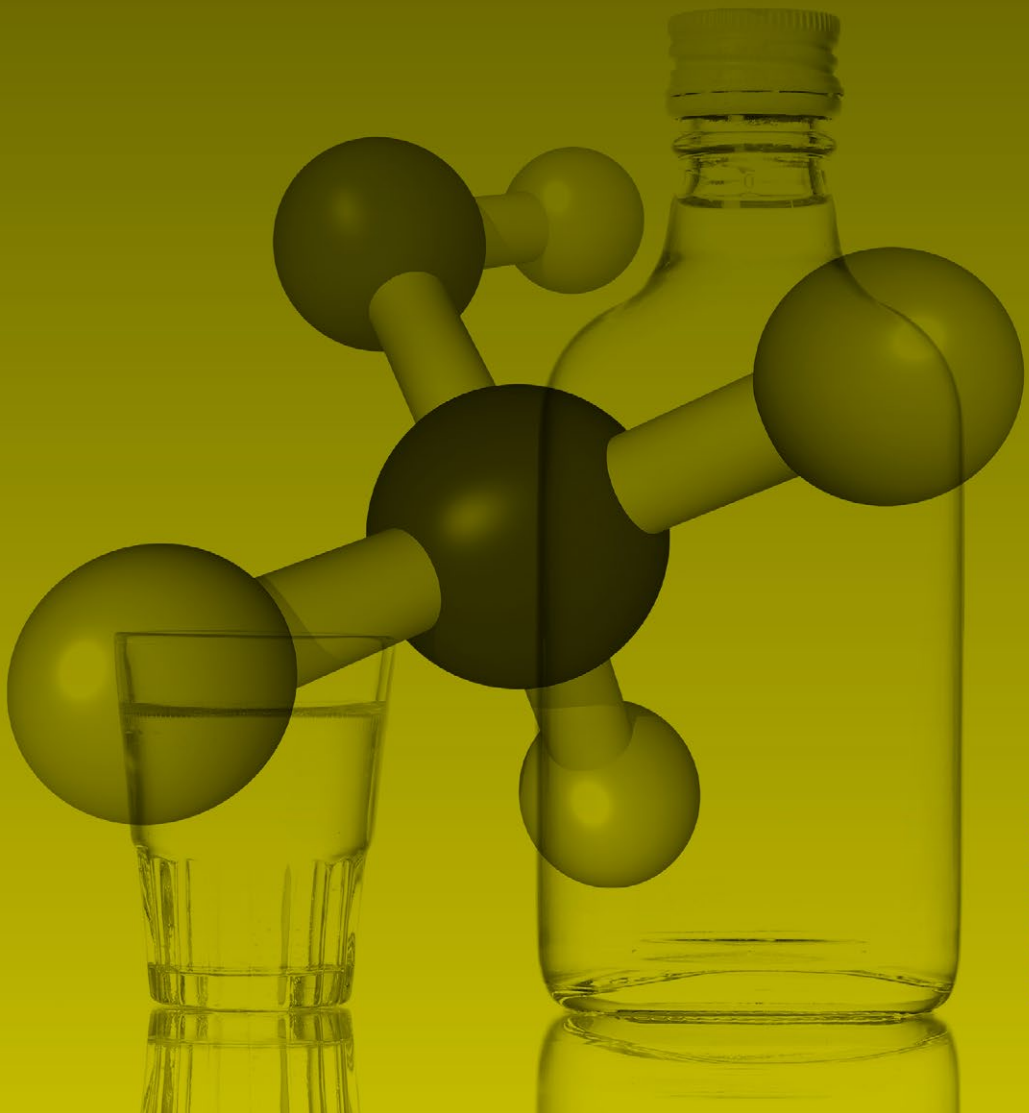
SERGEJ ZACHAROV

CHALLENGES OF MASS METHANOL POISONING OUTBREAKS

DIAGNOSIS, TREATMENT, AND PROGNOSIS OF LONG-TERM HEALTH SEQUELAE



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Challenges of mass methanol poisoning outbreaks
Diagnosis, treatment, and prognosis
of long-term health sequelae

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/1/ Introduction

Mass or cluster methanol poisoning outbreaks represent a real challenge for national health systems throughout the world for more than one hundred years. Despite effective treatment measures mortality may exceed 40% and permanent health sequelae may occur in up to 25–33% of patients. In September 2012, the Czech mass methanol poisoning outbreak occurred with more than 120 patients admitted to hospitals throughout the country and more than 40 deaths, representing one of the largest methanol "epidemics" in the world in the XXI century.

