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Neurotoxic Effects of Gasoline and Gasoline Constituents

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This overview was developed as part of a symposium on noncancer end points of gasoline and key gasoline components. The specific components included are methyl tertiary butyl ether, ethyl tertiary butyl ether, tertiary amyl methyl ether, butadiene, benzene, xylene, toluene, methyl alcohol, and ethyl alcohol. The overview focuses on neurotoxic effects related to chronic low-level exposures. A few general conclusions and recommendations can be made based on the results of the studies to date. *a*) All the compounds reviewed are neuroactive and, as such, should be examined for their neurotoxicity. *b*) For most of the compounds, there is a substantial margin of safety between the current permissible exposure levels and levels that would be expected to cause overt signs of neurotoxicity in humans. This is not the case for xylene, toluene, and methanol, however, where neurologic effects are observed at or below the current Threshold Limit Value. *c*) For most of the compounds, the relationship between chronic low-level exposure and subtle neurotoxic effects has not been studied. Studies therefore should focus on examining the dose–response relationship between chronic low-level exposure and subtle changes in central nervous system function.

Introduction

This overview was developed as part of a symposium on noncancer end points of gasoline and key gasoline constituents. The specific constituents included in the overview are methyl tertiary butyl ether, ethyl tertiary butyl ether, tertiary amyl methyl ether, butadiene, benzene, xylene, toluene, methyl alcohol, and ethyl alcohol. The overview is not meant to serve as an exhaustive review of the literature for all compounds. Instead, certain examples of the neurotoxic effects reported for each compound are included in the context of a discussion of a dose–response analysis or calculation of a no-observable-adverse-effect level (NOAEL) for human neurotoxic effects due to chronic low-level occupational or environmental exposure. Finally, the overview does not include studies of chemical mixtures other than gasoline. The focus for this overview is on specific key components of gasoline.

Gasoline

The effects associated with the intentional use of gasoline as an intoxicant (gasoline sniffing) are commonly neurologic in nature and include ataxia, tremor, and an acute or subacute encephalopathic syndrome [see Fortenberry for a review (*1*)].

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Occupational exposure to gasoline has been associated with numerous signs of neurotoxicity. Significant effects on intellectual capacity, psychomotor and visuomotor function, immediate and delayed memory, and an increased proportionate mortality ratio (PMR) due to mental and psychoneurotic conditions have been reported for gasoline service station workers (*2,3*). Symptoms such as headache, fatigue, loss of memory, and giddiness have also been reported (*4*). Neurological effects (dizziness, headache) have been reported in laboratory studies of human volunteers exposed to gasoline vapor. These effects were observed at a concentration of 2600 ppm but not at concentrations of 1000 ppm and below (*5,6*).

In animals, acute exposure of dogs to high concentrations of gasoline have been associated with neurologic effects at 10,000 ppm and death at 25,000 ppm (*7*). A preliminary study of rats exposed to 1500 ppm gasoline for 6 hr/day, 5 days/week for up to 18 months demonstrated more extensive axonal dystrophy and degeneration in the distal gracile tract of the spinal cord as well as abnormalities of anterior horn cells (*8*). Chronic exposure, 6 hr/day for 5 days/week for 90 days, of rats and monkeys to 400 ppm and 1500 ppm gasoline, however, did not produce overt neurotoxicity or changes in visual evoked responses (*9*). In another study, rats and mice exposed to 50, 275, or 1500 ppm gasoline for 6 hr/day, 5 days/week for up to 113 weeks also failed to show signs of overt neurotoxicity (*10*). A study of the effects of exposure to unleaded gasoline on the hypothalamo-pituitary-thyroid-adrenal system in rats has indicated a significant increase in serum corticosterone and adrenal catecholamines and a decrease in hypothalamic noradrenaline. These effects were observed

only after 60 days of exposure to > 600 ppm unleaded gasoline in air for 8 hr/day, 5 days/week. Effects were not observed after 1, 3, 7, 14, or 30 days of exposure (*11*).

