ALCOHOLS TOXICOLOGY

by

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IV. Methanol Toxicology

A. History of Methanol Poisoning

Methanol and ethanol are often confused by the lay public. It is a common practice to refer to ethanol or ethyl alcohol as just "alcohol" and is associated with the making of "alcoholic" beverages. However, methanol, commonly referred to as methyl alcohol or wood alcohol, is a deadly poison. Many of the cases of methanol poisoning were due to the connotation given to wood "alcohol", which implied to many that it was drinkable. This was especially true before the law required it to be labeled as a poison. It has been suggested that the IUPAC system (see II, Nomenclature) be used in naming alcohols in order to eliminate the word "alcohol" and thus reduce the confusion. Thus, "methanol" would be used instead of "methyl alcohol". Other alcohols, chiefly 1-propanol (isopropyl alcohol), suffer from the same misconception. The toxicity of methanol under industrial conditons was first noted by MacFarlan [4] in 1855 when he noticed the eye afflictions among cabinet makers, metal workers, and hatters using wood naphtha and methylated spirits in these occupations. Except for this, poisoning from methanol was virtually unknown prior to 1880. The only commercial source of methanol at that time was from the destructive distillation of wood. The disgusting odor and vile taste of this methanol were repugnant and thus rarely ingested. However, about 1890 a comparatively inexpensive method of "deodorizing" this crude methanol was introduced. It was packaged under various names, such as "Columbian Spirits", "Purified Wood Alcohol", "Colonial Spirits", etc. These products were widely and shrewdly advertised as having all sorts of virtues, including that of being an inexpensive and comparatively harmless substitute for ordinary ethanol. It could be used in making varnishes, liniments, tinctures, hair dyes, and as a fuel for lamps and stoves. In the beginning its poisonous character was denied completely, which led to it being used in the manufacture of Jamaica ginger, essence of lemon, alcoholic extracts, cheap whisky, and many proprietary "remedies".

In the years 1903-1904 when the sale of this ethanol substitute was in full swing, many deaths resulted. A concerned doctor (Dr. Frank Buller) took it upon himself to collect histories of death or blindness traced to the use of methanol, with undoubtedly many other cases escaping this inquiry [5] because many doctors either did not report cases in medical papers or failed to recognize methanol poisoning when occupationally related. Because methanol produces central nervous system depression, similar to ethanol, it is drunk by some derelicts whose poisonings are often not reported. Later tabulations indicated that between the years 1899 and 1913, there were almost one thousand cases of poisoning attributed to methanol. The results from some of the reported cases are shown in Table 3. [6, 7]

TABLE 3
METHANOL POISONING
1899-1913

	Total Cases	Deaths	Permanently Blind	Impairment Of Vision	Temporarily Blind
Ingestion	725	390	90	85	6-10
Inhalation	64	6	16	25	8
Inhalation [a]	60	(b)	(b)	(b)	(b)

(a) Additional cases heard before federal congressional committee

(b) Data not available

In late 1904, twenty persons were poisoned within a 24-hour period in Kentucky. Foreign countries that imported these products containing methanol also suffered similar misfortunes. For example, in the same year, twenty persons were killed and blinded in Dorpat, Russia, from its misuse. As the result of these "accidents", a campaign was waged by various U.S. newspapers and by the medical profession against the sale of these poisonous products. Resolutions were passed by the American Medical Association denouncing these products as substitutes for ethanol. A committee of manufacturers was formed to help in securing a cheaper ethanol for industrial purposes. After many discussions by various congressional committees and hearing much evidence, especially the testimonies from many workers blinded by using "Columbian Spirits" in their jobs, a bill was introduced and passed which resulted in "denatured alcohol". The denaturing process provides for adding various ingredients to ethanol that renders it unfit for human consumption and yet does not destroy its value for commerical use. This denatured ethanol was as inexpensive or more so than the dangerous "Columbian Spirits", and thus some of the dangers from the latter were alleviated. Even though the dangers of methanol and the many labels it was packaged under were widely publicized, it was not until 1923 when a group of dock workers in Hamburg, Germany were poisoned by its ingestion [7, 8] that the public finally realized that it was a poison. However, many other epidemics of methanol poisoning have occurred since that time, although less frequent. For example, in Atlanta, Georgia in 1953, 320 cases of acute methanol poisoning resulted in 41 deaths which occurred from drinking bootleg whiskey. During the years of World War II, servicemen often drank whatever alcohol that was available. It was estimated that six percent of all the nonfatal cases of blindness in the Armed Forces during this period was caused by methanol. The percentage would undoubtedly be increased if consideration had been given to the fatal cases. [7,9] In 1969, 18 persons were poisoned in Kentucky that resulted in six deaths when a relatively high methanol-containing product was substituted for the brand of shellac thinner regularly used in producing a "home"-derived cheap alcoholic beverage. Even today methanol poisoning is not uncommon.

B. Symptoms of Poisoning [10]

The symptoms of acute methanol poisoning usually occur 12 to 48 hours after it has been ingested, sometimes even sooner. The usual symptoms are visual disturbances, cerebral aberrations, severe acidosis, abdominal pain, nausea and vomiting, weakness, shortness of breath and dizziness. There is also a lowering of the CO_2 -combining power of the blood. The target areas of the body affected by the poisoning are the eyes, skin, central nervous system and the gastrointestinal system.[11] The amount necessary to cause serious damage varies greatly and will be discussed later (see below, C. Ingestion by Humans). It is usually after the start of severe acidosis that partial and complete losses of vision occur in victims. Retinal changes are characteristic of methanol poisoning and total bilateral blindness may develop after only a few hours or it may be delayed by several days. If observations are made on the victim at the onset of the visual disturbances, considerable retinal edema will be found and possible papillitis with swelling and dilation of veins. Some diminution of the pupillary light reflex will probably occur. Cases where patients have fixed and dilated pupils are usually fatal.[12] Up to 50% of the nonfatal cases have residual ocular defects. Death usually occurs as the result of the transient suspension of the taking in of air caused by the failure of the respiratory center. This failure is associated with severe damage to the central nervous system.