During the outbreak of mass methanol poisonings as a result of its use as a cheap substitute for ethanol in adulterated strong alcoholic drinks the national health system faced a number of challenges: delayed presentation and diagnosis, non-specific clinical signs and features at admission, need for gas chromatography method to detect methanol, limited availability of treatment resources in local hospitals (antidote fomepizole, sterile solution of ethanol, hemodialysis facilities, intensive care unit (ICU) beds) requiring triage of patients and modified treatment protocols, insufficient evidence of clinical effectiveness and safety of out-of-hospital and hospital therapeutic measures,

complications during the treatment, high mortality rate and prevalence of long-term health damage in the survivors.

In spite of the fact that mass or cluster methanol poisonings occur rather frequently globally, mainly in the developing countries, studies of larger outbreaks where complete clinical and laboratory data, medical treatment protocols, and outcomes are accurately documented and analyzed are scarce. In this monograph, we discuss the issues of diagnostic and prognostic value of serum formate concentration, the role of out-of-hospital ethanol administration as an early therapeutic intervention, and the pitfalls of hospital treatment with ethanol as an antidote. We analyze the results of the Czech experience with application of fomepizole in a mass methanol outbreak, the antidote included by WHO in 2014 to the Essential Medicines List, and propose the antidote-saving strategy for situations with limited stockpiles of fomepizole during mass poisoning outbreaks. We present the comparative data of clinical effectiveness and safety profile of both antidotes.

Extracorporeal elimination techniques are widely applied in the treatment of methanol-poisoned patients and a thorough evaluation of the effectiveness and limitations of various modalities of treatment is necessary. We present the data on elimination half-lives of both serum methanol and formic acid on intermittent and continuous modalities of hemodialysis and provide recommendations regarding a dialysis session of minimal duration for both modalities.

The prevalence of long-term visual and central nervous system (CNS) damage in the survivors of outbreaks of mass methanol poisoning is not known and may be underestimated due to the absence of prospective studies with adequate clinical examination protocol. In the monograph, the data are presented from the follow-up clinical study performed to determine the prevalence, character, and dynamics of long-term visual and CNS sequelae in the population of survivors of a mass methanol poisoning outbreak. We demonstrate the associations of health sequelae with key biochemical and toxicological parameters and treatment modalities applied in hospitals. Finally, we discuss the issue of the dynamics of long-term visual sequelae of methanol-induced optic neuropathy and outline the directions for further research.

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History of Methanol Mass Poisoning Outbreaks

Methanol was first isolated in 1661 by Irish chemist Robert Boyle through distillation of boxwood (Boyle, 1661). In 1855, MacFarlan proposed that a mixture of one part of impure methanol to nine parts of ethanol would constitute a cheap substitute for the use of ethyl alcohol in manufacturing processes (MacFarlan, 1855). According to Wood (1906), no more than three cases of serious poisoning had been known until 1904 because of the "nauseous taste and vile odor" of "wood naphtha." The process of purification developed in the late XIX century improved the organoleptic qualities of methanol and led to its wide use as a substitute for grain ethanol not only in different manufacturing goods (liniments, domestic toiletries, patent medicines, essences, perfumes, etc.), but in adulterated whiskey and other alcoholic drinks (Wood, 1906). Ziegler (1921) reported that as late as 1910, many wines, brandies and whiskeys sold on New York's East Side contained methyl alcohol in proportions ranging from 24 to 43 percent. Occasional instances of poisoning after ingestion were attributed to contaminants and impurities, but not to methanol as such (Røe, 1946).

In 1904 and 1905, Buller and Wood reported on 314 cases of methyl alcohol intoxication, with 158 cases of blindness and 156 cases of death (Buller & Wood, 1904). Later, in 1911 in Germany, 163 cases of poisoning with 72 deaths occurred in Berlin during the week of Christmas (Pincus, 1912; Stadelmann & Magnus-Levy, 1912). Before, during, and immediately after World War I, cases of mass or cluster poisoning occurred in Russia, Germany, Hungary, Poland and other countries (Røe, 1946). Nevertheless, the results of many early animal experiments were inconsistent or, at least, subject to more than one interpretation, and it was not until Reif demonstrated in 1923 that a group of dock-workers in Hamburg had been poisoned by chemically pure methanol that the toxicity of "wood alcohol" became generally accepted as a fact (Bennett, 1953; Reif, 1923). However, doubts regarding toxicity of methanol were still voiced as late as 1936 (Røe, 1946).