A summary of the neurotoxic effects reported for gasoline is shown in Table 1. Thus far, studies of human exposures to gasoline have provided little data regarding the actual level of gasoline exposure. Although some exposure data are available for the studies using animal models, the small number of studies and the use of different dosing schedules and neurotoxic end points make a dose–response analysis for the various end points reported very difficult. At this time, sufficient data are not available to support calculating a no-observed-adverse-effect level (NOAEL) for the neurotoxic effects of chronic low-level gasoline exposure.

Methyl Tertiary Butyl Ether

There have been no reports concerning the toxic (including neurotoxic) effects of methyl tertiary butyl ether (MTBE) in humans due to occupational exposure. The use of MTBE as a therapeutic agent for dissolving gallstones (*12*) has provided information regarding the side effects in humans of MTBE administered by infusion. These studies, however, do not provide data relevant to the evaluation of MTBE neurotoxicity.

Studies in animals have not provided evidence of overt neurotoxicity due to MTBE exposure at air concentrations from 100 ppm to 3000 ppm MTBE (*13–15*). In addition, gross teratogenic effects were not observed in rats and mice at air concentrations from 250 ppm to 2500 ppm MTBE (*16–18*). A decrease in offspring viability, however, has been reported at air concentrations of 1000 ppm and 2500 ppm (*19*).

More subtle neurotoxic effects due to MTBE exposure have been reported in two studies sponsored by the Methyl Tertiary Butyl Ether Task Force (*20,21*). The effects of a single 6-hr exposure to MTBE and exposure for 13 days, 6 hr/day were examined. Both studies used rats and MTBE air concentrations of 8000, 4000, 800, and 0 ppm. Several neurobehavioral effects were reported at all levels of exposure in both studies. The most consistent effects related to MTBE exposure were those on activity. At higher levels of exposure (8000 ppm), a reduction in overall activity, or a sedation effect, was observed. At the lower concentrations tested (4000 and 800 ppm), an increase in overall activity was observed. The authors stated that the increase in overall activity observed at the lower MTBE air concentrations tested (4000 and 800 ppm) "may reflect an exposure-related stimulant effect" (*20*).

A summary of the neurotoxic effects reported for MTBE is shown in Table 2. To date, studies of occupational exposures of workers to MTBE have not been reported. The two MTBE Task Force studies using rats do provide some dose–response data for MTBE effects in adult animals. These studies do not report a NOAEL of exposure for MTBE. Central nervous system stimulant effects were observed at the lowest dose studied.

Table 1. Summary of the neurotoxic effects of gasoline.

Humans
Chronic gasoline sniffing
Ataxia, tremor, encephalopathic syndrome
Occupational exposure
Headache, fatigue, memory loss, psychomotor and visuomotor dysfunction
Laboratory studies
Headache, dizziness at air concentrations above 2600 ppm
Animals
Acute exposure
Tremors and convulsions at air concentrations above 580 ppm, severe neurologic signs at 10,000 ppm, death at 25,000 ppm
Chronic exposure
No overt signs of neurotoxicity at air concentrations of 1500 ppm, degeneration in spinal cord and anterior horn cells at 1500 ppm, increase in serum corticosterone and adrenal catecholamines and decrease in hypothalamic noradrenaline at 650 ppm

Table 2. Summary of the neurotoxic effects of methyl tertiary butyl ether in animals.

Acute exposure
Reduction in activity at 8000 ppm, increase in activity at 4000 and 800 ppm
Chronic exposure
No overt neurotoxicity at air concentrations from 100 ppm to 3000 ppm, no overt teratogenic effects from 250 to 2500 ppm, decreased offspring viability at 1000 and 2500 ppm, reduction in activity at 8000 ppm, increase in activity at 4000 and 800 ppm

Ethyl Tertiary Butyl Ether

Reports concerning the neurotoxic effects of ethyl tertiary butyl ether (ETBE) could not be found. ETBE, like MTBE, can be used as a gasoline antiknock additive. To date, production of ETBE is very low; however, production is likely to increase because ETBE has several advantages over MTBE for use in reformulated gasoline (*22*).