C. Ingestion by Humans

Of the three ways that humans are subjected to methanol poisoning (ingestion, inhalation, and subcutaneous absorption), direct ingestion is the quickest way to bring a response. Even so, this response is relatively slow in methanol when compared to ethanol. Methanol has a latent period on the average of over twelve hours. This delay is thought to be the time required for methanol to be metabolized to the more toxic formaldehyde and formic acid.[13] The amount of methanol necessary to cause serious damage varies greatly and depends on the individual and the circumstances under which the poisoning occurred.

A book on methanol technology [14] edited by Paul states that the usual fatal dose of methanol is said to be between 50 to 100 millliliters, although 25 to 50 milliliters can also be fatal if not treated immediately. There are others that have determined what they consider to be lethal doses. As can be seen in Table 4, the amounts varies among the different researchers.

TABLE 4
LETHAL DOSE OF METHANOL (HUMANS)

Researcher	(grams)	Reference
Puka	15-250	(15)
Moeschlin	30-100	(16)
Paul	39.5 - 79.5	(14)
Gleason	55-255	(17)

The quantity of food stuff in the gastro-intestinal tract and the nutritional status of the victim are important [18], however, the intake of food is less liable to interfere with methanol concentration in the blood than in the case with ethanol. Death has resulted after ingesting as little as 15 milliliters of a 40 percent methanol solution in one individual while another person survived after drinking over 33 times that amount. [19] Drinking of ethanol prior to or with methanol will usually lessen the poisonous effect. No record exists as to whether this occurred with the above mentioned individual who survived the large consumption but one would strongly expect that this might be the case. A chemical epidemiologic study of a methanol poisoning outbreak in Kentucky involving 18 people of whom 8 died indicated a correlation between severity of the poisoning and the level of ethanol in the body. Of the 26 people screened in the emergency room of the University of Kentucky Medical Center for suspected methanol poisoning, those that also had ethanol in their blood showed less acidosis than the group that had only methanol. Ethanol competes very effectively (metabolized in a competitive preferential ratio of approximately 9:1 to methanol) for the enzyme responsible for the conversion of methanol to formaldehyde and formic acid. [20, 21]

Many years ago, Roe [22] attributed the toxicity of methanol to the metabolites that were produced by its metabolism. Since that time no definitive proof has been brought forth. Formaldehyde has not been found in humans or other primates during methanol poisoning but some researchers feel that is because of its high reactivity. They think that it still may be responsible for some of the toxicity that methanol exhibits. Formate is known to accumulate during methanol poisoning and correlates well with the beginning of metabolic acidosis and the usual ocular toxicity. [23, 24]

D. Inhalation By Humans

Inhalation of the vapor of methanol causes irritation to the mucous membrane. It also may cause headache, vertigo, tinnitis (sounds in the ear), nausea, gastric disturbances, convulsive twitchings, oppression in the chest, visual disturbances, and even loss of vision. In severe cases of exposure, tracheitis, bronchitis and blepharospasm (uncontrollable winking) may take place.[18] Because of methanol's high volatility, the vapors can easily become highly concentrated in a confined space. When at high concentrations, the vapor causes violent inflammation of conjunctiva and epithelial defects on the cornea of the eye. [25]

The permissible exposure limit is 200 ppm (260 mg/m^3) and the IDLH (Immediately Dangerous to Life or Health) level is set at 25,000 ppm. It is impossible for a human to remain in an atmosphere containing 65 mg per liter of methanol for any prolonged time. [25]

In a study it was estimated that exposure to methanol vapor at about 3000 ppm for eight hours a day may cause methanol accumulation in the body and thus might constitute a toxic hazard. Since the two human subjects used to obtain the data were at rest during the experiments, vigorous activity stimulating respiration probably would have increased the rate of absorption and thus increased the hazard. [26]

McCord [27] stated that if it is permissible to apply results he obtained from his inhalation experiments with *monkeys* to that of an assumed average-sized man, then one ounce of methanol inhaled as vapors within a 41 hour period, but without constant exposure, constitutes a threat to his well being or even his life.

After methanol is inhaled, the main quantity goes into the blood, but a considerable amount is dissolved in the fluids of the mouth and distribution to the various organs of the body occurs quickly. The estimated tolerance values for methanol are shown in Table 5. [7]

TABLE 5
ESTIMATED TOLERANCE VALUES FOR METHANOL[a]

Duration	Estimated Tolerance Values (ppm)
Single but not repeated exposure	
1 hr	1,000
8 hr	500
24 hr	200
40 hr (b)	200
168 hr	50
30 days	10
60 days	5
90 days	3
Single or repeated exposures	
1 hour out of every 24 hours	500
Two 1-hour exposures every 24 hours or One 2-hour exposures every 24 hours	200

(a) Advisory Center on Toxicology, 1959.
(b) Based on five, 8-hour working days.

