Leakage of acrylamides from a tunnel construction work: exposure monitoring and health effects to humans and animals

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Background

The construction of a railway tunnel through Hallandsås, a mountain ridge in the south-west of Sweden was initiated in 1992. The existing old railway passing this ridge was considered to be a needles eye for railway connections from western Scandinavia to the continent (Fig. 1). A tunnel together with the prospected bridge from Malmö to Copenhagen (completed in year 2000) would be economically important, narrowing Norway and Sweden to the continent.

The tunnel construction work, however, met difficulties primarily because of the properties of the rock. Above all a heavy leakage of water was encountered (as predicted by some geologists). This leakage led among other things to a lowering of the water-table in the area. Different methods to tighten the tunnel walls were discussed and after some testing it was decided to apply a chemical grouting agent, Rhoca Gil® (Rhone-Poulenc, France). Between August 5 and September 30, 1997, the grouting agent was used in full scale in a total amount of 1400 tons (Tunnel Commission, 1998).

Fig. 1. Map illustrating railway tunnel construction through the Hallandsås ridge at the Bjäre peninsula in the south west of Sweden.
On the ridge, close to a middle entrance opened to the prospected tunnel, a brook, Vadbäcken, run through the pasture. Drainage water from the tunnel construction was pumped out into the brook. Towards the end of September, 1997, dead fish in a fish-culture downstream the brook and paralysis of cows in a herd grazing around the brook showed that something was wrong. An analysis of water in Vadbäcken end of September showed very high concentrations of the Rhoca Gil components acrylamide and N-methylolacrylamide (Fig. 2). It was evident that the reactive monomers in the grouting agent, due to incomplete polymerization, had leaked and was spread into the environment.

Fig. 2. Rhoca Gil contains the monomers acrylamide and N-methylolacrylamide and also formaldehyde (in the ratio 1.5 %, 37 % and 0.9 % according to the manufacturer; according to later analysis the acrylamide concentration was around 5 %). This solution 1 of Rhoca Gil is mixed with sodium silicate and sodium persulfate and an accelerator to form the grouting agent.

This leakage developed rapidly into a complex exposure situation and a complicated risk panorama. Table 1 summarises the development of events.

Table 1. Sequence of important events during Autumn 1997 concerning exposure and ensuing administrative etc. actions due to leakage of grouting monomers at tunnel construction work (Tunnel Commission, 1998).

<table>
<thead>
<tr>
<th>Date</th>
<th>Event/action</th>
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<tbody>
<tr>
<td>August 5 – September 30</td>
<td>Full scale use of Rhoca Gil in tunnel construction.</td>
</tr>
<tr>
<td>August 14</td>
<td>Local authorities and county administrative board informed about use of Rhoca Gil.</td>
</tr>
<tr>
<td>September, last days</td>
<td>Dead fish in a fish-culture and paralysed cows around Vadbäcken.</td>
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<tr>
<td>September 30</td>
<td>Water from Vadbäcken showed very high concentrations of Rhoca Gil monomers. Use of Rhoca Gil in tunnel construction discontinued.</td>
</tr>
<tr>
<td>October 1</td>
<td>Three cows with hind-limb paresis euthanized.</td>
</tr>
<tr>
<td>October 2</td>
<td>Information to farmers around Vadbäcken. Press conference arranged by construction companies and local authorities. Massive coverage by media initiated.</td>
</tr>
<tr>
<td>October 3</td>
<td>Local authorities informed about the results on analysis of Rhoca Gil monomers in Vadbäcken. The public around Vadbäcken warned not to drink water from wells.</td>
</tr>
<tr>
<td>October 4</td>
<td>The local authority report the construction company, the Rail Administration and Rhone Poulenc to the police.</td>
</tr>
<tr>
<td>October 5</td>
<td>The local authority declared state of emergency.</td>
</tr>
<tr>
<td>October 6</td>
<td>Local authorities started continued information via media. Emergency telephone answering service opened for general public. Preliminary risk area defined.</td>
</tr>
<tr>
<td>October 7</td>
<td>Tunnel work stopped. Studies of tunnel workers initiated.</td>
</tr>
<tr>
<td>October 9 – November</td>
<td>Different governmental authorities presented, sometimes contradictory and uncoordinated, judgements and recommendations.</td>
</tr>
<tr>
<td>October 10</td>
<td>High levels of hemoglobin adducts from acrylamide in affected cows (proof of cause). Wells showed to contain grout monomers.</td>
</tr>
<tr>
<td>October 12</td>
<td>Large manifestation meeting by Hallandsås residents.</td>
</tr>
<tr>
<td>October 24</td>
<td>Concentration of Rhoca Gil monomers decrease, several wells declared riskless.</td>
</tr>
<tr>
<td>October 30</td>
<td>Risk area decreased.</td>
</tr>
<tr>
<td>March 16, 1998</td>
<td>Risk area abolished.</td>
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</tbody>
</table>
Risk assessment of health effects

