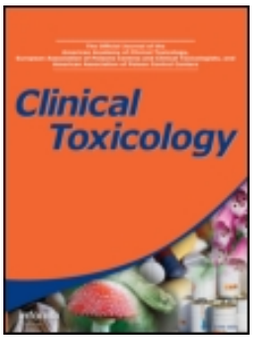

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Dirk W. Lachenmeier, Yulia B. Monakhova, Andriy V. Samokhvalov & Jürgen Rehm

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LETTER TO THE EDITOR

Causality between polyhexamethyleneguanidine occurrence in unrecorded alcohol and cholestatic hepatitis outbreak in Russia

To the Editor:

We read with great interest the study of Ostapenko et al.[1] reporting about an outbreak of acute cholestatic liver injury in Russia connected to the consumption of unrecorded alcohol. As background, it has to be mentioned that alcohol consumption is the most important risk factor for death and burden of disease in Russia (see Rehm et al.[2] and Zaridze et al.[3]). Of course alcohol-attributable liver disease plays an important role in this relationship.

In the study of Ostapenko et al.,[1] the alcohol that was consumed by the patients was an antiseptic liquid for indoor disinfection, which contained ethanol (93%), diethyl phthalate (DEP) (0.08–0.15%) and polyhexamethyleneguanidine hydrochloride (PHMG, CAS #57029-18-2) (0.10–0.14%). PHMG is an effective antiseptic and is commonly used for suppression of hospital infection in the Russian Federation,[4] and DEP is added to denature the alcohol.[5] Several previous studies had also detected PHMG together with DEP in disinfectants that were used as an ethanol source in other poisoning cases in Russia.[4,6,7]

On the basis of clinical manifestations and laboratory findings of 579 poisoned patients, Ostapenko et al.[1] concluded that the cholestatic hepatits was caused by PHMG, while a history of alcohol-induced hepatitis and cirrhosis contributed to a more severe course of the poisoning. Other factors such as DEP or chronic viral hepatitis may have further contributed to multifactorial liver damage.

While we agree with the authors that the outbreak may have been caused by PHMG, we disagree with the conclusion of an almost causal relationship. At least, the paper lacks adequate discussion of the alternative hypothesis, that is, that the outbreak was purely caused by extreme amounts of ethanol ingestion and high-risk drinking patterns.

This alternative hypothesis cannot be directly discarded, as cholestasis is not uncommon in patients with conventional alcoholic liver disease (i.e. without co-ingestion of PHMG or DEP) (see review by Tung et al.[8]). As early as 1911, the importance of histologic cholestasis in alcoholic liver injury was pointed out by Mallory.[9] Although the precise mechanism is still not understood, it was suggested that acetaldehyde – the first metabolite of ethanol – may bind to tubulin and thus impair the microtubule function.[8] Mild cholestasis is common among alcohol-abusers without clinically evident liver disease, and these changes are reversible on abstention.[10] Acute alcoholic cholestasis, a term suggested by Glover et al.,[11] typically manifests in patients who have been alcohol-dependent for several years, and were in poor nutritional state, and reported heavy drinking episodes in the weeks before the clinical manifestation.[11–14] Symptoms include jaundice or elevation in serum bilirubin.[8]

All these features were also reported for the patients of Ostapenko et al.[1] The alcohol doses reported certainly corresponded to the definition of heavy drinking. The effects of ingestion of extremely high strength alcoholic beverages (as in this case, 93% ethanol) are also under-researched. It is plausible that ingestion of this high amount of ethanol may lead to higher local acetaldehyde concentrations in the liver compared to the ingestion of recorded spirits (at about 40%). Therefore, we cannot completely exclude the possibility that the cholestatic liver injury is caused by the effects of ethanol alone.

If we want – on the other hand – to investigate the effect of PHMG, the situation becomes rather complex as only limited human data is available. Previous authors also assumed that consumption of surrogate alcohol containing PHMG induces significant disorders of lipid metabolism, which ultimately may lead to liver injuries, particularly toxic hepatitis.[15] However, there was again no clear evidence how the authors distinguished between the effects of PHMG and ethanol, which of course may also cause acute and chronic liver injury.[16,17]

Due to the lack of epidemiological data, animal experiments have to be taken as a basis for risk assessment. The LD_{50} (lethal dose for 50% mortality) for PHMG was found to be 450 mg/kg for mice and 630 mg/kg for rats.[18] In these experiments, liver, spleen and stomach injuries were reported. Condrashov et al.[18] determined 0.1 mg/kg bodyweight/day as 'no-observed adverse effect level' (NOAEL) in a 6-month oral study with rats. Increases in liver and spleen weights and also changes in blood enzyme levels were found in the animals in both 1.0 mg/kg bodyweight/day and 10 mg/kg bodyweight/day dose groups. No oral long-term study was available, which is normally used to extrapolate from animals to humans. To make a first judgment about the risk of PHMG in the alcohols, a provisional tolerable daily intake (TDI) of 0.5 µg/kg bodyweight/day (0.03 mg/day for a 60-kg-human) extrapolated from the animal NOAEL of 0.1 mg/kg bodyweight/day with an uncertainty factor of 200 can be postulated. If we assume an exposure of 300–400 mg/day (5–7 mg/kg bodyweight/day) based on a daily consumption of 300 mL of the above mentioned disinfectant, not only is the TDI exceeded by a factor of 10 000 but we also have reached levels of exposure that did cause adverse effects in the animal experiment. It is therefore plausible that in regions where disinfectants with PHMG were consumed, high levels of toxic hepatitis different from chronic hepatitis induced by long-term ethanol consumption were recorded. We also think it is plausible that ethanol contributes to the effects, as chronic alcohol intake is a known risk factor for drug-induced cholestasis, as it lowers the dose for hepatoxicity and accentuates hepatic lesions.[19]

In sum, both human epidemiological and toxicological evidence concur in pointing to consumption of alcohol per se as an alternative explanation of the outbreaks in Russia. Before we conclude causality with respect to other mechanisms, this alternative explanation should be excluded.

Dirk W. Lachenmeier
CVUA Karlsruhe, Karlsruhe, Germany
Yulia B. Monakhova
Saratov State University, Saratov, Russian Federation
Andriy V. Samokhvalov and Jürgen Rehm
CAMH, Toronto, Canada

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Address correspondence to Dr. Dirk W. Lachenmeier, CVUA Karlsruhe, Karlsruhe, Germany. E-mail: lachenmeier@web.de

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