Despite known toxicity of methanol, the "epidemics" of mass or cluster poisonings were not rare events even later in the XX century. In the United States during Prohibition, when the use of ethyl alcohol as a beverage was illegal and substitutes were sought, 400 fatalities were recorded during one 7-month period (Cooper & Kini, 1962). According to Potts & Johnson (1952), up to 6% of all cases of blindness in the U.S. Armed Forces during World War II were a result of methanol poisoning. The cluster poisonings commonly occurred in the circumstances of economic hardship or military mobilization (Jacobsen et al., 1945; Kaplan & Levreault, 1945; Pronnie et al., 1946). Methanol-containing liquids (shellac thinners, solvents, and others) were used as cheap intoxicants or as temporary alternatives when ethanol was not available, and poisonings occurred when higher than expected proportions of methyl to ethyl alcohol were used in these liquids due to unexpected technological changes and other reasons (Kane et al., 1968; Keyvan-Larijarni & Tannenberg, 1974; Swartz et al., 1981).

Methanol poisoning outbreaks have been reported throughout the world in groups of people who ingested antifreeze, mixtures of inflammable liquids, duplicating fluids, or adulterated vodka, whiskey, sake, rum, and other alcoholic beverages (Branch et al., 1945; Chew et al., 1946; Divekar et al., 1974; Jacobson et al., 1945; Keeney & Mellinkoff, 1951; Krishnamurthy et al., 1968; Naraqi et al., 1979; Sejersted et al., 1981; Tonning et al., 1956; Tonkabony et al., 1975). As an example of a major poisoning outbreak in a developed country caused by adulterated alcohol, the mass poisoning accident, or "catastrophe," in Atlanta, Georgia, USA, can be mentioned, where on October 20, 1951, a large quantity of bootleg whiskey containing 35 percent methyl alcohol and 15 percent ethyl alcohol was distributed and during the subsequent seven days affected 323 individuals, of whom 41 died (Bennett et al., 1953; Benton et al., 1953).

At the present time, most mass or cluster methanol poisoning outbreaks occur in the developing countries, where methanol is used as a cheap adulterant of illicit liquors. Many reports are from India (Bade & Sapre,1981; Dilip

et al., 2013; Mittal et al., 1991; Mohan et al., 2001; Ravichandran et al., 1984; Saxena, 1999; Shah et al., 2012), Bangladesh (Chowdhury et al., 2014), Turkey (Azmak, 2006; Duman et al., 2003; Gülmen et al., 2006; Kalkan et al., 2003; Karadeniz & Birincioglu, 2011; Unsal et al., 2012; Yaycia et al., 2003), Iran (Hassanian-Moghaddam et al., 2015a; 2015b; Massoumi et al., 2012; Moghadami et al., 2008), Indonesia (Giovanetti, 2013; Koehrer et al., 2011), Jordan (Abdallat et al., 2009), Kenya (Ahmad, 2000), Libya (Ben Taleb & Bahelah, 2014), Tunisia (Brahmi et al., 2007), Sudan (Abdul Rahim & Al Shiekh, 2012), and other countries from the Asian and African regions.

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Overview of Methanol Mass Poisoning Outbreaks in Estonia (2001) and Norway (2002–2004)

During 2000–2012, more than 50 methanol mass poisoning outbreaks with about 5000 poisoned subjects and more than 2000 fatalities had occurred worldwide (Zhang et al., 2012). Most of the events occurred in the developing countries, where the resources were limited and the epidemiological, laboratory and clinical data were insufficient for an adequate analysis. Nevertheless, recent mass methanol poisoning outbreaks in Estonia with more than 150 cases of poisoning (Paasma et al., 2007; Paasma, 2013), in Norway with more than 50 cases (Hovda et al., 2005c), and in the Czech Republic with more than 120 cases (Zakharov et al., 2014d) provide clear evidence of this public health emergency for the health systems of developed European countries as well.

Information on the Estonian methanol mass poisoning outbreak is cited from the studies of Paasma et al. (2007, 2009, 2012, and 2013). In September 2001, a large outbreak of methanol poisoning occurred in the western part of Estonia. Over the course of nine days, from September 9th to 17th, more than 100 patients were hospitalized, and more than 60 died from methanol poisoning. Illegal spirits containing 50–100% of methanol in strong alcoholic beverages with an alcohol content of around 40% alcohol by volume (ABV)

were sold and consumed in the Pärnu region of the country. The methanol was mostly diluted with water, but ethanol was also used in a few cases.