Exposure situation. - Several factors rendered the exposure situation difficult to appraise:

- Exposure of both workers and residents in the area and also of animals in the environment.
- Uptake of toxic substances by different routes (inhalation and dermal uptake among workers; risk of uptake by drinking water and dermally among residents).
- The effluent contained more than one chemically reactive component (acrylamide and N-methylolacrylamide) with toxic effects; furthermore the components are metabolized in the body (particularly to glycidamide) with other toxic effects (Fig. 3).
- Expressed threats of exposure via cultivated crops and foods.
- Limited access to analytical methods and data for the toxic compounds in the environment.

Dose-response relationships of health effects of toxic compounds. - According to literature the toxic effects of the reactive components in the grout comprise neurotoxic effects, increased risk of cancer, hereditary damage and reproductive effects (EU, 1997). In humans neurotoxic action of one of the components, acrylamide, has been demonstrated (Calleman et al., 1994; EU, 1997). Some toxic effects (neurotoxic and probably also effects on reproduction) are deterministic, i.e. these effects do not occur until a threshold dose have been exceeded and at higher doses they affect the majority of the exposed persons. Risks of cancer and heritable disease are stochastic, i.e. affect at random a fraction of the exposed. For these effects it is at present assumed that the risk increment because of exposure increases proportionally with the exposure dose without any zero-effect threshold. These types of dose-response relationships are illustrated in Fig. 4. It should be added that the neurotoxic action of acrylamide occurs rather soon after initiation of exposure, whereas the cancer risks may lead to tumours much later, at any time during the residual life-time. Another important difference between the two types of effects is that the severity of the neurotoxic effect increases with increasing dose and is reversible at least at low doses, whereas with regard to cancer it is only the frequency and not the severity that is affected by dose.

Characterization of the exposure situation. - A characterisation of the exposure situation was complicated due to the above factors. Furthermore, due to the reactivity and to the short life span of the compounds in the body the compounds cannot be analysed as such for instance in excreta or blood after the discontinuation of exposure. For reactive compounds/intermediates methods for determination of stable reaction products, e.g. hemoglobin (Hb) adducts, have been developed for assessment of uptake into the body, and of in vivo dose as a basis for risk estimation (Törnqvist and Hindø Landin, 1995). The laboratory at Stockholm University had experience from an earlier study of uptake of acrylamide among workers in a Chinese factory applying this method (Bergmark et al., 1993).

The observation of paralysed cows indicated but did not prove that their drinking water supply was contaminated by drainage water from the tunnel. The analysis of Hb adducts in blood samples from the affected cows demonstrated that acrylamide was the causative agent (Godin et al., 2000; Tareke et al., 2001). This conclusion was strengthened by the earlier measurement of acrylamide and N-methylolacrylamide in the brook water. Soon after this it was also demonstrated that the acrylamides had contaminated ground water and wells.
**Fig. 4.** Dose-response relationships for health effects. For deterministic effects increasing dose means increasing severity of symptoms. For stochastic effects the frequency of affected persons, but not the severity, increases with dose.