Tertiary Amyl Methyl Ether

Only one report concerning the toxic effects of tertiary amyl methyl ether (TAME) could be found (*23*). This study examined the effects of 125, 500, or 1000 mL/kg/day TAME administered to rats by gavage 7 days/week for 29 days. General observations for overt signs of neurotoxicity were included throughout the dosing period. The results of the observations did not indicate the presence of overt signs of neurotoxicity. Only a few of the observations were not listed as "within normal limits." Four of the animals in the 1000 mL/kg/day dosage group died during the study. Two deaths were related to dosing accidents, and the other two were related to exposure to TAME.

Few conclusions can be drawn regarding the neurotoxic effects of TAME from the single study available for review. In rats, oral doses of 1000 mL/kg/day TAME increased mortality. Eight doses of 500 and 125 mL/kg/day did not increase mortality or cause overt signs of neurotoxicity. Studies of humans or animals focusing on TAME neurotoxicity have not been reported.

Butadiene

Neurotoxic effects in humans due to exposure to butadiene have not been reported to date. Studies using animals, however, have reported species-specific teratogenic effects due to butadiene exposure (*24,25*). In mice, exposure to 1,3-butadiene for 6 hr/day on gestation days 6–15 has been related to a decrease in maternal, fetal, and placental weights and an increase in the incidence of fetal variations. Reduced fetal weights for males were observed at the lowest exposure concentration (40 ppm). The remaining effects were observed at 200 and 1000 ppm concentrations. In rats, reduced maternal body weights at 1000 ppm butadiene were the only effects observed. No signs of maternal neurotoxicity were observed in either study. Possible offspring neurotoxic effects were not examined.

Differences in the pharmacokinetics of butadiene have been reported for rats and mice (*26*). These differences result in an accumulation of epoxybutene, a primary reactive intermediate of butadiene, in mice but not in rats. A reported increased susceptibility of mice to butadiene carcinogenesis has been related to these differences (*26*). The species-specific teratogenic effects reviewed above may also be related to these pharmacokinetic differences.

Like TAME, very few conclusions can be drawn regarding the potential neurotoxicity of butadiene from the studies avilable to date. Air concentrations of butadiene as low as 40 ppm have been associated with reduced fetal weights for mice. Air concentrations as high as 1000 ppm were not associated with overt fetal effects for rats. Studies focusing on the neurotoxic effects of butadiene for humans or animals have not been reported.

Benzene

The primary effects associated with chronic benzene exposure in humans and animals are anemia and leukopenia (*27*). Neurotoxic effects in humans due to benzene exposure have not been reported.

In animals, overt neurotoxic effects, usually signs of narcosis, have been reported at air concentrations of benzene above 4000 ppm. Benzene exposures above 10,000 ppm may result in death (*28*). Maternal inhalation exposure to 100–2200 ppm benzene for 6 hr/day from day 6 to 15 of gestation did not result in overt neurotoxicity in adult rats, although maternal and fetal weight effects and fetal skeletal effects were observed (*29*). Subtle neurobehavioral effects in animals due to benzene exposure have been reported. Consistent and significant changes in mouse milk-licking responses have been reported after approximately 1 week of inhalation exposure to benzene at 300 ppm (*27*). Effects on adult rat motor activity and a decreased response to d-amphetamine challenge have been associated with neonatal exposure to benzene via SC injection at 550 mg/kg (*30*). Benzene neurochemical effects, in animals, have also been reported. Increases in the level of catecholamines in various regions of the mouse brain have been reported after exposure to benzene in drinking water at 8 mg/kg/day (*31*).

Table 3. Summary of the neurotoxic effects of benzene in animals.

Acute exposure
Narcosis at air concentrations above 4000 ppm, death at 10,000 ppm
Chronic exposure
No overt neurotoxicity at air concentrations between 100 and 2200 ppm, increase in milk-licking behavior at 300 ppm, increase in motor activity and decrease in response to *d*-amphetamine at 550 mg/kg IP, increase in catecholamines at 8 mg/kg/day in drinking water

IP, intraperitoneal.