A total of 141 patients were admitted to the local hospital in Pärnu, and six patients were admitted to other hospitals. Of these 147 patients, 36 did not have detectable serum methanol levels upon admission, leaving a total of 111 hospitalized patients with confirmed methanol exposure. During this outbreak, there were 68 fatalities: 25 in hospitals and 43 outside of hospitals. Thus, a total of 154 patients had confirmed methanol poisoning.

The most common clinical signs and symptoms upon admission were gastrointestinal disturbances (49%), visual disturbances (37%), and dyspnea (20%). Among the patients, 96 (87%) were administered ethanol as an antidote (fomepizole was not available in Estonia during the outbreak), 94 (85%) were administered bicarbonate as a buffer to correct acidosis, 79 (71%) were dialyzed, and 68 (61%) were intubated and mechanically ventilated.

The outcomes for hospitalized patients were the following: 66 (60%) patients survived without sequelae, 20 (18%) patients survived with visual and / or nervous system sequelae, and 25 (22%) patients died. The overall mortality was 44%, mainly due to the high number of patients who died before admission to the hospital.

The main challenges facing the health system during the methanol poisoning outbreak in Estonia were the lack of diagnostic tools in Pärnu hospital (blood samples were transported to the capital city Tallinn and the results of serum methanol measurement were available mostly 24–72 hours after admission) and of the therapeutic equipment (small number of intensive care beds in Pärnu hospital, insufficient number of dialyzers and ventilators, absence of antidote fomepizole).

Information concerning the Norwegian methanol poisoning outbreak is cited from the studies of Hovda et al. (2005c, 2005d). In the Norwegian outbreak, all the liquor probably came from the same origin in southern Europe and contained approximately 20% methanol and 80% ethanol. The liquor was illegally transported into the country and sold in plastic cans of approximately 10 L, and some was later bottled to look like the original bottles. This outbreak was the largest where serum-methanol, acid-base-status and serum formate (in 15 cases) were measured. The Norwegian outbreak was also the first large-scale outbreak in which fomepizole was mainly used as an antidote.

Fifty-one patients with a median age of 53 years were admitted from September 2002 until December 2004, of whom 33 were admitted in 2002, 13 in 2003 and five in 2004. Nine patients died in a hospital (hospital mortality 18%). Five patients were discharged from the hospital with sequelae (10%), whereas one died one year later from cerebral sequelae. Eight patients who died outside a hospital were diagnosed with methanol poisonings after autopsy.

Patients were given a buffer, ethanol (15 patients) or fomepizole (36 patients) as antidotes, and hemodialysis (37 patients). Median serum methanol in all the groups at admission was 25.0 mmol/L, range 3.1–147.0 mmol/L. Of those 39 (77%) who were symptomatic upon admission, 28 patients (55%) presented with visual disturbances, 21 (41%) with dyspnea, 22 (43%) with gastrointestinal symptoms, 12 patients (24%) were comatose, six (12%) with chest pain and eight (16%) with other symptoms (mainly fatigue). Eight patients (16%) presented with respiratory arrest.

Among five patients discharged with sequelae, of whom all had visual sequelae and four had CNS sequelae, two were comatose at admission. Respiratory arrest and coma at admission were robust markers of poor outcome: six of eight (75%) patients admitted with respiratory arrest died and eight of 12 (67%) comatose patients died (89% of the patients who died were comatose at admission), two of 12 (17%) were discharged with sequelae and two of 12 (17%) were discharged without sequelae. The mortality rate among the hospitalized patients was 18%, and the total mortality rate was 29%.

The main challenges during the Norwegian outbreak were associated with delayed diagnosis in some of patients because physicians were not trained properly in the use of osmolal and anion gaps in the lack of methanol or formate analyses. Only a few centers receiving the patients were able to perform methanol analyses on a 24-hour basis. Further, the mixture of methanol with ethanol ingested by the patients delayed the onset of symptoms and made it difficult to relate these to the intake of the liquor. Many of the patients were alcoh and interpreted the symptoms of methanol poisoning as alcohol withdrawal.

