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Biological monitoring to assess dermal exposure to ethylene oxide vapours during an incidental release

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HIGHLIGHTS

- Systemic exposure through the skin may occur in high ethylene oxide vapour exposure.
- Risk assessment of dermal exposure to ethylene oxide vapour by haemoglobin adducts.
- Additional risk management must be considered in incidental ethylene oxide release.

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ABSTRACT

During a short incident in an ethylene oxide (EO) producing plant, EO vapour was released under high pressure. Operators wore full respiratory protection during repairs to fix the leak. To check the adequacy of the applied personal protective equipment and to address concerns about potential dermal exposure and subsequent uptake of EO, biological monitoring was applied by determination of the haemoglobin adducts of EO in blood. Based on the results of the biomonitoring, a risk assessment of dermal exposure to EO vapour was made.

Calculations to estimate dermal exposure, based on two recently published models and using the relevant physical–chemical properties of EO, indicate that the dermal contribution to total exposure is expected to be negligible under normal operating circumstances. However, the models indicate that under accidental circumstances of product spillage, when high air concentrations can build up quickly and where incident response is conducted under respiratory protection with independently supplied air, the systemic exposure resulting from dermal absorption may reach levels of concern.

The model estimates were compared to the actual biomonitoring data in the operators involved in the accidental release of EO vapour. The results suggest that when incidental exposures to high EO vapour concentrations (several thousand ppm) occur during periods in excess of 20–30 min, additional risk management measures, such as wearing chemical impervious suits, should be considered to control dermal uptake of EO.

1. Introduction

Ethylene oxide (EO) is a mutagenic substance that was found to be carcinogenic in rodents. The International Agency for the Research on Cancer has classified EO as a human carcinogen based on the rodent carcinogenicity in combination with what was considered as compelling evidence that EO is a genotoxic substance, despite the fact that there is only limited evidence for EO being carcinogenic to humans (IARC, 2012). EO is an acute inhalation hazard and may cause irritation of the skin, eyes and respiratory tract. As a consequence, strict containment of EO is essential to secure a safe workplace. EO is also an extremely flammable and volatile substance, with a boiling point of 10.7 °C at atmospheric pressure and ambient temperature. Logically, the focus of exposure controls is on the inhalation route. Recently, the Scientific Committee for Occupational Exposure Limits included a 'Skin notation' in its updated advice for a European Occupational Exposure Limit for EO to reflect that 'clear signs of systemic toxicity were reported after local application of ethylene oxide' (EC, 2012).

SCOEL did not address the possible contribution from EO vapour in air to the total body burden through the dermal route. Nevertheless, when there is an incidental release of EO during manufacturing or transport, EO is usually present as a vapour rather than a liquid or aerosol due to its high volatility. Under experimental *in vitro*

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conditions, EO was shown to be able to penetrate the skin as vapour: the percutaneous absorption of EO from fabric was 46% of an experimental dose if the source material (fabric) was occluded on the skin (e.g. inside a glove), whereas only 1.3% of the dose was absorbed when the fabric/skin surface was open to surrounding air (Wester et al., 1997). There is evidence that vapours from various industrial chemicals can penetrate the skin and lead to systemic availability *in vivo* as well (Bader et al., 2008; Jones et al., 2003; Kezic et al., 2004).

The objective of the current investigations is to estimate this dermal contribution of exposure to EO vapours under normal operating circumstances and during response to product spillage when operators wear independent breathing apparatus, but no specific full-body dermal protection such as chemical impervious suits. The latter scenario, with exposure to high concentrations of EO during product release whilst wearing full breathing protection, was investigated during an incidental leakage. The model estimates were compared to the data measured through biological monitoring.

2. Materials and methods

2.1. Modelling of dermal uptake

Two recent models were used to estimate dermal uptake. The first model applied is an empirical model for estimation of the uptake fractions via inhalation and via the skin of airborne chemical substances which was developed recently by Rauma et al. (2013). This model (the 'Rauma model') requires volatility (V_p), octanol–water partitioning coefficient (K_{ow}), and molecular weight (MW) as parameters and was validated for a range of industrial substances. The model calculates a 'Dermal Contribution Ratio' (DCR), which is defined as the ratio (expressed as %) of the amount absorbed via the skin and the total amount absorbed (dermal and inhalation) and is calculated using the following formula:

$$\log(DCR) = -0.1982 \cdot \log K_{ow} - 0.6767 \cdot \log V_p + 0.8721 \cdot \log MW + 1.3475$$

For EO the following parameter values were used: $\log K_{ow} = -0.3$, $V_p = 175{,}200$ Pa, and $MW = 44.1$ g/mol.

The second model applied was IndusChemFate, version 2.0, which was developed under the chemical industry's Long-range Research Initiative (www.cefic-lri.org/lri-toolbox/induschemfate). The IndusChemFate model is a pharmacologically based toxicokinetic model, which also provides a modelling approach for dermal uptake of vapour (Jongeneelen and Ten Berge, 2011). The IndusChemFate model was run with the same physico-chemical parameters for EO as were used in the Rauma model, using the default physiological parameters of the IndusChemFate model.