A summary of the neurotoxic effects reported for benzene is shown in Table 3. The earliest indicators of effects due to benzene exposure in humans and animals is anemia and leukopenia. Although important neurotoxic effects have been associated with benzene exposure in animals, these effects are observed at exposure levels well above those associated with hematologic changes.

Xylene

The neurologic effects due to short-term exposure to xylene have been reported from laboratory studies of human volunteers. The results of these studies indicated that the odor threshold for xylene is approximately 1 ppm (*32*). Brief exposure to approximately 70 ppm xylene did not affect reaction time or short-term memory (*33*). Inhalation exposure at 90 ppm, however, caused deleterious effects on reaction time, manual dexterity, body balance, and EEG (*34*). Short-term exposure to xylene at 300 ppm has been associated with a decrement in performance on reaction time, memory span, and critical flicker fusion tests (*35*). Exposure at 100–400 ppm also caused an impairment of body balance and increased reaction time (*36*), and eye irritation occurred at 460 ppm (*32*).

In animals, repeated exposures to air concentrations of xylene in the range of 200–2000 ppm have been associated with effects on behavior and/or brain chemistry. Exposure to xylene for 4 hr/day for 3 consecutive days at 1600 ppm increased motor activity in rats (*37*). Changes in dopamine and noradrenaline levels and turnover in various regions of the rat brain have been observed after xylene exposure for 6 hr/day for 3 consecutive days at 2000 ppm (*38*). Changes in neurotransmitters have also been reported after a 30-day exposure from 200 to 800 ppm (*39*). The earliest neurochemical effect of xylene, a decrease in brain glutathione, occurred after 5 days of exposure at 50 ppm (*40*).

A summary of the neurotoxic effects reported for xylene is shown in Table 4. The results of studies of humans and animals indicate xylene neurotoxic effects below the current TLV level of 100 ppm. The results would predict that occupational exposure at the TLV would adversely affect human performance. The long-term effects from repeated exposures to xylene remain uncertain.

Table 4. Summary of the neurotoxic effects of xylene.

Humans
Acute exposure
Reduced reaction time, manual dexterity, disruption of body balance and EBG at air concentrations above 90 ppm
Animals
Chronic exposure
Increase in motor activity at 1600 ppm, changes in neurotransmitters between 200 and 2000 ppm, increase in brain glutathione at 50 ppm

Methanol

The deliberate ingestion of methanol has been related to several toxic effects. The symptoms associated with methanol intoxication include headache, dizziness, nausea, vomiting, severe abdominal pain, and periodic breathing. Coma and death from respiratory failure can occur in severe cases. Several visual symptoms have also been reported after methanol intoxication. These include blurred vision, altered visual fields, and total blindness. These symptoms are observed as a result of metabolic acidosis, which develops as a result of an accumulation of formic acid. Autopsies from lethal poisonings have indicated degenerative changes in the basal ganglia. Survivors of severe poisonings sometimes display motor distubances similar to Parkinsonism (*41,42*).

Prolonged occupational exposure to methanol has also been associated with several toxic effects (*43*). Significant increases in the prevalence of blurred vision, headaches, dizziness, nausea, and skin problems were observed for teacher's aides exposed to duplicating fluids of 99% methyl alcohol. Air concentrations of methyl alcohol near the duplicating machines were well above the permissible exposure limit time-weighted average of 200 ppm. Methanol air concentrations as high as 3080 ppm were observed. A recent study using human volunteers examined the effects of exposure to methanol vapor at 192 ppm for 75 min (*44*). Several tests were administered to the 12 subjects before, during, and after the exposure. Although performance on most tests was normal, a slight impairment on a memory and concentration test and minor changes in brain wave patterns in response to light and sound were detected. The results from these tests were within the range observed for the subjects without methanol exposure. The significance of the changes observed during methanol exposure, therefore, await further investigation.

