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Short-term health effects in the general population following a major train accident with acrylonitrile in Belgium

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ABSTRACT

Background: Following a train derailment, several tons of acrylonitrile (ACN) exploded, inflamed and part of the ACN ended up in the sewage system of the village of Wetteren. More than 2000 residents living in the close vicinity of the accident and along the sewage system were evacuated. A human biomonitoring study of the adduct *N*-2-cyanoethylvaline (CEV) was carried out days 14–21 after the accident.
Objectives: (1) To describe the short-term health effects that were reported by the evacuated residents following the train accident, and (2) to explore the association between the CEV concentrations, extrapolated at the time of the accident, and the self-reported short-term health effects.
Methods: Short-term health effects were reported in a questionnaire (n=191). An omnibus test of independence was used to investigate the association between the CEV concentrations and the symptoms. Dose-response relationships were quantified by Generalized Additive Models (GAMs).
Results: The most frequently reported symptoms were local symptoms of irritation. In non-smokers, dose-dependency was observed between the CEV levels and the self-reporting of irritation (p=0.007) and nausea (p=0.007). Almost all non-smokers with CEV concentrations above 100 pmol/g globin reported irritation symptoms. Both absence and presence of symptoms was reported by non-smokers with CEV concentrations below the reference value and up to 10 times the reference value. Residents who visited the emergency services reported more symptoms. This trend was seen for the whole range of CEV concentrations, and thus independently of the dose.
Discussion and conclusion: The present study is one of the first to relate exposure levels to a chemical released during a chemical incident to short-term (self-reported) health effects. A dose-response relation was observed between the CEV concentrations and the reporting of short-term health effects in the non-

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smokers. Overall, the value of self-reported symptoms to assess exposure showed to be limited. The results of this study confirm that a critical view should be taken when considering self-reported health complaints and that ideally biomarkers are monitored to allow an objective assessment of exposure.

1. Introduction

In the night of Saturday May 4, 2013, a train transporting butadiene, triethylaluminium and acrylonitrile (ACN) derailed in the village of Wetteren (Belgium). Several rail tank cars with ACN exploded and a fire developed. Toxic fumes of ACN as well as hydrogen cyanide and nitrogen oxides were released due to the fire-induced decomposition of ACN (Van Nieuwenhuyse et al., 2014; De Smedt et al., 2014). To avoid explosion of the rail tank cars with butadiene and triethylaluminium, water was used to extinguish the fire and to cool the intact rail tanks. This water partly passed into the stream along the railway track and ended up in the sewers which resulted in a further distribution of ACN. This atypical sequence of events resulted in the evacuation of more than 2000 residents living in the close vicinity of the accident and along the sewage system. The duration of the evacuation period varied from 3 days up to 3 weeks, mainly depending on the distance from the residence to the accident site. One resident living next to the sewage system died and two other residents experienced life-threatening symptoms. In total, around two hundred inhabitants of Wetteren presented at the emergency services of the surrounding hospitals between May 4 and 14.

