Biological Monitoring

An Introduction

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21.4.13 Methemoglobin Inducers

Methemoglobinemia is the excess formation of methemoglobin, the oxidized form of hemoglobin in which the iron in the heme component is oxidized from the ferrous to the ferric state, thus impairing transport and release of oxygen to and from tissues. There is usually about 1% methemoglobin relative to total hemoglobin, mostly in the red blood cells. Methemoglobinemia is a nonspecific biological monitoring marker.

Methemoglobinemia is caused by many aromatic amines [aniline, dimethylaniline, *N*-methylaniline, 4,4-methylene*bis*(2-chloroaniline), *p*-nitroaniline, Paraquat, toluidines, and xylidines] and aromatic nitro-compounds (dinitrobenzenes, dinitrotoluenes, nitrobenzene, nitrotoluenes, and *p*-nitroaniline), as well as nitric oxide, nitrogen dioxide, nitrogen trifluoride, hydroxylamine, and some aliphatic nitrates (propylene glycol dinitrate, *n*-propylnitrate). The above-named compounds have methemoglobinemia as their principal toxic effect. Not all aromatic or aliphatic amines (anisidine, 2-naphthylamine, and cyclohexylamine) and nitro-compounds (2-nitropropane, tetranitromethane, and 2,4,6-trinitrotoluene (TNT)) have methemoglobinemia as their major toxicity end point. The presence of bacterial flora facilitates conversion of nitrates to nitrites, and probably to nitrosamines and to amines. The presence of the major reducing agents (vitamin C or ascorbic acid, glutathione, $NADH_2$, NADPH, and the inhibition/induction of methemoglobin reductase) also may be a factor. Thus diet and general health also are important. All compounds appear to take unique time courses for the development of methemoglobinemia. Baseline levels are crucial to determine if the observed methemoglobinemia is caused by work-related exposure. The BEI is set at 1.5% methemoglobin content of total hemoglobin in a sample taken during, or at the end of, a shift.

Exposure to many recreational drugs (amyl nitrate and butyl nitrite), medications (acetanilides, benzocaine, bismuth subnitrate, lidocaine, nitrites, nitroglycerine, phenacetin, prilocaine, silver nitrate, and sulfonamides), photographic developers (aminophenol), food preservatives (sodium nitrite), dyes (anilines, benzidine, and nitrobenzenes), commercial products (fuel additives, wax crayons, laundry markers, and waters with high bacterial content), fertilizers (nitrates), nitrogen dioxide–generating sources (such as silos, stack emissions, and ambient air), and the chloral salts used in matches and oxygen generators also may produce methemoglobinemia. Bacteria growing in burns and in topical nitrate agents applied to burns are sources also. People with congenital methemoglobinemia due to methemoglobin reductase deficiency may have 10 to 30% methemoglobin; acatalasemia, deficiency in NADH-reductase, and defective globin caused by congenital mutations also may produce elevated levels of methemoglobin. Storage may increase or decrease the levels, but analysis must be done within 1 h of taking the sample.

The half-time of methemoglobin (80–100%) varies between 6 and 24 h. Most kinetics are biphasic, signaling some component due to metabolic activation. There is much interindividual sensitivity. Cyanosis is usually intense at 10 to 15% methemoglobin; levels between 40% and 60% cause weakness, fatigue, breath shortness, rapid heart rate, dizziness, headaches, and disorientation;

and levels above 60% cause stupor, coma, and death. The mean ± standard deviation in the general population is (0.78 ± 0.37)% methemoglobin.

The TLV for aniline (Section 21.4.1) of 2 ppm was set to prevent methemoglobinemia, as was the TLV of 1 ppm for nitrobenzene (Section 21.4.17). Because many of the chemicals causing methemoglobinemia are efficiently absorbed through the skin, and because this nonspecific end point integrates absorbed doses over all exposure routes and for different chemicals, the marker is recommended as a screening marker for biological monitoring health effects and also is utilized as a medical monitoring marker.

21.4.14 Methyl Alcohol

Methyl alcohol or methanol ($CH_3 \cdot OH$) is a colorless liquid with a boiling point of 65°C that is miscible with water. Methanol is a component in many paint removers, methylated spirits, antifreeze, organic cleaners, fruit juices, foods, and alcoholic beverages. It is the active ingredient of gasohol (up to 15%). The TLV-TWA of 200 ppm or 262 mg/m^3 is set to prevent severe recurring headaches and sight impairment. The methanol in ingested methylated spirits is known to cause blindness and death. Ingestion of as little as 30 mL methanol can cause death.

Methanol distributes with water throughout the body. This means that the concentration of methanol in urine is independent of the urine volume, and thus creatinine corrections are not appropriate. About 58% of inhaled methanol vapor is absorbed independent of air concentration, duration of exposure, or physical activity. The dermal absorption rate is significant, with a predicted rate of 2.0 mg/cm^2/h and a measured rate on forearm skin of 11.5 mg/cm^2/h. Methanol is excreted in urine (BEI, 15 mg/L end-of-shift from four studies and two field exposure investigations) and exhaled breath, and part of it is oxidized by alcohol dehydrogenase to formaldehyde ($H_2 \cdot CO$) and then also to formic acid ($H \cdot COOH$) (BEI, 80 mg/g creatinine end-of-work-week-shift corrected for background, as set from one field study).

It is recommended that workers in plants not characterized for air methanol be sampled for urine during their 8-h shift after a baseline sample is taken. The BEI under 8-h collection conditions is 6.5 mg/L for workers at rest and 13 mg/L for workers with pulmonary ventilation of 21 L/min. The final BEI selected was an average of the end-of-shift and 8-h collection values. The samples for methanol in urine must be analyzed within 3 days even after refrigeration at 4°C. A steady state of methanol in blood takes longer than 8 h to attain.

Methanol is formed endogenously through the action of bacteria or as a common intermediate in C_1 metabolism. The range for methanol-unexposed subjects is 0.32 to 2.9 mg/L urine. Methyl esters ($R \cdot CO \cdot OCH_3$, where R is any alkyl or aryl group) are metabolized to the free acid and methanol. Methyl ethers ($R \cdot O \cdot CH_3$, where R is any alkyl or aryl group) such as ethylene glycol monomethyl ether (2-methoxyethanol, $HO \cdot CH_2 \cdot CH_2 \cdot OCH_3$) are less metabolized, to produce methanol and the other alcohol, $R \cdot OH$. Workers unexposed to methanol and alcoholic beverages have urinary methanol concentrations between <0.6 to 2.9 mg/L. Alcohol imbibers have up to 5 mg/L in their urines.

The metabolic oxidation of methanol to formic acid accounts for about 70 to