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Assessment of long-term health risks after accidental exposure using haemoglobin adducts of epichlorohydrin

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HIGHLIGHTS

- A human biomonitoring study was performed to evaluate internal exposure after accidental release of epichlorohydrin.
- Haemoglobin adducts of epichlorohydrin, the *N*-(3-chloro-2-hydroxypropyl)valine (CHPV) and the *N*-(2,3-dihydroxypropyl)valine (DHPV), were measured in blood.
- In 6 out of 628 samples, CHPV adduct levels above the LOQ of 25 pmol/g ranged from 32.0 to 116.4 pmol/g globin.
- DHPV was not detected above the LOD of 10 pmol/g globin in any of the blood samples.
- Based on the quantified CHPV adduct values, estimates of the cumulative additional lifetime cancer risks range from 2.61×10^{-8} to 9.48×10^{-8}.

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ABSTRACT

On September 9th, 2002, two goods trains collided in Bad Münder, Lower Saxony, causing the release of more than 40 metric tonnes of epichlorohydrin (1-chloro-2,3-epoxypropane) into the environment. A human biomonitoring study was performed to evaluate the accidental exposure to epichlorohydrin and to assess the possible long-term, i.e. carcinogenic health effects. This was done on the basis of a biochemical effect monitoring using the *N*-(3-chloro-2-hydroxypropyl)valine and the *N*-(2,3-dihydroxypropyl)valine haemoglobin adducts of epichlorohydrin in blood to respond to missing ambient monitoring immediately after the crash. *N*-(3-chloro-2-hydroxypropyl)valine adduct levels above the LOQ (25 pmol/g globin) ranged from 32.0 to 116.4 pmol/g globin in 6 out of 628 samples. The *N*-(2,3-dihydroxypropyl)valine adduct was not detected above the LOD (10 pmol/g globin) in any of the blood samples. Based on the quantified *N*-(3-chloro-2-hydroxypropyl)valine adduct values, the body doses after two days of exposure were estimated to be in the range of 1.7–6.2 nmol/kg body weight. The reverse estimation of the external exposure leads to cumulative additional lifetime cancer risks ranging from 2.61×10^{-8} to 9.48×10^{-8}. The estimated excess lifetime cancer risks have to be assessed as extremely low. Our biomonitoring study facilitated the dialogue between individuals and groups concerned and authorities, because suspected or occurred exposures and risks to human health could be quantified and interpreted in a sound manner.

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1. Introduction

On September 9th, 2002, two goods trains collided head-on on the outskirts of Bad Münder, Lower Saxony, causing the release of more than 40 metric tonnes (MT) of epichlorohydrin (1-chloro-2,3-epoxypropane, ECH, CAS No. 106-89-8) into the environment. The emissions of ECH can be described as a thriphasic process: (a) the

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continuous phase of combustion which was steadily fed from leaking ECH and accompanied by a first minor burst, (b) a release during the second and significantly larger explosion, and (c) the residual release during the fire-fighting, which started immediately after the larger explosion. The fire was under control after about 4 h. From the originally 49.4 MT of ECH about 5 MT drained away into the subsurface of the close-up range of the collision site and 6–10 MT polluted the nearby river Hamel (Lilienblum et al., 2003; Lilienblum and Müller, 2004; Wollin et al., 2008). Further 29–33 MT of burnt, vapourised or hydrolysed ECH were released into the atmosphere and approximately 5 MT of ECH remained in the tank wagon. In the early phase of the accident, temporally and spatially dispersed systematic measurements of ECH were not performed and hence especially ambient air concentrations of ECH were virtually unknown. Police officials, firemen, officials of the Federal Railway Authority, other task force members, employees of a neighbouring firm and residents were potentially exposed to unburnt ECH as well as the hazardous gases and aerosols of its combustion. During the first twenty days after the accident, about 540 health practitioner consultations concerning temporary lachrymatory effects, irritation to throat and respiratory tract, headache and notable discomfort were registered (Lilienblum et al., 2003). The health impairments that obviously occurred widespread in the residents during the first days after the accident are not consistent with the observed plausible meteorological behaviour of a thermally exaggerated fire cloud (Lilienblum and Müller, 2004). However, these health complaints can partially be explained by low passing plumes in the main sector of the emission probably resulting from cooling/quenching effects of the fire water and hydrogen chloride formed. With regard to possible health outcomes of exposure that may be delayed in onset, an increase of excess lifetime cancer risk attributable to inhaled ECH or dermal uptake of ECH ranked first. This was the formative aspect in risk communication with those individuals or groups who were accidentally exposed. Admittedly, the extent of the individual exposure was unknown.