E. Cutaneous Absorption in Humans

Studies on human male subjects, using well devised experiments indicate methanol can be rapidly absorbed through the skin and cutaneous absorption can be a major route of methanol uptake in man. [28] Although exposure of the skin to methanol is quite tolerable, it has been known to cause irritation, eczema, and dermatitis. [29] Even a death has resulted when an infant had methanol packs applied to its chest.

Cutaneous exposure of human subjects to 15% methanol/petrol mixtures were found to be highly irritating to the skin while neat methanol was tolerable. It was suggested that absorption of methanol from its mixture with petrol is likely to be more irritating because of the de-fatting effect caused by the petroleum distillate. Because of the distillate's non-lipophilic nature, the permeability of the skin to methanol is probably enhanced. After a five-minute exposure to the 15% methanol/petrol mixture, alteration of the physical character of the epidermis was visible and the experiment had to be terminated. Inflammation of the skin remained for several days but no blistering occurred. (30A,30B) Synopses of these studies can be found in Appendix A in the two papers by Ferry, Temple, and McQueen. However, Tada (28) using urinary methanol concentrations concluded that cutaneous absorption could be a major route of methanol absorption in humans. He stated that toxicologically relevant amounts could be absorbed from relatively small areas of the skin in four hours if methanol was left in direct skin contact. A synopsis of Tada's study can also be found in Appendix A.

In many of the cases where toxic effects have been reported as the result of contact with methanol, the victims have also inhaled the vapors. For example, a painter went blind after accidentally spilling some methanol on his clothes and did not change them.(31) Although this indicates a considerable amount of methanol was absorbed through the skin, undoubtedly a large quantity was also inhaled.

The threshold of danger following skin absorption of methanol is approximately 0.5 cc/kg of body weight when applied four times daily. (27)

F. Animal Studies

1. Introduction and Overview

Study of the literature on methanol poisoning leaves the distinct impression that experimental investigations on nonprimates leave much to be desired in answering the many questions connected with human physiology. However, in most cases this is the only information that is available, since human experimentation is not very feasible. Nevertheless, some value can be obtained from animal studies but great care must be taken when drawing analogies with humans. Even studies with primates must be very carefully evaluated when applying this knowledge to man. It is in this context that the animal studies with methanol are discussed.

Methanol toxicity has been extensively studied using a variety of animals including mice, rats, frogs, rabbits, cats, dogs, and monkeys and has been the subject of many papers. McCord (27) in his studies with various animals demonstrated that sufficient quantities of methanol could be absorbed through the skin to cause death. Using a gas-tight cover to prevent inhalation exposure, he applied pads soaked with

methanol to the abdominal skin of monkeys, rabbits, and rats. All 29 of the experimental animals died and methanol was found in the tissues of all the animals. He found that methanol applied to the skin invariably led to damage similar to that found when ingested. He stated as evidence the optic atrophy observed clinically by ophthalmologists and the lipoidal degeneration noted after death of the animals. Methanol was regularly recovered via distillation from the organs of the skin-treated animals and was absent from the organs of the control animals.

Absorption rates of methanol in rabbits have been measured.[7,32] With methanol exposure of 12 to 30 minutes to the skin on the back of rabbits, an absorption rate of 0.015 ml/cm^2/hr was obtained. The rate decreased to 0.010 ml/cm^2/hr when the exposure time was increased to one hour.

Many of the more noteworthy studies are briefly outlined and arranged chronologically by experimental animals in Tables 6 to 12. Abstracts of some of these

TABLE 6
EFFECTS OF METHANOL ON MICE

Year	Principal Investigator	Means of Administering Dose	Approximate Dose Size	Summary of Facts	References
1927	Bachem	Inhalation	139,000 ppm	Lethal Dose	33
1928	Weese	Ingestion	10.5-12.00 cc	Death--Minimal fatal dose determination	34
		Inhalation	242,000-363,000 ppm	Death--Time duration 3.0-4.5 hrs. Minimal fatal dose determination	
		Inhalation	0.4-0.6 ml	Narcotic dose	
1936	Mashbitz	Inhalation	160,000 ppm	Deep narcosis in 94 min.	35
		Inhalation	100,000 ppm	Deep narcosis in 91 min.	
		Inhalation	90,000 ppm	Deep narcosis in 95 min.	
		Inhalation	76,000 ppm	Deep narcosis in 89 min.	
		Inhalation	60,000 ppm	Deep narcosis in 134 min.	
		Inhalation	46,000 ppm	Deep narcosis in 153 min.	
		Inhalation	30,000 ppm	Deep narcosis in 190 min.	
1943	Lehmann	Inhalation	42,000 ppm	Duration 7 hrs. Narcotic dose	25
1952	Gilger	Injection	Sufficient to cause acute toxicities	Experiments studies the effect of parentally administered substances on the systemic toxicity of methanol.	36
1978	McQueen	Inhalation	12,000 ppm	15% methanol in petrol alone. With either, there was normal exploratory behavior followed by increasing activity, then hyperactivity after 10 min., then gradual loss of coordination. See abstract or original paper.	37