In animals, metabolic acidosis and ocular toxicity have been observed in nonhuman primates and folate-deficient rats after high-dose methanol exposure (*45–48*). Studies of nonhuman primates have indicated that the minimum lethal oral dose for methanol is approximately 3 g/kg. A dose of 2 mg/kg has been associated with metabolic acidosis and ocular toxicity. Several neurotoxic effects have also been reported at lower levels of methanol exposure in nonfolate-deficient rats. Rats exposed to 3 g/kg methanol exhibited a disruption in thermoregulation due to an inhibitory action of methanol on heat production pathways (*49,50*). Altered auditory responses, which require temporal resolution, have also been reported after methanol exposure of rats at 0.25–3 g/kg (*51*). Studies of prenatal exposure to methanol in rats have reported effects on fetal development and postnatal behavior (*52,53*). Rats exposed to methanol via inhalation at 26,000 ppm exhibited an increase in maternal toxicity (unsteady gait) and fetal malformations. Fetal malformations were also observed at 13,000 ppm exposure, although the increase was not significant (*52*). Effects on newborn nesting behavior were observed in rat offspring at maternal exposure of 2.5 g/kg/day. These effects were observed without any signs of overt toxicity in the mothers or the offspring (*53*). Finally, studies of rats have also indicated effects of methanol on brain chemistry (*54–56*). Changes in levels of dopamine, norepinephrine, epinephrine, serotonin, and 5-hydroxy indole acetic acid in various brain regions have been reported after a single IP injection of methanol at 3 g/kg.

Table 5. Summary of the neurotoxic effects of methanol.

Humans
Methanol ingestion
Headache, dizziness, visual symptoms, motor disturbances, metabolic acidosis, degenerative changes in basal ganglia
Occupational exposure
Blurred vision, headache, dizziness at air concentrations between 300 and 3000 ppm
Animals
Acute exposure
Metabolic acidosis, ocular toxicity in nonhuman primates (2 mg/kg) and folate deficient rats (3g/kg)
Chronic exposure
Disruption of thermoregulation in normal rats at a dose of 3 g/kg, altered auditory response between 0.25 and 3 g/kg, changes in neurotransmitters at 3 g/kg, disruption of newborn nesting behavior at 2.5 g/kg/day maternal exposure, unsteady gait at air concentration of 26,000 ppm

A summary of the neurotoxic effects reported for methanol is shown in Table 5. The recent study by Cook et al. (*44*) provides preliminary evidence of methanol effects on concentration, memory, and brain-wave patterns at an exposure concentration of 192 ppm, which is below the current TLV for methanol (200 ppm). Studies using animal models provide results for a narrow range of high doses and do not provide sufficient data to determine a NOAEL of chronic low-level exposure to methanol.

Toluene

The primary CNS effects associated with chronic toluene abuse are ataxia and tremor, with cerebellar and cerebral atrophy present in severe cases (*57*). Short-term exposure to toluene at about the curent TLV (100–150 ppm) affects performance on a number of tasks. Volunteers exposed to toluene for 7 hr experienced alterations in temperature and noise perception, an increase in feelings of intoxication, lower scores on vigilance tests, altered short-term memory, and poorer manual dexterity performance. These effects were not observed at 75 ppm (*58,59*). These effects are similar to those reported in studies of occupational exposure to toluene (*60–63*); effects on neuropsychological functioning are usually observed.

Short-term exposure to toluene in animals has also been associated with several behavioral effects. In rodents, alterations in response rates, locomotion, and avoidance learning have been observed (*64*). The effects on operant response rates are dose dependent. Exposures at approximately 1000 ppm have been shown to increase response rates, whereas exposures at approximately 2000 ppm and above decrease rates (*65*). Effects on locomotor activity are also dose dependent. An increase in activity has been reported after exposure at 5000 ppm, whereas a biphasic response (increase then decrease) was observed at higher exposure concentrations [10,000 ppm and 15,000 ppm (*66*).]

A decrease in shock avoidance responses has been reported after exposure to toluene above 1000 ppm. Exposure at 500 ppm and below did not affect responding (*67*). In monkeys, short-term exposure to toluene has been shown to increase response time and decrease performance on a cognitive task at 2000 ppm. Exposure to 100, 200, or 500 ppm, however, did not affect performance (*68*). The effects observed in the studies above appear transient. Response typically returns to normal soon after the exposure has ended.

