARC. Toluene. In: IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol 47. Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting. Lyon:International Agency for Research on Cancer, 1989;79–123.

223. IARC. Xylene. In: IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol 47: Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting. Lyon:International Agency for Research on Cancer, 1989;125–156.

224. NTP. Toxicology and Carcinogenesis Studies of Toluene (CAS No. 108-88-3) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies). TR 371. Research Triangle Park, NC:National Toxicology Program, 1990.

225. Mehlman MA. Dangerous and cancer-causing properties of products and chemicals in the oil refining and petrochemical industry. Part I. Carcinogenicity of motor fuels: gasoline. Toxicol Ind Health 7:143–152 (1991).

226. Mehlman MA, Legator MS. Dangerous and cancer-causing properties of products and chemicals in the oil refining and petrochemical industry. Part II: Carcinogenicity, mutagenicity, and developmental toxicity of 1,3-butadiene. Toxicol Ind Health 7:207–220 (1991).

227. Mehlman MA. Dangerous and cancer-causing properties of products and chemicals in the oil refining and petrochemical industry: Part VIII. Health effects of motor fuels: carcinogenicity of gasoline-scientific update. Environ Res 59:238–249 (1992).

228. Mehlman MA. Dangerous and cancer-causing properties of products and chemicals in the oil refining and petrochemical industry: Part XV. Health hazards and health risks from oxygenated automobile fuels (MTBE): lessons not heeded. Int J Occup Med Toxicol 4:219–236 (1995).

229. Mehlman MA. Dangerous and cancer-causing properties of products and chemicals in the oil-refining and petrochemical industry. Part XXII: Health hazards from exposure to gasoline containing methyl tertiary butyl ether: study of New Jersey residents. Toxicol Ind Health 12:613–627 (1996).

230. Lotti M. IARC Ranking of carcinogenicity evidence: how is the message delivered and perceived? Regul Toxicol Pharmacol 19:236–241 (1994).

231. IARC. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol 53: Occupational Exposures in Insecticide Application, and Some Pesticides. Lyon:International Agency for Research on Cancer, 1991.

232. Caprino L. Evaluation of drug safety by toxicological test procedures as provided by regulatory laws: an overview. Pharm Res 22:253–262 (1990).

233. Murphy EF. The Macmillian Treasury of Relevant Quotations. London:The Macmillian Press, 1979;124.