In this situation it appeared urgent to clarify the exposure to tunnel workers and after the observation of contamination of the ground water, also to residents within the area. This initiative was taken by Dept. of Occupational and Environmental Medicine, University Hospital in Lund. To get an early impression of the situation blood samples were collected (October 7) from a few workers for Hb adduct analysis. The relatively high levels observed led to a decision to investigate all of the workers that wanted to be investigated. Out of 242 workers judged by the contractor to be potentially exposed, 223 were subjected to medical examination and from 210 blood samples were obtained and analysed with respect to Hb adduct levels.

Risk zones were defined in the surrounding area and about 200 persons living within these zone were medically examined and blood samples were collected. Blood samples from 23 persons who were assumed to have run relatively high risks of exposure were analysed with regard to Hb adducts.

It has earlier been shown that acrylamide form 2-carbamoylethyl adducts to N-terminal valines in Hb, which could be detached and analysed by a modified Edman degradation method (Törnqvist, 1994; Bergmark, 1997). Initiated studies of N-methylolacrylamide showed that the same adduct was formed (in vivo in rats) at a level that was one third of the value observed for acrylamide, calculated per amount absorbed (in mmol per kg) (Tareke et al., 2001). Thus the observed Hb adduct levels in humans exposed to leakage of Rhoca Gil are measures of the effective amounts of mixtures of the two acrylamides. The adduct levels are expressed in e.g. nanomol per gram of globin (nmol/g = 10⁹ mol/g). From the adduct levels the absorbed amounts could be calculated as well as the dose in the body, from which risks could be inferred (see below).

Seventy-four of the tunnel workers had a level of Hb adduct from acrylamide above 0.3 nmol/g globin, of these 38 had higher levels than 1 nmol/g globin (Hagmar et al., 2001). There was one worker with a four times higher value than the next highest value of 4.3 nmol/g (Hagmar et al., 2001). The analysis of samples from residents showed, throughout, rather low adduct levels (below 0.3 nmol/g) and for economical reasons no further samples from residents were analysed (Albin et al., 1998). In non-smoking control persons the adduct level is in the range 0.02 – 0.07 nmol/g.

**Observed health effects.** - Fifty-one of the medically examined workers reported neurological symptoms acquired after onset of the engagement in the tunnel work (Hagmar et al., 2001). For these the neurophysiological examination were followed up after six months with reinvestigation another 6 and 12 months later for those with remaining symptoms. It was judged that for 23 workers there was a significant relationship between exposure to acrylamides and reduced function capability of peripheral nerves. In general there was a strong correlation between neurotoxic symptoms and acrylamide adduct levels, i.e. of uptake of acrylamide. After 18 months 3 of the workers had remaining symptoms.
Among the residents in the risk-zone subjected to medical examination there were no significant association between exposure and symptoms of neurotoxic effects (Albin et al., 1998).

**Estimation of risks of health effects** - For the neurotoxic effects it is assumed that the acrylamides are causative agents although the mechanism of action is not known. According to literature (IARC, 1994) N-methylolacrylamide is 3-5 times less effective than acrylamide with regard to neurotoxic effects. This relative effectiveness of N-methylolacrylamide agrees with the measured in vivo dose of acrylamide from exposure to N-methylolacrylamide in rodents (see above). Thus the Hb adduct levels measured reflect the “effective acrylamide” dose, with regard to neurotoxic effect, received in a mixed exposure to the two compounds.

As for the neurotoxic effects an evaluation of the previous study of Chinese factory workers (Calleman et al., 1994) indicated that the no-effect threshold from exposure from a few months is an uptake of acrylamide that leads to an adduct level in the range of 0.3 – 1 nmol/g (Törnqvist et al., 1998). By and large the observed data from exposed workers at Hallandsås are in agreement with this provisional value for a threshold.