Several biochemical effects have been reported in studies of animals after short-term toluene exposure. These studies typically used a design that includes a single exposure to toluene or repeated exposures over a few days before the sacrifice of the animal (immediately following the last exposure). The neurochemical effects of toluene after a single IP injection to rats at 200, 400, or 600 mg/kg include a significant dose-dependent increase in 5-hydroxytryptamine (5-HT), a significant dose-dependent increase in noradrenaline (NA) and 3-methoxy-4-hydroxyphenyl-glycol (MHPG), and a significant dose-dependent decrease in 5-hydroxyindoleacetic acid (5-HIAA) in various regions of the brain (*69*). The neurochemical effects of short-term inhaled toluene at 80, 500, 1500, or 3000 ppm included a significant reduction in the affinity in striatal [^{3}H]spiperone-binding sites and in cortical [^{3}H]5-HT-binding sites at 3000 ppm, a decrease in dopamine (DA) levels in the marginal zone of the nucleus caudatus and anterior part of the nucleus accumbens, a decrease in DA turnover in the marginal zone and the medial and central part of the anterior nucleus caudatus at 80 ppm, and a dose-dependent effect, from 80 to 1500 ppm, on β-adrenergic receptors (*70,71*).

Studies of chronic toluene exposure in animals have reported numerous behavioral and biochemical effects. These studies typically use a design that includes repeated exposures to toluene over a period from 1 week to several months. The behavioral assessments usually take place during toluene exposure. Some studies, however, examine the nature of the behavioral effects by testing subjects after the exposure has ended. Typically, biochemical studies are conducted immediately after the last exposure or after the last behavioral assessment. Chronic exposure to high concentrations of inhaled toluene in rodents to simulate human toluene abuse is associated with alterations in visual, auditory, somatosensory, and peripheral nerve evoked potentials, locomotor activity, and motor coordination (*72–75*). A transient decrease in total sleep and an increase in locomotor and drinking activity have been reported during 2 weeks of toluene exposure via IP injection at 200 mg/kg/day. Neurochemical changes were also observed. Levels of 5-HT and 5-HIAA were significantly decreased, but MHPG, DOPAC and HVA concentrations were significantly increased. Effects were not observed at 100 mg/kg/day (*76*). Chronic exposure (4 weeks) of rats to toluene via inhalation has also been associated with neurochemical changes in various regions of the brain. A significant decrease in amino-acid decarboxylase (AAD) at 250 ppm and 1000 ppm, glutamic acid decarboxylase (GAD) at 50 ppm, and receptor binding of glutamate and GABA binding at all levels of exposure have been reported. In addition, a significant increase was observed in glutamine synthetase activity (GLN-S) at 1000 ppm and receptor binding of glutamate and GABA binding at 50 and 1000 ppm (*77*).

Developmental exposure to toluene has been associated with several behavioral effects in exposed offspring. Fluid consumption, maternal and infant mortality, weight gain, eye and ear opening, and startle and surface-righting responses were not affected by toluene exposure. Activity in the open-field and rotorod performance, however, were altered by toluene and nearly all of the exposed animals were observed to have splayed hindlimbs (*78*).

A summary of the neurotoxic effects reported for toluene is shown in Table 6. The data regarding toluene neurotoxic effects indicate that the current TLV of 100 ppm provides little or no margin of safety. In humans, short-term exposure to toluene at about the TLV alters perception and lowers performance on motor and cognitive tasks. These effects are similar to those reported in studies of occupational exposure to toluene. In animal models, short-term exposure to toluene below the TLV decreases dopamine levels and turnover in the brain and selectively increases the number and decreases the affinity of β-adrenergic receptors. Developmental exposure to toluene alters activity and motor coordination.

Ethanol

In humans, some of the neurotoxic effects associated with long-term alcohol abuse include anterograde and retrograde amnesia, dementia, ataxia, dysarthria, and peripheral-nerve disorders. Wernicke's syndrome and Korsakoff's syndrome are associated with chronic alcohol abuse primarily due to an alcohol-induced thiamine deficiency. Histologic features of these syndromes include microscopic lesions in the thalamus, hypothalamus, mesencephalon, and brainstem as well as cerebellar and cortical lesions (*79–82*).