Due to its chemical reactivity, ECH is locally toxic if inhaled, swallowed and in contact with skin (IPCS, 1984; U. S. EPA, 2008; DFG, 2012; HSDB, 2014). It causes delayed erythema, oedema, and papules along with burning, and itching when the liquid comes into contact with the skin (U. S. EPA, 2008; HSDB, 2014). Severe eye irritation, skin irritation, and delayed contact skin sensitisation in animals have been noted after topical application of undiluted or diluted ECH (U. S. EPA, 2008). Human volunteers showed significant cardiotoxic effects when they were exposed to vapours of ECH (IPCS, 1984). Burning of the eyes and nasal mucosa were reported along with throat irritation (HSDB, 2014; U. S. EPA, 2008). Systemic toxicity (damage of liver, kidney, adrenal gland and CNS and annoyance of reproduction) besides local effects was observed after long-term exposure in animal studies (HSDB, 2014; U. S. EPA, 2008). Genotoxicity in vitro and in vivo has been demonstrated in numerous studies (IPCS, 1984; DFG, 2012; U. S. EPA, 2008). Because of its alkylating properties, the mechanism of primary genotoxicity via formation of DNA adducts (Singh et al., 1996; Koskinen and Plná, 2000; Sund and Kronberg, 2006) and DNA interstrand cross-linking (Romano et al., 2007) is relevant for ECH. Human carcinogenicity data indicates possible weak effects that require validation (IARC, 1999; AGS, 2012). ECH acts via the electrophilic carbon of the chloromethylene group and the C3 of the epoxy ring as a bifunctional directly alkylating epoxide. Because of the higher reactivity of the C3 in the epoxy moiety, the predominant reaction of ECH with macromolecules in cells such as DNA and haemoglobin is the formation of open-chain chlorohydroxypropyl adducts which can be transformed into the corresponding dihydroxypropyl adducts by hydrolysis. The formation of the ultimate dihydroxypropyl adduct of ECH can however also result from the ECH metabolite glycidol, respectively.

According to the CLP Regulation (2008), ECH is categorised into the health hazard classes Carcinogenicity 1B (presumed to have carcinogenic potential for humans, classification is largely based on animal evidence), Acute Toxicity 3 (hazard statement H331, toxic if inhaled), Acute Toxicity 3 (H311, toxic in contact with skin), Acute Toxicity 3 (H301, toxic if swallowed), Skin Corrosion 1B (H314, causes severe skin burns and eye damage) and Skin Sensitization 1 (H317, may cause an allergic skin reaction).

The combustion of ECH and/or hydrolysis in the presence of fire-fighting water or air moisture produces irritant and toxic gases. Combustion by-products include hydrogen chloride, chlorine, and phosgene. Quantitatively, hydrogen chloride is the most important secondary product of ECH in case of fire or from hydrolysis, exhibiting a pronounced irritant potency. Remarkably, the lowest acute exposure guideline level value (AEGL-1) of hydrogen chloride (U. S. EPA, 2013a) is lower if compared to ECH's AEGL-1 (U. S. EPA, 2013b) (1.8 ppm vs. 5.7 ppm (interim value)); both AEGLs (as airborne concentrations) are based upon the respective substance-related no-effect level for irritation in humans.

This study aims: (1) to evaluate the extent of the accidental exposure to epichlorohydrin of the persons concerned and (2) to assess the possible long-term, i.e. carcinogenic health effects on the basis of a biochemical effect monitoring using the chlorohydroxypropyl- and dihydroxypropyl haemoglobin adducts of ECH to respond to missing ambient monitoring immediately after the crash. The dihydroxypropyl haemoglobin adduct of ECH has already been used as quantitative biomarker of the internal body burden in humans and in the Wistar rat model (Hindsø Landin et al., 1996) and to investigate long-term exposure at the workplace (Hindsø Landin et al., 1997), but the chlorohydroxypropyl adduct precursor was not considered comprehensively so far in biological monitoring. In general, the chlorohydroxypropyl- as well as the dihydroxypropyl adducts should also be suitable for evaluating the individual internal body burden in case of acute exposure after accidental release of ECH. Moreover, haemoglobin adduct data is considered more relevant for assessing internal exposure than extrapolations from chemical concentrations, e.g. in soil, water or air. Haemoglobin adducts are surrogates of DNA adducts, and as such, they provide a measure of both exposure and biochemical effect. Due to their high specificity and the sensitivity of the detection methods, haemoglobin adducts are preferable to the analysis of genotoxic substances and their metabolites in human body fluids (Angerer et al., 2007; Pavanello and Lotti, 2012). Used in such a way, they have the advantages of an individual health assessment which integrates the inhalational, dermal and – if applicable – the oral route of exposure. If exposure to ECH is proven by haemoglobin adduct data, it would be possible to utilise the individual internal ECH dose for extrapolating to airborne ECH exposures. A reasonable approach to estimate the excess lifetime cancer risk of people involved in the emergency could then be based on established quantitative estimates of the carcinogenic risk from inhalation exposure.

2. Material and methods

2.1. Sampling

The management of blood sampling was conducted by the public health department of the administrative district Hameln-Pyrmont and the Institute for Occupational Medicine of Hannover Medical School. Samples were obtained from Lower Saxony state policemen, employees of the federal police, railway officials and

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