Hematopoietic and reproductive toxicity of 2-bromopropane, a recently introduced substitute for chlorofluorocarbons

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Abstract

2-Bromopropane and hydrochlorofluorocarbons (HCFCs), whose toxicity has scarcely been known, have recently been introduced as main substitutes for chlorofluorocarbons (CFCs). A major corporation in Korea replaced CFCs with 2-bromopropane and this actually led 23 Korean workers to be the world’s first 2-bromopropane intoxication victims. Out of 25 female workers in the tactile switch assembling section, 17 (68%) were diagnosed as having ovarian failure. Two affected female workers showed marked pancytopenia with markedly hypoplastic marrow. In the same section, two out of eight male workers showed azoospermia and four some degree of oligospermia. The above toxicity of 2-bromopropane was reproduced in experimental animal studies. Recently, health effects of HCFC 123, including toxic hepatitis, have been reported by several authors. The principle of replacement of toxic substances with non-toxic or less toxic chemicals is important in risk management, but substances still poorly known should not be confused with non-toxic or less toxic substances. Measures aimed at reducing exposure to chemicals with known toxicity rather than using new unknown alternatives may be a rational and effective approach to risk management. © 1999 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Chlorofluorocarbons (CFCs) have the useful physical properties of low boiling points, low specific heats and heats of vaporization, high insulating value, low surface tension and viscosity, high vapor densities, and non-flammability. Furthermore, CFCs are relatively safe and do not seem to give rise to adverse health effects. Thus, CFCs find extensive use in four major applications: as refrigerants; as blowing agents in the manufacture of foam plastics; as cleaning solvents; and as propellants. However, CFCs and their destruction in the stratosphere have been implicated in the depletion of the stratospheric...
Table 1

<table>
<thead>
<tr>
<th>CFCs</th>
<th>Uses</th>
<th>Alternatives in use</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFC 11</td>
<td>Foam-blowing agents, refrigerants, propellants,</td>
<td>HCFC 141b, HCFC 123</td>
</tr>
<tr>
<td></td>
<td>cleaning solvents</td>
<td></td>
</tr>
<tr>
<td>CFC 12</td>
<td>Refrigerants, foam-blowing agents, propellants.</td>
<td>HCFC 142b</td>
</tr>
<tr>
<td>CFC 113</td>
<td>Cleaning solvents, foam-blowing agents.</td>
<td>HCFC 141b, HCFC 225, 2-bromopropane,</td>
</tr>
<tr>
<td>CFC 114</td>
<td>Foam-blowing agents, propellants.</td>
<td>1-bromopropane</td>
</tr>
<tr>
<td>CFC 115</td>
<td>Refrigerants, etching agents.</td>
<td>HCFC 142b</td>
</tr>
</tbody>
</table>

ozone layer. Adverse effects resulting from the depletion of the stratospheric ozone layer include an increased incidence of cataract formation and skin cancer.

An international agreement was reached in June, 1990, in Montreal, Canada, to reduce the use of CFCs, stimulating research aimed at CFC replacement. 2-Bromopropane and hydrochlorofluorocarbons (HCFCs) have recently been introduced as main substitutes for CFCs (Table 1). 2-Bromopropane, a relatively new substitute for CFC 113, has recently been used as cleaning solvent. 2-Bromopropane is a colorless liquid at room temperature and has a sweet smell. It has been used mostly as an intermediate for medicines, pesticides and other chemicals in closed systems, but no previous studies had reported it to be toxic to humans or animals until we reported the world’s first 2-bromopropane intoxication cases (Kim et al., 1996; Park et al., 1997).

1,1-Dichloro-2,2,2-trifluoroethane (HCFC 123), and 1-chloro-1,2,2,2-tetrafluoroethane (HCFC 124) are major candidate substitutes for CFCs 11, 12 and 114, used as refrigerants in chillers for industrial air conditioning (Table 2).

The toxicity of HCFC 123 as well as that of 2-bromopropane has scarcely been known. Unfortunately, this point has been misconstrued as an indication of their non-toxicity. Hence, some corporations in industrialized countries have introduced these substances to replace CFCs despite the relatively high cost.