Both the Rauma model and the IndusChemFate model were run for three scenarios. The first scenario was a worst-case scenario under normal operating conditions: an operator working for 8 h per day, without respiratory protection at the current Dutch occupational exposure limit of 0.5 ppm (0.84 mg m^{-3}) as an 8-h time weighed average (8-h TWA). The second scenario is based on the situation of an operational problem causing a product spillage which is addressed using self-contained breathing apparatus (SCBA) but without specific dermal protection. It was assumed that the operators addressing the problem were exposed during 30 min to an average concentration of 500 ppm (840 mg m^{-3}) EO. The third scenario describes the situation of an emergency response worker involved in the response to a spillage incident and exposed to the AEGL-2 or similar guideline value (i.e. the value above which irreversible or other serious, long-lasting health effects could occur). The current AEGL-2 values are: 80 ppm for 10 min and 30 min, 45 ppm for 60 min, 14 ppm for 4 h and 7.9 ppm for 8 h (NRC, 2010).

2.2. Modelling of airborne concentrations

The maximum airborne concentrations of EO vapour in the proximity of a single leak were calculated for several wind conditions and distances using the dispersion module of Shell FRED ("Fire, Release, Explosion, Dispersion") programme (version 6.0), a proprietary software programme that uses inputs that reflect process pressure and temperature as well as the leak diameter and the physicochemical properties of the substance. The 'pressurised release' option in the dispersion module of Shell FRED allows estimation of airborne concentrations in the initial jet of released product in the first metre up to a few decameters, followed by atmospheric dispersion over a greater distance as described to Gaussian theory using wind speed and an indicator of atmospheric stability.

The airborne concentrations of EO vapour in the proximity of a leak were also calculated using the Advanced Reach Tool (Version 1.5) (ART, www.advancedreachtool.com) (Fransman et al., 2011; Schinkel et al., 2011, 2013; Tielemans et al., 2011).

2.3. Study population and adduct measurements

Three male workers, aged 26, 30 and 42 years, were involved in the repairs following an incidental leak of EO in an EO-manufacturing plant. All three were non-smokers with no recent exposure to EO. From these workers two blood samples of approximately 5 ml were collected from the antecubital vein into Vacutainer tubes containing sodium edetate as anticoagulant, using γ-irradiated syringes and needles, between 20 and 21 h following the incident. The samples were kept at room temperature and immediately transported to the laboratory. Isolation of globin and subsequent analysis of 2-hydroxy-ethylvaline (HOEtVal) by GC–MS was performed as described previously (Boogaard, 2002). From the measured HOEtVal concentrations, the actual internal exposure were calculated as described previously (Boogaard et al., 1999).

3. Results and discussion

In its most recent recommendation, the EU Scientific Committee on Occupational Exposure assigned a skin notation to EO (SCOEL, 2012). This led to concerns that dermal exposure to EO vapour, which may occur during certain activities in EO-producing facilities, might lead to an unacceptable health risk, despite the use of respiratory protection. Indeed, two *in vitro* studies provide evidence that EO is taken up via the skin, both from the vapour phase and from aqueous solutions (Baumbach et al., 1987; Wester et al., 1997). To develop a quantitative understanding of the relevance of dermal uptake of vapours, calculations were done with two models, the Rauma model and the IndusChemFate model, using various scenarios reflecting normal operational conditions and accidental release of EO.

The Rauma model is based on an empirical evaluation of the combined literature of dermal uptake of vapours for a range of chemicals, mostly solvents. The model is essentially a multiple linear regression model using three physical–chemical properties (octanol–water partitioning, volatility and molecular weight). The correlation in the model is reasonable ($R^2 = 0.69$ based on 32 studies with different substances), but in view of the seriousness of potential health effects it was deemed necessary to conduct an uncertainty assessment to ensure that any health advice would be sufficiently protective. Therefore, the output of the Rauma model was compared to that obtained by using the IndusChemFate model, which calculates the dermal uptake based on physiologically based toxicokinetics modelling using the physico-chemical parameters of EO and the physiological parameters as provided in the Technical Guidance documents for REACH (ECHA, 2008).

For the first scenario (normal working conditions), both models indicated a small dermal contribution when compared with the dose received via inhalation when exposed to the current Dutch occupational exposure limit (0.5 ppm as 8-h TWA). The result of the Rauma model calculated a DCR of 0.2% and the IndusChemFate model predicted a dermal uptake of approximately 1%, therefore under normal operating circumstances the dermal contribution to systemic EO exposure appears to be negligible in comparison with the contribution of the inhalation route. In fact, the SCOEL-recommended Skin notation does not appear justified as it requires a contribution the systemic exposure by the dermal route of at least 10% under normal working conditions with exposure equal to the occupational exposure limit.

In accidental circumstances, involving spillages of EO, the concentrations of EO in air can be very high due to the high volatility of EO. Under such circumstances, it is standard practice that response personnel uses breathing apparatus with independently supplied air, which provides a high level of respiratory protection. Typically, these operations with breathing apparatus with independently supplied air are limited to less than 30 min. A scenario was considered with a leak of liquid EO under pressure of 4 bar from a small