TABLE 7
EFFECTS OF METHANOL ON RATS

Year	Principal Investigator	Means of Administering Dose	Approximate Dose Size	Summary of Facts	Reference
1910	Muller	Inhalation	50,000	1 hr; Drowsiness; Survived	38
1914	Loewy	Inhalation	2,000 -2,700 ppm	2-8 hrs. no effect	39
		Inhalation	4,300 -4,800 ppm	2-8 hrs. With prolonged exposure, moderate depression	
		Inhalation	8,300 -8,800	2-8 hrs; Moderate depression	
		Inhalation	22,500 ppm	2-8 hrs. No effect during first 2 hrs; later, progressive depression of central nervous system	
		Inhalation	60,000 ppm	Narcosis after 1 hr.	
		Inhalation	31,000 ppm	10.0 -20.0 hrs. Minimal fatal concentration determination.	
1920	Sollmann	Ingestion	5% in drinking H_2O	Considerable decrease in weight and finally death	40
		Ingestion	2-5% in drinking H_2O	Growth inhibited, more than with 10% ethanol	
1927	Bachem	Inhalation	176,000 ppm	Minimal fatal concentration determination	33
1929	Macht	Inhalation	Unspecified	Studied behavior in a maze - less severe depression of central nervous system than with ethanol.	41
1943	Lehmann	Inhalation	5,000 ppm	After 2-5 hrs., deep narcosis	25
1955	Gilger	Gavage	4.50 g/kg as 50% aqueous solution	Of 23 rats, 70% died. Blood samples indicated CO_2 capacities ranged from 47 to 80 volume % in samples. No acidosis seen.	42
1964	Tephly	Injection	0.05 -3.0 g/kg	Studied methanol metabolism in the rat. Concluded peroxidative system involving hepatic catalase plays a major role in the oxidation of methanol in the rat.	43
1964	Tephly	Injection ip	1.0 g/kg ^{14}C-Methanol	Oxidation rate of methanol was 24 mg/kg/hr for first 28 hrs. At end of 36 hrs, 77% of the methanol had been oxidized to ^{14}C- labeled CO_2 and 24% was excreted unchanged in the pulmonary & combined urinary and fecal routes.	43
1976	Makar	Ingestion	4g/kg	In a rate study, ^{14}C- methanol oxidation to $^{14}CO_2$, the latter was decreased to about 50% in rats fed a folate-deficient diet.	44
1979	Ferry	Dermal Contact	Cottonwool pad 32 cm^2 in area saturated 1 min. contact time	Either 15% methanol in petrol or neat methanol. In blood samples methanol levels with 15% methanol were 3 times higher than with neat methanol.	30

TABLE 8
EFFECTS OF METHANOL ON FROGS

Year	Principal Investigator	Means of Administering Dose	Approximate Dose Size	Summary of Facts	Reference
1933	Sammartino	Intravenous	5.3 cc	Death--minimal fatal dose determination	45
		Intravenous	Not specified	Clonic-tonic convulsions, opisthotonus, finally progressive paralysis	
1933	Bonnet	Contact	0.5-1.0% solution	Decreased but more often increase of chronaxy	46
		Contact	2.0%, 3%, 5%		
1934	Gradinesco	Contact	5.0% solution	Frequently caused first a decrease and later an increase of chronaxy (hyperexcitability), ending in inexcitability	47
		Contact	15-30% solution	Definite paralyzant effect but temporary since it could be reversed by lavage	

papers are also included in Appendix A. A more detailed account of the experimentation mentioned in the tables can be, of course, found in the original papers whose references are included in the tables. One will sometimes find a wide variation in results from one researcher to the next and this should probably be expected. For example, in inhalation experiments with animals, there are a variety of ways to vaporize methanol; there are differences in the methods of exposing the animals; there are variations in the age and health status of the animals; and there are variability of the analytical procedures for determining the actual concentration of methanol in the air breathed by the animals. In addition, the early researchers did not have the advantage of today's sophisticated instruments.

Animals such as mice, rats, dogs, and rabbits vary in their tolerance to methanol and in general can tolerate larger doses of methanol than humans.[78,79,80] For example, the lethal dose for rats is approximately nine times the equivalent dose in humans.[42] The rat is a methanol insensitive species as it does not accumulate formate after the administration of methanol. Monkeys are more susceptible to methanol vapors than guinea pigs, dogs, or rabbits; the latter being more resistant than most animals. Some of the differences in methanol poisoning between humans and nonprimates are listed in Table 13.

TABLE 9
EFFECTS OF METHANOL ON RABBITS

Year	Principal Investigator	Means of Administering Dose	Approximate Dose Size	Summary of Facts	Reference
1875	Dujardin-Beaumetz	Ingestion	8.8cc/kg	Death - mimimal fatal dose determination	48
1900	Birch-Hirschfeld	Ingestion	Not specified	Dilation and rigidity of pupils, absence of defense reflexes, inability to orient themselves in space. Autopsy found degenerative changes in the ganglionic cells of the retina.	49
1902	Friedenwald	Ingestion	Large amt.	Confirmed destructive effect on the ganglionic cells of the retina.	50
1912	Nicloux	Intravenous injection	16.1cc/kg	Death - minimal fatal dose determination	51
1913	Langgaard	Ingestion	14.0cc/kg	Death - minimal fatal dose determination	52
1914	Kasass	Ingestion	Toxic dose	Pathologic examination of 40 rabbits showed changes in the vascular membrane, in the membrane of the optic nerve, in the retina beginning with parenchymatous degenerated neuritis up to axial atrophy.	53
1915	Tyson	Inhalation	High concentration	Loss of consciousness, loss of pupillary reflexes, slight constriction of pupils, & death.	54
1922	Schwarzkopf	Stomach tube	Chronically poisoned	Retinal ganglion cell degeneration & occasional optic nerve degeneration but no definite clinical or ophthalmoscopic evidence of ocular damage	55
1925	Munch	Gavage	18ml/kg	Lethal dose	56
1926	Rost	Ingestion	13.0 cc/kg	Death - minimal fatal dose determination	57
1927	Bachem	Inhalation	176,000 ppm	Minimal fatal concentration determination	33
1937	Lehmann	Intravenous	10.5g/kg	Anesthetic dose (approximately ½ that of ethanol)	58
1937	Lehmann	Intravenous	20.1cc/kg	Death - minimal fatal dose determination	58
1955	Gilger	Ingestion	21 g/kg as 30% aqueous solution	All three rabbits died between 1 and 3 days. Acidosis studies were ambiguous.	42
			3.5g/kg as 50% solution	This rabbit died in less than 24 hrs. after given dose.	
1957	Renkonen	Intracutaneous Intracutaneous	10 mg 35 mg	No skin reaction 9-sq mm skin reaction occurred	59