2. An outbreak of reproductive and hematopoietic disorders

An occupational health manager in an electronics factory in South Korea reported to the Republic of Korea Department of Labor a cluster of cases of secondary amenorrhea among female workers exposed to solvents containing 2-bromopropane in the tactile switch assembly section in 1995 (Kim et al., 1996; Park et al., 1997). The physicians and industrial hygienists of the Industrial Health Research Institute of the Korea Industrial Safety Corporation (KISCO) performed an emergency investigation. The investigation team identified 33 workers (eight men and 25 women) in the section who served as the study population.

Detailed medical and occupational histories were taken, including questions regarding the use of medications. Thorough physical examinations together with clinical laboratory tests were done.

Table 2

<table>
<thead>
<tr>
<th>CFCs</th>
<th>Health hazards to workers</th>
<th>Depletion of ozone layer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Bromopropane</td>
<td>Reproductive toxicity,</td>
<td>More potential</td>
</tr>
<tr>
<td></td>
<td>hematopoietic toxicity</td>
<td></td>
</tr>
<tr>
<td>HCFC 123</td>
<td>Hepatotoxicity</td>
<td>Less potential</td>
</tr>
</tbody>
</table>

...
2-Bromopropane had been used as a substitute for CFC 113 in the section for 18 months. The whole process was done in a large room separated from other processes. There were seven assembly lines, each with one cleaning bath and hood, and three or four automatic assembling machines. Serially connected tactile switch parts were first delivered to the cleaning bath and dipped in the cleaning solution for several seconds. The solution degreased the parts and also filled the chinks between the resin and terminals with polytetrafluoroethylene, a component of the solution. This component prevents flux from infiltrating into the chinks between the resin and terminals of the part when lead soldering is done in a later process and makes the tactile switch function well. After passing through the cleaning bath, the parts were fed into the automatic assembling machine and assembled into a complete tactile switch. The same cleaning solution was used in all seven cleaning baths. All the workers did 12-h shifts.

The major component of the solvents used in the process was identified by GC-MSD analysis to be 2-bromopropane (97.4%). Other components of the solvent were n-heptane (0.33%), 1,2-dibromopropane (0.2%), and 1,1,1-trichloroethane (0.01%). In air samples, 2-bromopropane and n-heptane were identified. The mean 9 standard deviation (range) of the 2-bromopropane concentration from 14 area samples in the tactile switch assembling room was 12.4 ± 3.13 ppm (9.2–19.6 ppm) under a simulated setting of over 3 h.

Short term exposure level monitored inside the hood of cleaning baths was 4140.7 ppm in 2-bromopropane.

Although previous and present exposures had been investigated in detail by industrial hygienists, except for the cleaning solution containing 97.4% of 2-bromopropane, any previously known physical or chemical agents responsible for bone marrow and reproductive hypofunction including ionizing radiation, lead, ethylene glycol ether and their acetates, benzene, and dibromochloropropane, were not identified.

The workers, not being informed of any potential hazards from these chemicals, had often put their heads inside the hoods of cleaning baths or had dipped their bare hands into the solution without using any personal protective devices. Local ventilation systems were inadequate and exposure levels may have been relatively high.

Out of 25 female workers in the section, 17 (68%) reported secondary amenorrhea for various periods (2–14 months). In clinical interviews and examinations they reported to have had normal menses up to this outbreak and they had not used any special medications or oral contraceptives during the period on the job. In 17 female workers, FSH levels were elevated (range 27.8–118.6 mIU/ml), and most of them complained of hot flushes. LH levels were also elevated in most female workers. Prolactin levels were, however, within the normal range. Progesterone withdrawal bleedings were not observed in any workers with amenorrhea. Estradiol levels in three female workers were below the detection limit. All the affected workers were diagnosed as having ovarian failure. Concurrently, a total of eight workers with amenorrhea were found to have various degrees of pancytopenia. Other female co-workers showed mild either anemia or leukopenia. Bone marrow biopsy was carried out in two workers with marked pancytopenia. The biopsy findings showed a markedly hypoplastic marrow (15 and 25% cellularity, respectively) compatible with aplastic anemia. The results of a number of other clinical tests aimed at investigating the coagulation, and the function of the kidney, liver, and thyroid were within the reference interval. Chest films, urinalyses, and EKG were also found to be normal in the affected workers. Many workers in the section complained of non-specific symptoms such as headache, dizziness, or weakness. The two workers with marked pancytopenia especially complained of easy bruisability. In female workers, the duration of exposure prior to the onset of amenorrhea was 4–16 months. The duration of exposure in male workers was 16–19 months.