Both the physicochemical and toxicological properties of ACN are responsible for the impact of the train derailment. ACN (C_3H_3N) is a monomer used as an intermediate in the manufacturing of acrylic fibres, styrene plastics, and adhesives. At room temperature, ACN is a volatile, flammable, water-soluble, colourless liquid with a garlic or onion-like odour (EU Risk Assessment Report, 2004). ACN vapours are heavier than air and may thus travel along the ground over a long distance. Absorption of ACN may occur by inhalation, dermal contact, or oral ingestion and is rapid and extensive (Kedderis et al., 1993; Pilon et al., 1988; van Hooidonk et al., 1986). Following absorption, ACN is readily distributed throughout the body (Sandberg and Slanina, 1980). There is no evidence for significant accumulation of the substance itself in any organ. However, ACN can react at electrophilic sites of endogenous macromolecules, e.g. haemoglobin (Hb) proteins, and thus can generate adducts. Hb adducts accumulate during the life span of the red blood cells and thus can reflect the exposure during the past 4 months. Metabolism of ACN primarily takes place by two pathways (Gargas et al., 1995; Burka et al., 1994; Kedderis et al., 1993; Fennell et al., 1991; Dahl and Waruszewski, 1989), i.e. (i) conjugation with glutathione and (ii) oxidation by the cytochrome P450 isoenzyme CYP2E1. The first pathway results in the formation of an ACN-glutathione conjugate which will be further converted into a mercapturic acid, representing the final urinary excretion product. Consequently, this pathway is generally considered to be a detoxification step. Within the second pathway, the epoxide 2 cyanoethylene oxide (CEO) is formed as a primary metabolite. CEO is mutagenic and therefore this metabolic pathway is considered as the activation step. CEO can also undergo extensive secondary metabolism which includes the interaction with glutathione forming a series of cysteine or N-acetyl cysteine derivatives and the production of the highly toxic metabolite cyanide through the action of epoxide hydrolase. Cyanide can be detoxified by the mitochondrial enzymes rhodanese and mercaptopyruvate S-transferase to thiocyanate and excreted in the urine. The principal route of elimination for ACN, administered by oral or other routes, and its metabolites is urine with smaller amounts excreted in either the faeces or exhaled breath (Kedderis et al., 1993; Tardif et al., 1987; Ahmed et al., 1983). Acute toxicity of ACN mainly includes respiratory and neurological symptoms. ACN is an acute respiratory tract irritant causing effects such as irritation of the mucous membranes of the nose, eyes and upper respiratory tract. More serious exposures may lead to respiratory arrest and even death. Neurological symptoms may include limb weakness, dizziness, nausea and vomiting, headache, tremor, convulsions, coma and eventually death. The mode of action for neurological effects may involve both the parent chemical and the release of cyanide during metabolism. The mode of action for irritation effects is not known but may involve the binding of ACN or its primary metabolite to cellular macromolecules or depletion of tissue glutathione levels (ATSDR, 1990; WHO, 2002; AN Group, 2004).

Biomonitoring has been revealed as a powerful tool for the individual exposure assessment and risk estimation for citizens and rescue workers affected by chemical incidents (Müller et al., 2014, Scheepers et al., 2014). Particularly, Hb adducts excel for this task because of their long half-live, which enables exposure estimation also from samples withdrawn several days or weeks after the exposure scenario (Bader et al., 2014; Kloth et al., 2014; Leng and Gries, 2014).

We previously reported on the ACN exposure of the residents and emergency responders in a biomonitoring study in which *N*-2-cyanoethylvaline (CEV) in the venous blood was monitored (De Smedt et al., 2014; Van Nieuwenhuyse et al., 2014). CEV is the adduct formed by reaction of ACN with the N-terminal valine in human globin. This adduct is highly specific for exposure to ACN and, because it is built in erythrocytes, follows zero order kinetics after a single exposure event, gradually disappearing as the erythrocyte pool is being replaced, i.e. after 126 days in humans (Granath et al., 1992, Bader et al., 2014). Based on the CEV concentrations measured in blood, values were extrapolated by back-calculation to the concentrations that were to be expected at the time of the accident, i.e. May 4, using the formula: extrapolated CEV = measured CEV/$(1 - t \times 0.008)$, where "t" is the number of days between the accident and the blood sampling (Granath et al., 1992; Bader and Wrbitzky, 2006). As smoking is a known confounder for ACN exposure, cotinine measurements in urine were used to differentiate (Benowitz, 1996) between smokers (urinary cotinine > 100 μg/L) and non-smokers (urinary cotinine < 25 μg/L). For those in between, the smoking status was determined based on the self-reported questionnaire: 'smokers' and 'occasional smokers' were categorised as 'smokers', and 'ex-smokers' and 'non-smokers' as 'non-smokers'. Within these manuscripts, health effects of ACN exposure were not considered.

The objectives of the present study are therefore (1) to describe the short-term health effects that were reported by the evacuated residents following the train accident, and (2) to explore the association between the extrapolated CEV concentrations and the self-reported short-term health effects.