With regard to reproduction-toxicological effects it may be judged that the risk of these effects is small compared to neurotoxic effects. It has been estimated that NOAEL values are at least ten times higher than the thresholds for neurotoxicity (US EPA, 1990).

Both acrylamide and N-methylolacrylamide are carcinogenic in animal tests (IARC, 1994). With regard to the cancer risk from acrylamide the metabolite glycidamide is assumed to be the active principle (Fig. 5). The dose of glycidamide was not measured in the initial studies of exposed workers at Hallandsås, but inferred from the earlier studies of acrylamide-exposed Chinese workers (Bergmark, 1992; Bergmark et al., 1993). In follow-up studies these estimates of the dose of glycidamide have been improved. N-methylolacrylamide has a lower genotoxic potency than acrylamide (IARC, 1994). In animal experiments with N-methylolacrylamide the observed dose of glycidamide (measured as Hb adducts) is compatible with acrylamide being the precursor (Paulsson et al., to be published). The observed level of acrylamide adducts in mixed exposure of the two components is thus a measure of “the effective dose” of acrylamide also with regard to the cancer risk increasing action and could be used as a basis for cancer risk estimation.

**Fig. 5.** Formation of the reactive metabolite glycidamide from acrylamide in vivo.

The estimated cancer risks were expressed as probabilities of contracting a cancer disease at any time later in life, in comparison with and as increments above the background value (about 30 % of the population). In the evaluation the probabilities of all kind of tumours were pooled.

The risks corresponding to the median adduct level among workers, 0.25 nanomol/g globin, measured a short time after the end of a 55 days exposure period, were estimated. The accumulated uptake and in vivo dose of acrylamide and N-methylolacrylamide treated as “effective acrylamide” (see above) were calculated from the adduct level, with allowance for the decay of erythrocytes during the exposure period (Granath et al., 1992), and by methods described by Törnqvist and Hindsø Landin (1995) and Törnqvist et al. (1998). In the estimation the multiplicative model developed at Stockholm University was applied (Granath et al., 1999), which had been shown to be valid for acrylamide (Paulsson et al., 2001).

The average exposure is expected to lead to an increase of the probability by 0.04 %, i.e. from 30 % to 30.04 %, a small and undetectable increase compared to the value for unexposed persons (see Table 2). The estimated risk increment is small, e.g. in comparison with the effect of smoking. For the residents in the area the cancer risk increments could be considered negligibly small.
Table 2. Measured levels of adducts to hemoglobin from acrylamide (relative doses) and estimated contribution to life-time cancer risk for workers at Hallandsås.

<table>
<thead>
<tr>
<th>Hb adduct level</th>
<th>Cancer risk</th>
<th>Probability that any one in the group gets cancer due to the acrylamide exposure.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background (0.04 nmol/g)(^a)</td>
<td>30 %</td>
<td>-</td>
</tr>
<tr>
<td>Tunnel workers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median dose (0.25 nmol/g)</td>
<td>30.04 %</td>
<td>0.08 (out of 200)</td>
</tr>
<tr>
<td>High dose (about 3 nmol/g)</td>
<td>30.5 %</td>
<td>0.1 (out of 20)</td>
</tr>
<tr>
<td>For comparison: smokers</td>
<td>~ 40 %</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) An acrylamide adduct occurs regularly at levels in the range 0.02-0.07 nmol/g Hb from nominally unexposed non-smoking persons. Its major origin seems to be fried food (Tareke et al., 2000). An adduct level increment amounting to about 0.006 nmol/g per cig/day occurs in smokers (Bergmark, 1997).