Among eight male workers, two showed azoospermia and four oligospermia (defined as sperm count less than 20 million/ml or reduced sperm motility defined as < 50%). Male workers who were single or married with several children had not tried to have children. FSH levels were
near the upper normal range, but testosterone levels were within the normal range. Some male workers complained non-specific subjective symptoms such as headache or dizziness, but none loss of libido. Affected male workers were diagnosed with germ cell failure. One with azoospermia also had mild pancytopenia.

Apart from hematopoietic and reproductive dysfunction, we were unable to detect any other abnormalities. Hence, the bone marrow hypofunction and the testis or ovarian failure were shown to be the main health hazards in the tactile switch assembling process. There had been no cases among workers who quit before the replacement of CFC 113 with 2-bromopropane. Nor were such effects found among the workers in other processes, not implying exposure to 2-bromopropane containing solvents. Whereas hematopoietic disorders have recovered after the cessation of exposure to 2-bromopropane, reproductive disorders have subsequently been diagnosed as permanent sterility.

3. Animal experiments of 2-bromopropane

Several animal experiments, carried out after the outbreak, revealed that 2-bromopropane had a severe toxic effect on both female and male reproductive and hematopoietic systems. Ichihara et al. (1997) conducted an inhalation animal experiment with 36 male Wistar rats to clarify the reproductive toxicity of 2-bromopropane, which was found to have a specific toxicity on the testes, especially on spermatogonia. In an animal experiment with female Wistar rats, inhalation exposure resulted in a disturbed estrous cycle, atresia of ovarian follicles, and loss of oocytes in the remaining ovaries (Kamijima et al., 1997). In the inhalation experiment, Ichihara et al. (1997) also observed a dose-dependent pancytopenia in the peripheral blood. Nakajima et al. (1997) examined the megakaryocyte and adipose cells in the bone marrow of rats inhaling 2-bromopropane. The number of scattered adipose cells in the bone marrow increased in the exposed group in a dose-dependent manner.

These results show that 2-bromopropane has a peculiar hematopoietic toxicity in rats. Male/reproductive and hematopoietic impairment was also observed in Sprague Dawley rats with intraperitoneal injection of 2-bromopropane (Lim et al., 1997; Yu et al., 1997).

As a whole, these experimental findings confirmed that 2-bromopropane was the causative agent of the hematopoietic and reproductive disorders observed in Korean electronic workers.

4. Health impairment caused by HCFC, other substitute for some CFCs

Hoet et al. (1997) recently reported an outbreak of toxic hepatitis caused by a mixture of HCFC 123 and 124. Takebayashi et al. (1998) also reported a cluster of severe liver dysfunction among workers who had been exposed to HCFC 123.

In guinea pigs, a single exposure to 1000 ppm of HCFC 123 for 4 h caused increases in aspartate aminotransferase and alanine aminotransferase compatible with hepatocellular necrosis (Marit et al., 1994). The mechanism of the hepatotoxicity of HCFC 123 was suggested to be probably similar to that of halothane (1-bromo-1-chloro-2,2,2-trifluoro-ethane; Parkinson, 1996), whose structure is very similar to that of HCFC 123.

5. Issues in introducing alternative chemicals

2-Bromopropane and HCFC 123, recently introduced substitutes for CFCs, have caused unexpected and severe health impairments. We must learn from these cases and be extremely cautious when substituting known chemicals with poorly known substances. These new intoxication cases remind of several outbreaks of polyneuropathy all over the world, mainly in Japan and in Italy, in workers exposed to high levels of $n$-hexane, thought as a safe substitute for benzene. $n$-Hexane-induced polyneuropathy was diagnosed in 93 out of 1662 workers at that time (Yamamura, 1969). These two examples are similar in that both benzene and CFCs were substituted, with
substances causing new and unforeseen health impairments. Alternatives that are entirely safe and free from hazards are seldom or never available. Strict control on exposure to the new alternatives substituting substances thought to be more toxic is always necessary.

Substituting hazardous chemicals with less toxic substances is an important principle in risk management, but substances whose toxicity has not been established should not be confused with non-toxic or less toxic substances. Hence, it appears realistic to use a known chemical whose toxicity is well documented with extreme caution rather than using new alternatives whose toxicity has not been thoroughly studied. These substances should be treated as if they were equally dangerous as those they substitute.

References