TABLE 10
EFFECTS OF METHANOL ON CATS

Year	Principal Investigator	Means of Administering Dose	Approximate Dose Size	Summary of Facts	Reference
1920	Macht	Intravenous	5.9cc/kg	Death - minimal fatal dose determination	60
1931	Witte	Inhalation	290,000 ppm	3.5 hrs. minimal fatal concentration determination	18, 61
1931	Witte	Inhalation	20,000 ppm	Tolerated without after effect	18, 61
			37,000 ppm	After 3-4 hrs, staggering. 1 cat recovered, 1 died after 2 weeks with marked loss of fat	
			74,000 ppm	After 4.5 hrs, toleration of side position. 1 Animal recovered, 1 died on 3rd day, showing hyperemia of abdominal organs	
			160,000 ppm	After 2.5 hrs, toleration of side position, after 5.5 hrs deep narcosis; after 6 to 5 hrs. clonic convulsions. Death after some days.	
			130,000 ppm	Less than 6 hrs. Only moderate narcosis	
1952	Gilger	Intraperitoneal	10.0g/kg	Usually lethal within 4 days after injection.	36

D'Eliscu studied the effects of methanol spills and methanol fuel emission on both terrestrial and freshwater organisms. (80B) The effects appeared to be minimal and short in duration. He found many organisms are tolerant at low concentrations. (80C) Concentrations of approximately one percent methanol in sea water or freshwater are tolerated by many common members of intertidal, mud-flat, estuarine, and limnetic ecosystems as long as heavy metals are not present. Using statistical analysis on the effects of methanol toxicity on "keystone" organisms which regulate the habitats, he found indications that very few situations exist where methanol would cause permanent or long term disruptions. (80D) More details on the tolerance and physiological impact of methanol in aquatic marine and freshwater habitats can be found in the synposes of D'Eliscu's papers in Appendix A.

2. Toxic Effects[82]

Many studies of methanol toxicity in animals were conducted at the beginning of the century during the period when human occupational poisonings were frequent. Most investigations showed that the toxicity of methanol in animals adhered to Richardson's rule [18] which states that "in a homologous series of alcohols, toxicity increases as the number of carbons atoms increases." Thus, in comparative studies of ethanol and methanol, ethanol was found to be more toxic than methanol. Hunt[87], for example, reported that experimental animals died earlier after administration of ethanol than after equal doses of methanol. According to Schieck[83], Loewy and van der Heide

TABLE 11
EFFECTS OF METHANOL ON DOGS

Year	Principal Investigator	Means of Adminstering Dose	Approximate Dose Size	Summary of Facts	Reference
1896	Jeffray	Inhalation	Not specified	Motor & sensory disturbance & changes in the body temperature and respiration.	62
1899	Holden	Ingestion	50cc + 50cc 2 doses, 5 days apart	Second day after last dose temporary blindness which later gradually subsided. Eighth day a diffuse turbidity of the cornea developed without signs of congestion. Autopsy revealed extensive degenerative changes of ganglionic cells of the retina and destruction of some medullary sheaths of fibers of the optic nerve.	63
1914	Loewy	Inhalation	10,000-14,000 ppm 1,500 -2,000 ppm	Time duration: 2.0 -4.0 hrs. No effect Time duration: 24 hours No effect	39
1914	Tyson	Inhalation	High methanol concentration	Four exposures over 1 month. Reduction of body temperature and a primary stimulation and subsequent depression. Died after fourth exposure.	64
1921	Haskell	Ingestion	8.0cc/kg	Death - minimal fatal dose determination	65
1923	de Schweinitz	Ingestion	Chronically poisoned	Oral doses given every 2 to 3 days for 9 to 80 days. Dogs showed marked intoxication but gave no indication of defective vision. No retinal ganglion cell degeneration found.	66
1934	Gradinesco	Intravenous	1cc/kg	Increase of the respiratory amplitude	67
		Intravenous	10cc/kg	Severe depression	
1942	Sayers	Inhalation	450-500 ppm	8 hrs/day for 379 days. No significant toxic effect, no unusual behavior, no impairment of vision, no loss of weight.	68
1955	Gilger	Ingestion	2.5g to 9.0g/kg	Seven dogs survived: One dog (4.0g/kg) died between 29 & 46 hrs. after administration One dog (9.0g/kg) died between 28-42 hrs. Highest non-lethal dose was 8.0g/kg This dog had largest decrease in CO_2 combing capacity. CO_2 capacities dropped below the normal range (42-56 vol%) in only 2 of 9 treated dogs and returned to normal 55 hrs. later.	

