Effects of exposure to Isopropyl nitrite

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Two analysts in a pharmaceutical production facility were exposed to isopropyl nitrite and benzene while clearing up a small spill. The article describes the physiological effects on the men and the procedural changes that took place subsequently.

Key words: Exposure; Isopropyl nitrite; pharmaceutical.

INTRODUCTION
Isopropyl nitrite (IPN, C3-H7-N-O2) is used as an intermediary in the production of pharmaceuticals at a plant in North London. IPN is a highly energetic shock-sensitive compound which has uses, for instance as rocket fuel and in explosive detonation. It boils at 39°C and exothermic reactions in enclosed containers occur at about 60°C. It can ignite by shock or friction.

Samples were taken during the manufacturing process and stored in a 2.5 litre Winchester in a refrigerator. The composition at this stage was of 65% IPN, 30% benzene and 5% isopropyl alcohol.

At 07.30 on the morning of the incident a shattering noise was heard from the refrigerator and liquid was seen to run out onto the floor. Subsequent investigation appears to indicate that the Winchester broke because it had been overfilled leaving no expansion room and the refrigerator was running above its design temperature at 8°C.

The staff involved (analysts) stemmed the flow using paper towels and 'pigs' (effectively like sausage-shaped draught excluders filled with inert absorbent material). These were then picked up by the analysts using their hands protected only by thin latex gloves and no respiratory protection. At the same time the windows and doors were opened.

The analysts sought advice from the occupational health adviser as they had developed headaches and had felt dizzy (although the dizziness had gone by then). This was about 75 minutes after the incident. They seemed slightly flushed but there was no sign of cyanosis or shortness of breath. Pulse, blood pressure, respiratory rate and body temperature were taken and they were observed by the occupational health department during the day. Additionally spirometry was carried out. We chose to take blood for full blood count and liver function tests at three days and at two weeks after exposure, having reasoned rightly or wrongly that an immediate test was unlikely to be helpful as we had baseline values from their annual assessments eight weeks before.

The headaches settled during the day and the two men exhibited no other physical symptoms. This included the skin of their hands which showed no ill effects. Their observations remained normal.

These ill effects were, we believe, due solely to the IPN present in the mixture.

The blood tests were normal on both occasions for one of the analysts. The other, however, was slightly abnormal. He is known to have Gilbert's syndrome and showed his usual slightly raised bilirubin level. The full blood count however showed a depressed neutrophil count of 1 x 10⁹ g/l (1.5-7.5). This had returned to normal at two weeks.

Our hazard data sheet only mentioned the physical hazards and the fact that IPN is a potent vasodilator. Because of its structure and other properties we thought that pulmonary irritation and methaemoglobinaemia were a possibility. On contacting the poisons unit at Guy's hospital we had a very useful discussion, as they also felt this was a possibility. Fortunately this did not appear to occur.

DISCUSSION

During the investigation after the incident the above sequence of events was established. The personnel concerned had received training in dealing with spillage...
incidents as part of their induction; this was, however, relatively informal. In this case the procedure was to rapidly place ‘pigs’ to contain the spill, ventilate if possible and evacuate the area to then allow the in-house emergency team to deal with the spill (while wearing full self-contained breathing apparatus and protective clothing). Because they did not follow this procedure a more formal procedure has been put in writing and training has become more formal.

The procedures were reassessed following a risk assessment performed by the staff in association with occupational hygiene and health and safety. The above spill would now be classified as a large spill as it was greater than 100 ml and staff are expected to consider calling the emergency team in every such case. Additionally a system is in place to check equipment so that an abnormally high storage temperature is less likely to occur. For even a minor spillage suitable protective equipment must be worn including eye protection, an overall and suitable gloves and footwear. Respiratory protective equipment must be considered even for minor spills — the type is specified.

There are, however, a number of problems. As a spill occurs the personnel present must of necessity make a rapid risk assessment. The Winchester might have contained de-ionized water for instance and clearly evacuation would not have been appropriate. Secondly, most compounds do not have formal exposure limits. Of course chemical companies have their own limits for many in addition to those to be found in publications such as the Health and Safety Executives’ EH40. However in this company these exist for compounds and intermediates that may have to be handled during the production process. It does not apply to intermediates that are usually in closed systems such as the sample in this case.

Subsequent research and an updated data sheet list the short-term effects of exposure to IPN as: possible irritation with additional possible effects of vomiting, diarrhoea, difficulty breathing, low blood pressure, irregular pulse, headache, drunkenness, bluish skin colour (due to methaemoglobin), convulsions, shock and coma. Occasionally visual disturbance may act as a warning.

Effects of long-term exposure include methaemoglobinemia, haemolytic anaemia and haemoglobinuria. Prolonged feeding studies in animals have revealed possible carcinogenesis, probably due to nitrosamine production.

Additionally IPN can explode spontaneously in contact with materials such as paper (as in the towels used to contain the spill).

The second compound present in the mixture was benzene, the effects of which are better known. Acutely, it intoxicates with dizziness, then vomiting, loss of consciousness and in high enough concentrations, death. The better know chronic effects are of late onset bone marrow depression with possible malignant change or aplastic anaemia being the most serious sequelae. It is subject to a maximum exposure limit of 5 ppm (16 mg/m$^3$) for an 8 hour time weighted average. In fact in this plant there is an ‘in-house’ limit of 1 ppm. We have speculated that it may have been this that caused the depressed neutrophil count.

We feel that the isopropyl alcohol in the mixture was of much less significance.

CONCLUSION

We have learnt of the value of quickly accessible, accurate and comprehensive product data sheets and of never assuming that just because staff are highly intelligent and aware of the properties of a substance that they will deal with it in an appropriate way. Training has become more formal and is audited regularly.