The few studies of ethanol effects after inhalation exposure have indicated that, in humans, the initial symptoms

Table 6. Summary of the neurotoxic effects of toluene.

Humans
Toluene sniffing
Ataxia, tremor, cerebellar and cerebral atrophy
Occupational or short-term exposure
Reduced manual dexterity and vigilance scores, short-term memory loss, disruption in perception at air concentrations above 100 ppm
Animals
Short-term exposure
Dose-dependent changes in response rates at air concentrations of 1000 ppm and above, increase in activity at 5000 ppm, decrease in activity at 15,000 ppm, decrease in shock avoidance responses at 1000 ppm but not at 500 ppm, decreased performance on cognitive task at 2000 ppm but not at 500 ppm and below, changes in neurotransmitters at 80 ppm and above
Chronic exposure
Transient decrease in sleep, increase in activity and drinking, changes in neurotransmitters at 200 mg/kg/day IP, changes in neurotransmitters at air concentrations above 50 ppm, increased activity and motor incoordination after developmental exposure

of ethanol exposure are coughing, eye and nose irritation, which appear at a concentration of approximately 5,000–10,000 ppm. At about 15,000 ppm, these symptoms increase, and continuous lachrymation and coughing occur. Concentrations of 20,000 ppm and above were judged as intolerable (*83*). In rodents, constant exposure to air concentrations of ethanol from 7,500 ppm to 15,000 ppm for 4–10 days produces signs of alcohol intoxication, dependency, and withdrawal. Pregnant rats exposed to air concentrations of ethanol at 16,000 ppm or 20,000 ppm exhibit signs of intoxication and reduced weight gain. Twenty-day-old fetuses of dams exposed at the 20,000 ppm concentration exhibited a significant increase in visceral and/or skeletal malformations. Rats exposed to 10,000 ppm showed no maternal or fetal effects (*84–87*).

The developmental deficits associated with fetal alcohol syndrome (FAS) and fetal alcohol effects (FAE), as well as "social drinking" during pregnancy, have been the topic of numerous publications. FAS and FAE infants display increased irritability, tremulousness, and reduced weight gain. Older children display increased social and emotional problems and intellectual impairment that may continue into adulthood. Offspring of social-drinking women display lower birthweights, abnormal state regulation, lower scores on infant developmental tests, growth retardation, increased restlessness, short attention span, and motor dysfunction. The pattern of alcohol consumption most related to the effects observed in offspring of social drinkers is more than two drinks/day during midpregnancy and binge drinking (more than five drinks/occasion) in the months just before pregnancy recognition (*88–91*).

Several animal models have been developed to replicate the behavioral findings reported for humans (*92*). In addition, studies using animal models have investigated the neuroanatomical and neurochemical effects of prenatal alcohol exposure. Most of the studies concerning the neurochemical effects have focused on the GABAergic system (*93,94*). The results of these studies, however, have not provided a consistent pattern of effects. The inconsistency may be due to a biphasic dose-dependent response of GABA to ethanol. Results indicate that glutamine and GABA increase at low-level exposure (2 g/kg ethanol) but decrease at higher exposure concentrations (3 and 8 g/kg) (*94*). Not all studies on the neurochemical effects of alcohol have focused on the GABAergic system. Rats intubated with 4 g/kg ethanol every 12 hr for 11–15 days exhibited a significant reduction in the binding of mesolimbic dopamine receptors (20%). The binding of serotonin receptors was significantly increased in the striatum (63%) and brainstem (32%) and was significantly decreased in the hippocampus (20%). The binding of acetylcholine receptors was also significantly increased in the striatum (7%) and significantly decreased in the cerebral cortex (5%) (*95*). Finally, recent results from studies of nonhuman primate infants exposed to weekly doses of ethanol have provided some data regarding prenatal alcohol effects. Microphthalmia, retinal ganglion cell loss, and altered striatal dopamine concentrations have been reported thus far (*96*).