TABLE 12
EFFECTS OF METHANOL ON MONKEYS

Year	Principal Investigator	Means of Administering Dose	Approximate Dose Size	Summary of Facts	Reference
1915	Tyson	Inhalation	high conc.	Loss of consciousness, loss of pupillary reflexes, slight constriction of pupils & death.	54
1931	McCord	Skin absorption	0.5 cc/kg x4	Lowest lethal dose. After 4th application, death within 24 hrs.	27
		Skin absorption	1.3 mg/kg x4	Desperate illness occurs by end of day, death following day.	
		Skin absorption	1.3 mg/kg x1	Dilated pupils within 1 hr.	
		Inhalation	1000 ppm	Lethal after a few 18 hr exposures.	
1935	Gilger	Ingestion	3g/kg	Minimal lethal dose	42
1955	Gilger	Ingestion	1.0 g/kg	Survived. Did not become acidotic	42
			2.0 g/kg	Survived. Severly acidotic - CO_2 combining capacity returned to normal in 21 days.	
			3.0 g/kg	Died 32-38 hrs - severly acidotic	
			4.0 g/kg	Died 29-36 hrs - severly acidotic	
			6.0 g/kg	Died at 29 hrs - severly acidotic	
			8.0 g/kg	Died between 6-23 hrs.	
1961	Cooper	Ingestion	7g/kg	Minimal lethal dose	69
1968	Makar	Injection ip	0.5g/kg of ^{14}C- methanol w/equimolar amts. of ethanol	Ethanol reduced the oxidation of methanol 90%	70
1968	Makar	Injection ip	6g/kg ^{14}C-methanol	^{14}C- methanol was oxidized at rate of 47 mg/kg/hr. between 1st & 4th hrs., 49% of methanol was oxidized to 14-C CO_2, 35% removed by pulmonary 16% elimated unchanged by kidneys.	70
			1g/kg of	^{14}C- methanol was oxidized at rate of 37 mg/kg/hr between 1st and 4th hrs.	
1975	McMartin	Nasogastic tube	3g/kg of 20% (w/v)	Studied role of formic acid in development of metabolic acidosis in monkey & reversal with 4-methyl pyrazole	24
1977	Baumbach	Oral	Sufficient to be non-lethal but cause acidotic state	Studied the alteration of the ocular morphological findings produced by methanol with light & electron microscopy. light & electron microscopy.	71
1977	Hayreh	Ingestion	2g/kg and subsequent doses to maintain attenuated & prolonged intoxication	In all 6 monkeys, fundus change developed within 43 to 171 hrs after ingestion. The only fundus lesion seen was optic disc edema and associated changes.	72

TABLE 12 (Cont'd)

Year	Principal Investigator	Means of Administering Dose	Approximate Dose Size	Summary of Fact	Reference
1977	Martin-Amat	Ingestion	2g/kg and subsequent doses to maintain attenuated & prolonged intoxication	Metabolic acidosis developed concurrently with increasing formic acid concentration. A mechanism to explain toxicity is proposed.	23
1977	McMartin	Cannula		Results suggest that folate-dependent pathway is the major route of formate metabolism in the monkey	73
1978	Martin-Amat	Intravenous infusion		Infusion at rate calculated to produce formate concentration similar to those seen in methanol-intoxicated monkeys in which ocular toxicity was produced. Results similar to that of methanol poisoning.	74
1979	McMartin	Nasogastic tube	2g/kg	Comparison of effects on folate-deficient monkey and untreated control monkey suggest formaldehyde is not a major factor in the toxic syndrome. The predominant role of formic acid is certified.	75
1979	Blomstrand	Ingestion	3-4g/kg	Monkeys were allowed to develop signs of methanol toxicity. Within a few hours after the injection of 4-methyl-pyrazole signs of recovery from toxic syndrome were noted. They were alert, strong, competitive & hungry.	76
1980	Noker	Nasogastic tube	2g/kg of 20% w/v ^{14}C methanol in water	Studied role of folates in methanol toxicity	77

showed that ethanol is much more toxic than methanol in mice and dogs and the same was shown by Hammersten in rabbits. In rabbits and dogs, the lethal oral dose of methanol was reported to be about twice that of ethanol.[84] By intravenous injection, the relative toxicities of methanol, ethanol, propanol and butanol were reported by Baer in 1898 as 0.8, 1.0, 2.0 and 3.0, respectively.[85] In man, however, the toxicity of methanol is an exception to Richardson's rule and even one gram per kilogram of body weight or less can produce blindness or even death.[78]

The symptoms produced by methanol in most experimental animals are rather uniform and are similar to the general anesthetic effects observed after administration of ethanol and other alcohols of this series.[82] Although animals differ in their tolerance to methanol, most laboratory animals tolerate high doses of this alcohol. In mice, the symptoms produced by various doses are as follows[86]: after 4g/kg of body weight, slight ataxia of less than one hour duration; after 5.5 g/kg, more pronounced

TABLE 13
METHANOL POISONING[42,81]