In the Norwegian “epidemics”, the experience with fomepizole as an antidote was good. The metabolism of methanol was effectively blocked and, compared with ethanol, fomepizole was easier to administer and there was no need for therapeutic drug monitoring. Fomepizole caused no respiratory depression and many patients could be treated outside the ICU or they needed only a brief stay. Fomepizole was expensive [for a 70-kg patient, the average price in Scandinavia was approximately € 7,800 for a 3-day treatment (six doses)], but the spared ICU costs, sober patients, and lower need for dialysis might have balanced these expenses. The problems with the costs and shorter shelf-life of fomepizole compared with ethanol were solved by stock-keeping in regional centers. If fomepizole was not available at once, the patients were treated with ethanol until fomepizole was obtained.

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Challenges of Timely Diagnosis and Treatment in Methanol Mass Poisoning Outbreaks

Methanol itself has a low toxicity, but its metabolites, formaldehyde and formic acid, are highly toxic. In humans, methanol is oxidized by alcohol dehydrogenase (ADH) to formaldehyde and then by aldehyde dehydrogenase to formic acid (Eells et al., 1981a; 1981b; McMartin et al., 1975, 1977, 1979). Formaldehyde does not accumulate in the blood, because its conversion to formic acid is very rapid with a half-life of 1–2 minutes (Eells et al., 1981b; McMartin et al., 1979, 1980). In the presence of tetrahydrofolate, formic acid is metabolized to carbon dioxide and water with a half-life as long as 20 hours (Shahangian et al., 1984; Tephly, 1991). The rate of formate oxidation is dependent on hepatic tetrahydrofolate pool, which is relatively low in humans, and activity of 10-formyl tetrahydrofolate dehydrogenase, which is also approximately two times lower than in rats (Black et al., 1985; Eells et al., 1981a, 1982; Johlin et al., 1987). Therefore, formic acid accumulates as its generation exceeds the capacity to eliminate it. As a moderate inhibitor of cytochrome *c* oxidase (K_i ~ 6 mmol/L), formate impairs tissue utilization of oxygen resulting in excess lactic acid production and depletion of ATP in cells (Erecinska & Wilson, 1980; Seme et al., 2001; Timbrell, 2000; Tong, 1982). A direct correlation exists

between formic acid accumulation and toxicity of methanol (Tephly, 1991). Brent et al. (2001) identified a direct relationship between high serum formic acid concentrations and increased morbidity and mortality in methanol poisonings.

Clinical features of methanol poisoning are nonspecific and usually limited to gastrointestinal upset, CNS depression progressing to coma, seizures, dyspnea, and signs of visual toxicity in some patients (blurred vision, "snowflakes," decreased visual acuity, photophobia, and others); nevertheless, the absence of symptoms does not exclude serious methanol poisoning (Bennett et al., 1953; Røe, 1946; Shadnia et al., 2013). More than 25% of patients can be asymptomatic when first observed (Hovda et al., 2005c, 2005d). The co-ingestion of ethanol in adulterated alcoholic beverages typically delays the onset of symptoms beyond 24 hours; therefore, most of the patients in "epidemics" of methanol poisoning are so called "late-presenters" (Røe, 1946; Naraqi et al., 1979; Paasma et al., 2007). Highly specific and resource-consuming treatment of acute methanol poisoning to be efficient requires rapid diagnosis, because any delay leads to further deterioration of metabolic acidosis, failure of respiratory compensatory mechanisms, and poor prognosis (Coulter et al., 2011a, 2011b; Kraut, 2015; Paasma et al., 2012). If specific interventions are inadequate or delayed, mortality exceeding 40% as well as serious health sequelae in survivors may occur (Abramson & Singh, 2000; Hassanian-Moghaddam et al., 2007; Hovda et al., 2005c; Paasma et al., 2007, 2009; Roberts et al., 2015). Nevertheless, the chromatographic method of methanol detection is the only reliable analysis, but it requires high-quality toxicological laboratory equipment unavailable in many hospitals even in developed countries (Hovda et al., 2005d; Kraut, 2015; Paasma, 2007). According to Paasma (2013), the typical delay between admission and the results of serum methanol measurement during the Estonian outbreak was 24–72 hours. Therefore, the decision regarding treatment initiation was based on the results of arterial blood gases (ABG) and indirect measurements of osmolal and anion gaps. Descriptions of enzymatic methods for methanol detection in blood or urine have been published, but they are complex and hampered by interference with ethanol (Vinet, 1987, 1988); due to their limitations these methods have not been widely used in clinical practice.