These considerations tried to show that the cancer risks run because of acrylamide exposure in the tunnel work were negligibly small. It was on the other hand obvious that this comforting information could be given because of the shortness of the exposure period, the tunnel work being discontinued less than two months after the start of full-scale use of Rhoca Gil. A continuation for a longer time of work under the condition in the tunnel would definitely have been impermissible primarily because the cancer risk increase proportionately to the duration of the work, but probably also with neurotoxic symptoms becoming both aggravated and more common. In the present situation these symptoms were light and mostly reversible.

Communication of assessed risks. - After the revelation of the exposure situation the turmoil of events (cf. Table 1) may have contributed to uneasiness and anxiety among concerned persons. To this the covering by media often with alarming articles was added and prohibition of use of water and food-stuffs (milk, meat, vegetables) produced in the area. Furthermore, the fact that exposure and other consequences of the tunnel construction were not self-chosen but something forced on the individuals might have influenced the risk perception among residents.

In efforts to describe the cancer risk in an understandable, not alarming, way the assessed risk increments were:
- compared with the background values of cancer incidence in the western population;
- expressed as the life-time risk morbidity in % increment;
- compared with the effect of smoking.

The results from Hb adduct measurements and the assessed risks from the first studied workers (7 exposed, 3 controls) were presented individually and to the whole group of workers in the middle of October. On later occasions results from studies on remaining part of worker group and residents were presented in a similar way. On these occasions also press conferences were given. This way of presenting the risk situation to the workers and residents has not been evaluated but appeared to have been successful in its purpose of counteracting anxiety about health consequences of the exposure.

Other effects

The use of water from wells in the area was prohibited. By way of precaution a number of about 400 animals (mainly cattle) were put away and milk and vegetables produced in the area had to be discarded. A secondary effect was buying resistance against agricultural products from the Bjäre peninsula west of the risk zones (Fig. 1). The yearly hunting of elk, as well as other hunting in the area was restricted. Fishing in several brooks was affected. The water leakage also had other effects e.g. on vegetation and drying out of wells.
Lessons learnt with regard to the ALARA principle
- Correlations of neurologic symptoms (or uptake) with questionnaire answers showed that considerable protection would have been gained from better information motivating simple measures such as change of gloves and other clothes after wetting by the grouting agent or drainage water.
- Importance of clarifying the exposure and risk situation, not the least with regard to genotoxic carcinogens which presumably give rise to non-thresholded stochastic effects. Especially after events of short duration, e.g. accidental leaks, anxiety is often a dominating consequence that could be alleviated by an estimation of the uptake and the magnitude of the associated risk. In many cases these figures can be determined by measurement of adducts. A statement that a toxic release occurs, without quantitation of consequences and risk, may be disastrous.
- A large number of chemical carcinogens are active by a genotoxic mechanism. Like ionizing radiation these chemical carcinogens lead, as far as can be judged at present, to a risk increment which at low doses depends linearly on dose, without no-effect threshold. Experience from persons exposed to carcinogenic chemicals at Hallandsås and at other accidental exposures show that the anxiety, a dominating effect among exposed, is aggravated by the perception of the risk as an all-or-none phenomenon. Such perception may have support in the labelling of the chemicals as “carcinogenic”, (although sometimes preceded by “probably” or “possibly”), carcinogenic being taken to mean “causing cancer”. It might contribute to a more realistic perception – and be more in line with facts – if these chemicals were denoted “cancer-risk increasing”. This would also improve the motivation for application of the ALARA principle.
- The perception of a risk is often rendered more realistic by comparison with a factor for which there is a general knowledge about associated risks. The genotoxic cancer-risk increasing factor which is best characterized with regard to the risk-dose relationship is ionizing radiation, and risk estimates of chemicals may gain in accuracy through a determination of the radiation-dose equivalents of chemical doses (Granath et al., 1999). This would favor a generalized application of the ALARA principle to chemicals and radiations, and may increase the motivation for risk-reducing measures on the individual as well as the group level.

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References