HUMANS VS. NONPRIMATES

	Humans	Nonprimates
Lethal Dose	0.85 -1.4 g/kg in humans	6 to 10 times the equivalent human dose in rodents and dogs (3 times the equivalent human dose in monkeys)
Symptoms Intoxication	Less early intoxication followed by symptomless latent period, then sickness and death.	Severe and early intoxication with narcosis, lasting until death. Narcosis is predominant symptom
Eye changes	In many cases, partial or complete blindness accompanied by eye ground changes such as hyperemia of the optic discs and venous engorgement.	Early pupillary changes and corneal opacification following exposure keratitis. Eyeground changes not seen in non-primates
Acidosis	Often severe acidosis (CO_2 - combining capacity less than 20 vol.%)	Rarely occurring and only at near lethal or lethal doses
Treatment	Treatment with sodium bicarbonate to control acidosis and ethanol to inhibit oxidation rate.	Treatment with sodium bicarbonate and ethanol useless.
Metabolism	Dehydrogenation of methanol catalyzed by the enzyme alcohol dehydrogenase (ADH)	Catalase - peroxidase system

ataxia and slight anesthesia in some animals; after 7.5 g/kg, slight to deep anesthesia; and after 10 g/kg, deep anesthesia within a few minutes after administration. Some deaths occur from this dose range of 4 to 10 g/kg but, in surviving animals, activity is practically normal within 48 hours. In rabbits, 3 ml/kg produces practically no effects. After 7 ml/kg or more, these animals exhibit almost immediate ataxia, loss of fighting reflexes and coma.

In 1955, a comparative study of methanol was conducted in rats, rabbits, dogs and rhesus monkeys by Gilger and Potts.[42] Administration of methanol was accomplished by gavage except for some of the experiments with rabbits in which administration was by the intravenous route. In rats, methanol at a dose of 4.75 g/kg resulted in an approximately 70% lethality rate. In rabbits, oral administration of doses of either 2.1 g/kg or 3.5 g/kg caused death within three days. In neither the rats nor the rabbits, did

analyses of CO_2-combining capacity of blood demonstrate an acidotic condition nor did ophthalmic examinations reveal any alterations or damage to the eye. In this same study, methanol was administered orally in doses ranging from 2.5 g/kg to 9.0 g/kg to nine dogs. The two animals that received 4.0 g/kg and 9.0 g/kg died between 28 and 46 hours after administration and the remaining animals survived. Eight grams per kilogram (8.0 g/kg) was the highest nonlethal dose. In only two of the nine treated dogs were CO_2- combining capacities below normal range, and in none of the animals were ophthalmoscopic changes detected.

The effects in rats, rabbits and dogs are in contrast to those observed when methanol was administered to rhesus monkeys.(42) Monkeys which received 1.0 and 2.0 g/kg respectively of methanol survived, while the four animals which received 3.0, 4.0, 6.0 and 8.0 g/kg, respectively, died between 6 and 29 hours following administration of the dose. Of these six animals, the monkey which received the lowest dose did not become acidotic and the one which received the highest dose died before the CO_2" combining capacity was determined. All of the remaining monkeys became severely acidotic. Two of the six animals exhibited ophthalmoscopic abnormalities consisting of retinal hemorrhage in one animal and bleeding of the disc, venous engorgement and possible hyperemia of the disc in the other.

From the results of their studies and those of other investigators, Gilger and Potts determined that only primates showed similarities in their response to methanol poisoning.(42) Although the series of experiments they conducted with monkeys were too small to get accurate toxicity data, they found the single oral lethal doses to be in the same order of magnitude as those for humans (0.85 - 1.4g/kg). They found the approximate single oral lethal doses in the following experimental animals to be as indicated: (42)

Animal	Times Mean Human Lethal Dose
Monkeys	3
Rabbits	7
Dogs	9
Rats	9

3. Mechanism of Action(82)

Considerable animal experimentation has been conducted in an effort to determine the mechanism of the toxic syndrome produced by methanol. In humans, this syndrome is characterized by a latent period of 12 to 24 hours, followed by metabolic acidosis, ocular toxicity, coma and death.(75, 82)

Selection of an appropriate animal model for the toxic syndrome observed in man has been a major difficulty in elucidating the mechanism of human methanol toxicity.

Early studies of methanol toxicity were conducted with mice, rats, rabbits and dogs. These species did not exhibit the typical clinical syndrome observed in human poisoning cases, particularly the severe acidosis and visual disturbances.[82] After conducting a comparative study of methanol toxicity in rats, rabbits, dogs, and rhesus monkeys, Gilger and his colleagues[88,89] concluded that the responses of primates more closely approximated human responses than did those of nonprimates and proposed the rhesus monkey as a model for methanol toxicity. However, in 1961, Cooper and Fertig[90] reported a study in which they administered methanol orally to 12 rhesus monkeys and were unable to confirm the results of Gilger and Potts.[42] Unlike Gilger and Potts who found lethality in monkeys at doses as low as 3 g/kg, Copper and Fertig reported that all monkeys which recieved doses of methanol of 6 g/kg or less survived. From the data they determined the LD_{50} to be approximately 7 to 9 g/kg. They found only one monkey where blindness was observed and this occurred transiently and at four days after a dose of 9 g/kg of methanol. The consistent features of methanol toxicity were not observed in this study, except for a central nervous system depression, similar to that observed in nonprimates. From their results they suggested that the monkey was an animal model intermediate between humans and nonprimates.