Analyses of osmolal and anion gaps as the most common alternative means are useful, since methanol increases the osmolality of serum and its metabolite formate increases the anion gap (Aabakken et al., 1994; Hoffman et al., 1993; Hovda et al., 2004; Jacobsen et al., 1982a; Kraut & Xing, 2011; Smithline et al., 1976; Srivali et al., 2014). These methods are, however, indirect with inherent limitations (Krasowski et al., 2012; Sweeney & Beuchat, 1993; Kraut, 2015). The osmolal gap is increased in the cases of intake of other osmotically active substances, such as ethanol, isopropanol, among others (Berendt et al., 1987; Demedts et al., 1994; Dorwart & Chalmers, 1975; Glaser et al., 2006;

Haviv et al., 1998). The sensitivity of osmolal gap for low concentrations of serum methanol under 20 mmol/L is generally low, because the osmolal gap in many cases remains under 19 mmol/kg.H_2O (Hovda et al., 2004; Whittington et al., 2010).

In the late-presenting patients, most of the methanol may have already been metabolized to formic acid and even in the subjects with negative finding of the parent compound in blood serum methanol intoxication is possible in the late stage of poisoning (Hovda et al., 2004; Kraut, 2015). The generation of formate and lactate contributes to the anion gap (Emmett & Narins, 1977; McMartin et al., 1980). Anion gap measurement has a low sensitivity as well: serum formate concentration must increase several times above its upper reference limit of 0.4 mmol/L before the anion gap is significantly increased (Hovda et al., 2004, 2005d; Iberti et al., 1990; Kraut & Nagami, 2013).

Serum formic acid concentration measurement (using the enzymatic method by means of formate dehydrogenase) is a third way of diagnosing methanol poisoning (Hovda et al., 2005d, Kerns et al., 2002; Schaller & Triebig, 1984; Urdal, 1984). Formate is one of the normal intermediates in human metabolism; it takes part in the metabolism of one-carbon compounds, and its carbon may appear in methyl groups undergoing transmethylation (Cook et al., 2001; Fox & Stover, 2008; Fu et al., 2001). It is typically produced by the catabolism of several amino acids including serine, glycine, histidine, tryptophan, by the recycling of methylthioadenosine from the polyamine biosynthesis pathway, as a by-product in the production of acetate, and further oxidized to carbon dioxide and water, primarily by the action of 10-formyltetrahydrofolate dehydrogenase, but under some conditions by at least two other pathways including erythrocyte catalase (Cook et al., 2001; Fu et al., 2001). Normal blood serum concentration of formate in healthy human subjects is 0.02–0.25 mmol/L (Bouhifd et al., 2014; Osterloh et al., 1986, 1996; Psychogios et al., 2011; Sivilotti et al., 2001). In patients with methanol poisoning, formate anions accumulate due to saturation of their folate-dependent elimination, resulting in the gradual accumulation of this metabolite and lactate, deterioration of metabolic acidosis, and subsequent delayed toxic effects (Johlin et al., 1987; Martinasevic et al., 1996).

It is known that serum lactate concentration correlates with the clinical outcome in critically ill patients and can be used as a prognostic indicator of mortality (Jansen et al., 2008; Schuster, 1984; Smith et al., 2001), whereas only scarce data exist on the role of serum formate concentration in the diagnostics, clinical management, and prognosis of outcome in patients with acute methanol poisoning (Hovda et al., 2005d; Kerns et al., 2002; Lukasik-Głębocka et al., 2014; Mahieu et al., 1989; Osterloh et al., 1986; Sejersted et al., 1983). Hantson et al. (2000) found great variability in formic acid concentration in the cases of fatalities due to methanol poisoning. Hovda et al. (2005d) found that asymptomatic patients had formate concentration in the range of

20.0–380.0 mg/L (0.5–8.3 mmol/L) whereas in the patients with clinical features formate concentration was above 460.0 mg/L (10.0 mmol/L). The data presented by Jones et al. (2007), Wallage & Watterson (2008), and other authors suggest fatal outcomes if formic acid levels are greater than 500.0 mg/L (11.0 mmol/L). Nevertheless, most of the data on serum formic acid concentration in methanol poisoned patients were collected from the episodic case reports, and blood formate was often measured post-mortem (Ferrari et al., 2003; Jones et al., 2007; Tanaka et al., 1991).