A summary of the neurotoxic effects reported for ethanol is shown in Table 7. Thus far, the most sensitive indexes of alcohol exposure effects are those observed after maternal alcohol intake during pregnancy. Offspring effects on behavior have been reported at blood alcohol concentrations associated with the intake of ≥ 1 oz of absolute alcohol per day.

Table 7. Summary of the neurotoxic effects of ethanol.

Humans
Alcoholism
Ataxia, dysarthria, dementia, amnesia, peripheral-nerve disorders, cerebellar and cortical lesions
Developmental exposure
Fetal alcohol effects observed at exposure to > 1 oz absolute alcohol/day
Animals
Chronic exposure
Alcohol intoxication, dependence and withdrawal at air concentrations from 7500 ppm to 15,000 ppm, intoxication and reduced weight gain at maternal exposure of 16,000 ppm but not at 10,000 ppm, changes in neurochemistry at doses from 2 to 8 g/kg, microphthalmia, retinal ganglion cell loss, altered dopamine concentrations after maternal "binge" drinking

Discussion

Determining the neurotoxic effects associated with chronic low-level occupational or environmental exposures requires dose–response data for several neurotoxic end points from well-designed studies. Data may come from studies of occupational exposure of workers, studies using animal models and, for some compounds, studies from controlled exposures in the laboratory. The studies should include several exposure levels and procedures for determining a NOAEL. Studies of occupational exposure and effects should include a complete work history, neurological examination, and neuropsychological test battery of the workers, measures of workplace (and other potential) exposures, and procedures for estimating internal dose. The studies should include an appropriate control group as well as sufficient exposed workers for a dose–response analysis. Studies using animal models should focus on subtle neurotoxic effects after chronic low-level exposure and include procedures for assessing the effects of exposure on behavior, neuroanatomy, and neurochemistry. Procedures for examining the transient or permanent nature of the effects should be used. Studies of both adults and developing animals should be performed because the effects from developmental exposures may be different from those observed in adult animals.

This report provides an overview of studies that are available for the evaluation of the neurotoxic effects associated with chronic low-level exposure to gasoline and certain gasoline constituents. In general, the occupational studies of these compounds do not even meet the first criterion discussed above because most do not include measures of workplace exposures. For toluene, xylene, and methanol, studies of controlled laboratory exposures indicate neurologic effects near or below the current TLV. Although these effects may be transient, they can influence workplace safety. In addition, the long-term consequences of these effects have not been studied.

Little dose–response data are available from studies using animal models. Many of the studies examined only one dose level. Results from other studies sometimes provided data for determining a NOAEL but only for signs of overt neurotoxicity. In general, data for determining a NOAEL for more subtle neurotoxic effects (e.g., learning and memory) are not available. Finally, except for ethanol, none of the compounds has been studied extensively using a developmental approach.

A few general conclusions and recommendations can be made based on the results of the studies to date. *a*) All of the compounds reviewed are neuroactive and, as such, should be examined for their neurotoxicity. *b*) For most of the compounds, there is a substantial margin of safety between the current permissible exposure levels and levels that would be expected to cause overt signs of neurotoxicity in humans. This is not the case for xylene, toluene, and methanol, however, where neurologic effects are observed at or below the current TLV. *c*) For most of the compounds, the relationship between chronic low-level exposure and subtle neurotoxic effects has not been studied. Studies, therefore, should focus on examining the dose–response relationship between chronic low-level exposure and subtle changes in central nervous system function. *d*) Limited data are available concerning the neurotoxic effects associated with exposure to MTBE, ETBE, and TAME. The extensive use of MTBE in gasoline is a relatively new development. The use of ETBE and TAME remains low but is expected to rise. Additional studies of these compounds should be prioritized because they seem to represent the future for reformulated gasoline. *e*) Except for ethanol, few studies are available concerning the potential developmental neurotoxicity of the compounds. Further studies should be developed focusing on this issue. These studies should follow the guidelines recently published by the EPA for testing potential developmental neurotoxic compounds.

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