Despite the conflicting results reported by Cooper and Fertig[90], a number of more recent studies have confirmed the results of Gilger and Potts[42] and established that various strains and species of monkeys are an appropriate experimental model for methanol intoxication in the human.[23,24,71,72,73,91] In sufficient dosage, methanol produces in monkeys a syndrome that is characterized by a latent period of 8 to 12 hours and the development of metabolic acidosis, ocular toxicity, coma and death.[23,24,71,72]

Results of biochemical studies have provided evidence that differences in methyl alcohol toxicity between nonprimates and primates, including man, are due to differences in the enzymatic metabolism of this alcohol. In both nonprimates and primates, methanol undergoes enzyme-catalyzed oxidation to formaldehyde which is then rapidly oxidized to formic acid. The formic acid, in turn, is converted to carbon dioxide or eliminated in the urine. Although the same metabolic products are formed in nonprimates and primates, there is evidence that the enzymatic pathways of metabolism are different in the two groups of animals. In 1964, Tephly et al.[43] conducted a study in which the simultaneous administration of ethanol with methanol resulted in a 90% decrease of methanol oxidation in monkeys but only a 50% decrease in rats. Since previous in vitro studies indicated that catalase-peroxidase had an equal affinity for methanol and ethanol whereas the affinity of alcohol dehydrogense (ADH) was 10-50 times greater for ethanol than for methanol, these investigators concluded that the catalase-peroxidase system was primarily responsible for methanol metabolism in rats and other nonprimates. Makar et al.[70] also examined the inhibition of methanol metabolism in the rat and monkey, but after administration of 3-amino-1,2,4-triazole (AT), an inhibitor of catalase. This inhibitor did not affect methanol

metabolism in the monkey but reduced the metabolism of this alcohol in rats by 50%. The results indicated to these authors that the catalase-peroxidase system was important in the oxidation of methanol in the rat but did not play a significant role in the monkey. Evidence that methanol is primarily metabolized by ADH in primates was provided by the study of Clay et al.[91] who reported that administration of 4-methyl- that various strains and species of monkeys are an appropriate experimental model for pyrazole, which is a specific inhibitor of hepatic ADH, prevented metabolic acidosis and other signs of methanol toxicity in the pigtail monkey.

During the past few years, studies of methanol in rats and, particularly in monkeys, have resulted in substantial progress in our understanding of the metabolism of this alcohol. It is now accepted that the initial oxidation of methanol to formaldehyde is catalyzed by ADH in primates and by a catalase-peroxidase system in nonprimates.[92] Formaldehyde, in turn, is oxidized to formic acid in a reaction mediated by formaldehyde dehydrogenase. Formic acid is either eliminated in the urine or oxidized to carbon dioxide and water by a folate-dependent on carbon system, or to a limited degree, by catalase-peroxidases. Despite this progress in understanding the metabolism of methanol, controversy still exists as to the mechanism of toxicity of methanol in primates, including man, and as to the differences in toxicity produced by this alcohol in primates and non-primates.

The ocular toxicity produced by methanol in primates has been attributed by some investigators to the formation of formaldehyde and, by others, to the formation of formic acid. Potts and his coworkers, who proposed the rhesus monkey as a model for methanol toxicity, suggested that the effects of methanol were related to the generation of formaldehyde.[89] This view was also held by Cooper and Kimi[10] who concluded from the results of in vitro experiments and studies with rabbits that formaldehyde does more damage to retinal cells than methanol or formic acid. These authors postulated that blindness occurs in victims of methyl alcohol poisoning because formaldehyde is formed directly in retinal cells and inhibits the formation of adenosine-5'-triphosphate (ATP) in these cells. However, direct evidence that formaldehyde is the toxic agent in methanol poisoning is not available. In a recent study, McMartin et al.[75] reported that formaldehyde could not be detected in the urine, cerebrospinal fluid, vitreous humor, liver, kidney, optic nerve and brain in monkeys at a time when marked metabolic acidosis and other characteristics of methanol poisoning were observed. Even in a folate-deficient monkey, which is especially susceptible to the effects of methanol, McMartin and his coworkers[73] did not detect formaldehyde in either body fluids or tissues after methanol administration. According to the authors, the results suggest that formaldehyde is not a major factor in the toxic syndrome produced by methanol although it is not possible to completely eliminate this chemical as a toxic intermediate. Formaldehyde could be formed slowly within cells and interfere with normal cellular function without ever reaching levels that are detectable in body fluids or tissues.

In contrast, considerable evidence has accumulated that supports the role of formic acid as the toxic agent in methanol poisoning. McMartin et al.[24] and Clay et al.[91] have shown that the accumulation of formic acid coincides with the metabolic acidosis and other toxic effects resulting from methanol administration to the monkey.

Additional evidence that formic acid is responsible for the toxic effects of methanol has been provided by other studies in which the production or metabolism of formic acid has been altered in the rat and monkey. In both species, a folate-dependent one carbon system is involved in the oxidation of formate to carbon dioxide[73,93] and methanol toxicity can be altered by manipulation of the folate status of the animal. Makar and Tephly[94] reported that rats made folate deficient by maintenance on an folate-deficient diet not only metabolize formate at a reduced rate but also accummulate formate and develop metabolic acidosis following methyl alcohol administration. In monkeys, McMartin et al. [23] have shown that the toxic syndrome of methanol is greatly intensified during states of folate deficiency. Studies in other species, notably the dog, have confirmed that when folate deficiency is induced, an increased susceptibility to methanol is exhibited.[95] Most recently, Noker and Tephly[77] reported that, after administration of methanol to monkeys, stimulation of formate metabolism by repetitive doses of 5-formyltetrahydrofolic acid or folic acid resulted in a marked decrease in blood formate accumulation and absences of metabolic acidosis and blood bicarbonate depletion. Also, methanol toxicity, once established in the animal, was reversed by 5-formyltetrahydrofolic acid administration. Although these studies provide evidence that formic acid is a major determinant of methanol toxicity, the results of the studies by McMartin et al.[24] suggest that this chemical is not the only determinant. These investigators reported that, in their studies with monkeys, insufficient formic acid was generated to account for the metabolic acidosis produced by methanol and, therefore, other organic anions may also be involved.

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